The role of parental genetic and environmental factors in the aetiology of childhood ADHD and comorbid disorders

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Abstract

Despite being one of the most thoroughly studied disorders in psychiatry, several aspects of the aetiology of attention-deficit hyperactivity disorder (ADHD) remain poorly understood. For example, while ADHD is consistently found to be among the most highly heritable disorders, the specific genetic risk factors and their mechanisms remain largely unknown. Similarly, the smaller but consistently observed environmental influences on ADHD and its common comorbid disorders have not been satisfactorily documented. More broadly, research on ADHD has primarily focused on individuals with ADHD; on their symptoms, the heritability and neural correlates of those symptoms, whether certain treatments can alleviate symptoms, and the effect children's symptoms can have on families. Relatively little research has looked at the role of families, and in particular parents, in the aetiology of ADHD.

Recently, the role of parents has received increased recognition, due in part to the growing body of literature on adult ADHD, and findings that at least one parent of a child with ADHD will usually either meet diagnostic criteria for ADHD themselves or display subthreshold symptoms. These findings have led to a conceptual repositioning of ADHD from being a disorder specific to a child and which affects the child and their family, to a continuous phenotype that clusters within families, and which may manifest at clinical or subclinical levels in several generations of a family simultaneously. In other words, whereas research has conventionally focused on children with ADHD, or 'families of children with ADHD', it may be more appropriate to adopt an approach of studying 'families with ADHD'. This approach means that certain questions regarding the aetiology of childhood ADHD need to be reconsidered to account for the potential effects of being raised by parents who share genetic risk for ADHD with their children. Indeed, parents with ADHD have been shown to suffer a range of parenting impairments, but it is as yet unclear whether these impairments exert an environmental effect on their children's development. Parental factors stand to affect not only the severity and persistence of children's core ADHD symptoms, but also children's risk for a range of comorbid

disorders that commonly co-occur with ADHD. A high rate of psychiatric comorbidity is the rule rather than the exception in ADHD, but the mechanisms behind this comorbidity are not well understood. Overlapping genetic influences have been shown to partially account for the co-occurrence of childhood symptoms of ADHD and common comorbidities such as oppositional-defiant disorder (ODD), conduct disorder (CD), anxiety and depression. However, it remains unclear whether parents with elevated ADHD symptoms contribute to children's risk for comorbid disorders, and the extent to which this contribution is genetically or environmentally mediated.

In this thesis, I investigate the extent to which several parental factors, both genetic and environmental, predict, overlap with, or otherwise affect children's symptoms of ADHD and several of its most common comorbid disorders. The thesis comprises three studies. In Study 1, I investigate whether ADHD symptoms in childhood and adulthood are aetiologically distinct using a novel family design. Specifically, I assess the extent to which symptoms of ADHD in adult mothers share genetic overlap with their children's symptoms of ADHD, ODD, CD, anxiety and depression at age 8, using a Multiple-Children-of-Twins-and-Siblings (MCoTS) design. I also assess the extent to which children's aforementioned symptoms at age 8 share genetic overlap with children's own earlier ADHD symptoms at age 5, using an extended bivariate twin design. I find that phenotypic correlations between mothers' adult ADHD symptoms and children's ADHD and comorbid disorder symptoms at age 8 are all underpinned by large genetic correlations, similar to or larger than genetic correlations with children's own earlier ADHD symptoms at age 5. This suggests that adult ADHD symptoms in mothers are not aetiologically distinct from child ADHD, but share a common genetic architecture with ADHD and common comorbid disorders in childhood.

In Study 2, I investigate whether there are indirect genetic effects of parental genotypes on children's ADHD symptomatology, including genetic nurture effects wherein parents' heritable behaviours exert environmental effects on children's symptoms. Specifically, I assessed the extent to which children's ADHD symptoms at ages 5 and 8 were explained by the direct

genetic effects of their own genotype and by the indirect genetic effects of their mothers' and fathers' genotypes, using trio genome-wide complex trait analysis (trio-GCTA). I find evidence for maternal indirect genetic effects on children's symptoms at ages 5 and 8 and paternal indirect genetic effects at age 8. This suggests that genetic nurture, and/or other aspects of the environment associated with mothers' and fathers' genotype, exerted additional effects on children's ADHD symptoms over and above the effect of their own genotype.

In Study 3, I investigate longitudinal relationships between self-rated child-directed hostility in adoptive parents and partner-rated symptoms of ADHD and several comorbid disorders in their adopted children, from mid-childhood to early adolescence. Specifically, I assess whether relationships between children's early ADHD symptoms and their later ODD and anxiety symptoms are mediated by evoked maternal and paternal hostility, using a longitudinal adoption-at-birth design including cross-lagged panel models (CLPMs) and random-intercept cross-lagged panel models (RI-CLPMs). I find that neither maternal nor paternal hostility are evoked by children's early ADHD symptoms, but that paternal hostility at age 6 predicts children's ODD and ADHD symptoms at age 11 via its effect on ADHD symptoms at age 8. This suggests a unidirectional effect of early paternal hostility on both children's ODD and their core ADHD symptoms by early adolescence, unconfounded by genetic relatedness between parents and children, and as rated by independent parents several years apart.

These studies contribute to a growing body of genetically sensitive research on the role of parents in the aetiology of ADHD and several of its most common comorbid disorders in childhood. They also contribute to knowledge on the aetiological overlap between child and adult ADHD. In sum, this thesis situates parental factors as playing a substantial role in the aetiology of childhood ADHD and several comorbid disorders, and supports adopting a 'families with ADHD' approach that accounts for the roles of both children and parents who share genetic risk for ADHD in shaping the family environment.

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Statement of Authorship

All work presented in the thesis is my own, except where acknowledged in the text. All investigations were conceived and carried out by me, as first author, in collaboration with colleagues included in the author lists at the start of each chapter. Data collection for all study samples used herein was completed by research teams prior to my involvement. Chapter-specific author contribution summaries are shown below.

Daniel L. Wechsler

Chapter 2. D.W. conceived and designed the investigation with support from T.M.; D.W. carried out statistical analyses with support from T.M. and F.R.; D.W. wrote and revised the manuscript; all co-authors critically reviewed the manuscript.

Chapter 3. D.W. conceived and designed the investigation with support from T.M., E.Y., and N.A.; D.W. carried out statistical analyses with support from E.E. and Y.A.; E.E. and R.C. conducted genotype data quality control; D.W. wrote and revised the manuscript; T.M., N.A., and E.E. critically reviewed the manuscript.

Chapter 4. D.W. conceived and designed the investigation with collaborative input from all co-authors; D.W. carried out statistical analyses, wrote and revised the manuscript; all co-authors critically reviewed the manuscript.

1. Background

Attention-deficit hyperactivity disorder (ADHD) is one of the longest-studied disorders in psychiatry, with physicians describing a condition causing debilitating symptoms of excessive inattention, impulsivity and hyperactivity in children as early as the 18th century (Faraone et al., 2021). Thought of at various times to represent a mild form of brain damage, a chemical imbalance, or a temporary developmental delay, ADHD is now understood to be a neurodevelopmental disorder relying on a complex interaction of genetic and environmental risk factors (Tarver et al., 2014). ADHD is consistently found to be among the most highly heritable disorders in the behavioural genetic literature (Nikolas & Burt, 2010), and treatments for ADHD are primarily pharmacological, with stimulant medications being the most efficacious and commonly prescribed (Faraone et al., 2021). However, these medications are often costly, are not effective for everyone, and carry a host of side effects (Holmskov et al., 2017; Kidwell et al., 2015; Solmi et al., 2020). Even when they are effective, these medications do not fully reverse ADHD symptoms and associated functional impairments (Safren et al., 2010).

There is a need for a greater understanding of the overall aetiology of ADHD, particularly the identification of environmental risk factors that could facilitate preventative or interventive measures early in childhood (Sonuga-Barke & Halperin, 2010). Such measures could improve ADHD symptom trajectories, ameliorate lifelong functional impairments, and ultimately increase quality of life for people with ADHD (Modesto-Lowe et al., 2008). As described in section 1.1.4., a growing body of research has indicated that parental factors are likely to play an aetiological role in childhood ADHD. Parental factors may also affect the risk of developing a range of comorbid disorders commonly seen in children with ADHD. As detailed in section 1.1.3., these comorbid disorders are the rule rather than the exception in ADHD and contribute to substantial functional impairment over and above that caused by core ADHD symptoms. As such, comorbid disorders are important targets for early interventions, and there remains a

need for research on the effect of parental factors on these comorbid disorders in families where both children and parents may share genetic risk for ADHD.

1.1. Overview of ADHD

1.1.1. Definition and clinical features of ADHD

The core symptoms of ADHD are divided into two groups: 1) Hyperactive-impulsive symptoms; and 2) Inattentive symptoms. The ICD-11 and DSM-5 diagnostic manuals divide patients into primarily hyperactive-impulsive, primarily inattentive, and combined groups (American Psychiatric Association, 2013; World Health Organization, 2018). However, most people display some hyperactive, impulsive and inattentive behaviours in various contexts of daily life. These behaviours are relatively normal, expected to occur more in certain contexts, and are not necessarily maladaptive or clinically significant. There are therefore additional diagnostic criteria for severity, impairment, pervasiveness, and persistence of symptoms which are required for a clinical diagnosis of ADHD. The ICD-11 describes ADHD as *"a persistent pattern (at least 6 months) of inattention and/or hyperactivity-impulsivity that has a direct negative impact on academic, occupational, or social functioning"* (World Health Organization, 2018). Similarly, the DSM-5 describes it as *"a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development"* (American Psychiatric Association, 2013). Both the ICD and DSM also specify that symptoms should typically be present before age 12 and be present across several settings. Moreover, even when an individual's symptoms are severe, impairing, pervasive, and persistent enough to be considered clinically significant, they may be caused by a variety of other conditions which must be ruled out before diagnosing ADHD.

As with most psychiatric disorders, there is no objective biomarker or test to establish the presence of ADHD. The diagnosis of ADHD is therefore intended to be made by a specialist clinician only after a thorough clinical assessment that includes the patient's self-reports of symptoms and resulting impairments and, where possible, teacher reports and family

interviews assessing a patient's developmental history. Based on this information and the guidance set out in either the ICD or DSM, a judgement is made as to whether the patient has a longstanding history of experiencing a sufficient number of symptoms of inattention, impulsivity and/or hyperactivity that are not explained by other conditions, and whether these cause significant impairment in several areas of the patient's life (Asherson et al., 2016). However, there are several issues with this process as well as the wider clinical definition of ADHD as a categorical condition. The first is the issue of arbitrary diagnostic cut-offs. The DSM-5 (but not the ICD-11) specifies that an arbitrary minimum of 6 symptoms of hyperactivity-impulsivity and/or 6 symptoms of inattention must be met for a diagnosis (American Psychiatric Association, 2013). While this could be seen as a strength as it reduces the role of subjectivity in diagnosis, it means that of two patients reporting a very similar profile of symptoms, one could be undiagnosed despite having a similar or even higher level of symptom severity and/or impairment. The second issue is, conversely, the subjectivity of requirements for symptom severity and associated impairment. While both the DSM-5 and ICD-11 specify that symptoms should significantly impair functioning and/or be significantly out of keeping with that expected for one's age and developmental level, neither manual specifies any objective indicators of impairment that must be met for a diagnosis, nor provide explicit guidance for what severity of symptoms would be considered developmentally normal at different ages, or for different groups (American Psychiatric Association, 2013; World Health Organization, 2018). Both manuals do provide some general notes on age and gender differences, for example stating that hyperactivity is more prominent during childhood, that ADHD is more common in males, and that females are more likely to exhibit inattentive symptoms. Overall, however, both manuals leave much to the clinician's judgement, their preconceptions about developmentally appropriate behaviour and impairment at different ages, and their biases regarding the likelihood of ADHD occurring in different groups. Such biases have been suggested as one of several reasons for the underdiagnosis of ADHD in

girls, as clinicians have been found to be less likely to attribute symptoms to, and subsequently diagnose, ADHD in girls (Bruchmüller et al., 2012).

An overarching conceptual issue with clinical definitions of ADHD is that a binary diagnostic decision is ultimately made for a complex and heterogeneous condition. While this is perhaps a diagnostic and clinical necessity, the validity of a binary diagnosis in describing or explaining ADHD as a phenotype is questionable. The wider categorical model in psychiatry, wherein psychiatric and neurodevelopmental disorders are seen as distinct entities that a given individual either does or does not 'have', has received growing criticism (Maser et al., 2009; Yee et al., 2015). Particularly for complex traits, i.e., those not caused by a single gene or environmental exposure, but which rely on a combination of common genetic and environmental risk factors, there have been increasing calls for adopting a dimensional approach (Hengartner & Lehmann, 2017). Such an approach acknowledges that most complex traits that are common in the population exist on a continuum, with every person falling somewhere on a distribution of lower to higher scores on a given trait (Kotov et al., 2021). In these terms, psychiatric and neurodevelopmental disorders represent the most extreme ends of these distributions, where an abnormally high or low level of a trait causes distress and/or impairment that is significant enough to justify clinical intervention. Quantitative genetic research has supported this characterisation for ADHD by showing a high degree of genetic overlap between clinical diagnoses of ADHD and subclinical measures of ADHD symptoms (Larsson et al., 2012; Levy et al., 1997). This suggests that non-clinical measures encompassing the ADHD symptoms of hyperactivity, impulsivity and inattention are likely to accurately capture the underlying construct of ADHD on a neuropsychological and aetiological level, as long as those measures have undergone adequate psychometric validation and have been shown to have a high degree of concordance with clinical diagnoses.

This thesis will take a dimensional approach reflecting the core neuropsychological construct of ADHD as it has been empirically characterised to date, namely that of a highly heterogeneous condition for which each individual may score higher or lower on certain

symptom distributions, with higher scores typically being associated with functional impairment and elevated risk for comorbid disorders (Katzman et al., 2017). In the context of the cohort-based studies that comprise this thesis, it is acknowledged that the continuous measures of ADHD symptomatology in children and their parents will not necessarily capture the full clinical definition of ADHD. For example, a child scoring very highly on a dimensional ADHD scale may not have exhibited their symptoms at such a high level for at least 6 months, as would usually be required for a clinical diagnosis. Similarly, parents scoring highly on ADHD symptoms in adulthood may not have had those symptoms during childhood, which would also usually be required for a clinical diagnosis. As such, while the measures of ADHD symptomatology used in the studies contained within this thesis are well-validated and have been demonstrated to be concordant with clinical diagnoses, care is taken to maintain clear use of language and to refer to what they measure: ADHD symptomatology at one or more points in time. Nonetheless, these measures do ultimately represent the positions of children and adults on the distributions of ADHD symptoms that exist in the population, with the endorsement of a substantial number of items typically indicating a significant degree of ADHD symptomatology and associated impairment (Conners et al., 1998; Silva et al., 2005). Therefore, these measures are useful indicators of the core neuropsychological construct of ADHD, and their associations with symptoms of other disorders and parenting behaviours can be considered empirical indicators of aetiological relationships. The analyses contained in this thesis further benefit from stringent methodologies that control for several sources of confounding on these associations, so as to provide the strongest possible evidence for aetiological underpinnings.

The clinical symptom clusters of hyperactivity, impulsivity and inattention are nosological umbrella terms for deficits in various related areas of executive functioning, all of which rely on the healthy development of frontal regions of the brain and their functional connectivity with other areas, as described in section 1.2.1. The common theme among these deficits is that they are failures in normal regulation of brain activity (Petrovic & Castellanos, 2016);

hyperactivity reflects a failure in motor regulation, impulsivity may reflect failures in behavioural and/or emotional regulation, and inattention reflects failures in various forms of attentional regulation (e.g., engagement, disengagement, and task-switching). As these deficits do not rely on one single brain region, pathway, or neurotransmitter, each deficit can occur to varying degrees in each person with ADHD, resulting in a pattern of considerable heterogeneity in symptom profiles and resulting functional impairments (Luo et al., 2019). A prominent example of heterogeneity in ADHD is the different symptom presentations typically seen in boys and girls. The prototypical symptom of ADHD in boys has historically been hyperactivity, an obvious and disruptive symptom that clearly distinguishes ADHD from other disorders in school-aged children. However, excessive hyperactivity is much less common in girls with ADHD, who tend to experience more inattentive symptoms than do boys with ADHD, as well as lower rates of comorbid externalising disorders (Hinshaw et al., 2021). This difference in overt hyperactivity and associated disruptive behaviour has been identified as one reason girls with ADHD are diagnosed less early and less often than boys, and why parents underreport ADHD symptoms in girls even when they are matched with boys on objectively observed symptoms (Meyer et al., 2020). As discussed in section 1.1.2., additional heterogeneity is seen in symptom trajectories across development, with hyperactivity usually subsiding with age in both boys and girls while impulsivity and inattention subside for some but not for others.

While symptoms of ADHD were traditionally seen as primarily causing disruptive behaviour and trouble paying attention at school, a wealth of research has since demonstrated that people with ADHD experience substantial functional impairment in virtually every area of daily living across the lifespan (Gjervan et al., 2012), a reduction in multiple facets of quality of life (Gjervan et al., 2014), and reduced life satisfaction (Lensing et al., 2015). People with ADHD tend to have lower educational attainment (Biederman & Faraone, 2006; Miranda et al., 2014), lower occupational attainment (Gjervan et al., 2012), lower income and higher rates of unemployment (Biederman & Faraone, 2006), higher rates of debt and trouble managing bills (Beauchaine et al., 2020), higher rates of early pregnancy and sexually transmitted infections

(Miranda et al., 2014), more family conflict and lower family functioning (Miranda et al., 2014), higher rates of loneliness (Stickley et al., 2017), higher rates of accidental injury, particularly due to risky behaviours including dangerous driving (Chien et al., 2017; El Farouki et al., 2014), higher suicide rates (Barbaresi et al., 2013; Fuller-Thomson et al., 2020; Furczyk & Thome, 2014), trouble sleeping (Hvolby, 2015), disordered eating and obesity (Cortese & Peñalver, 2010), more problems with alcohol, tobacco and other substance use and addiction (Miranda et al., 2014), gambling addiction (Jacob et al., 2018), and higher rates of crime and incarceration (Mohr-Jensen et al., 2019), among others. In sum, these impairments drive the reduced quality of life, high rates of physical multi-morbidity, and early mortality seen in people with ADHD (Schiavone et al., 2022; Stickley et al., 2017).

The executive impairments caused by ADHD may directly account for some of these functional impairments, most specifically via impulsivity increasing the risk of engaging in risky behaviours (Shoham et al., 2021). However, there is evidence that some of these impairments may be accounted for in part by commonly co-occurring disorders rather than being purely due to core ADHD symptomatology (Miranda et al., 2014). For example, one study found depressive symptoms to fully mediate the association between adult ADHD and loneliness (Seo et al., 2014), while another found that comorbid disorders including depression, anxiety, borderline personality disorder, and alcohol dependence partially mediated associations between adult ADHD and problem gambling (Jacob et al., 2018). Trouble sleeping can be a feature of various sleep disorders, may warrant a separate sleep disorder diagnosis, and would not be effectively treated with ADHD medications, which have been shown to worsen sleep problems (Kidwell et al., 2015). Similarly, a high rate of criminal behaviour is not a feature of ADHD, but if forming a recurring pattern, is often a feature of conduct disorder (CD) in children and of antisocial personality disorder in adults, both of which commonly co-occur with ADHD (Katzman et al., 2017; Larsson et al., 2011). Substance abuse and addiction, while potentially driven and made more severe by the executive and reward processing deficits in ADHD, exist as separate alcohol use and substance use disorders with different treatments

(World Health Organization, 2018). Clearly, the full profile of functional impairments across the lifespan seen in ADHD relies not only on its core symptoms and underlying executive deficits, but also on a variety of disorders that commonly co-occur with ADHD, which are further discussed in section 1.1.3.

1.1.2. Onset, symptom trajectories, and ADHD in adulthood

Symptoms of ADHD typically have an onset in early childhood, with a recent meta-analysis of prevalence studies across a range of countries reporting a pooled prevalence estimate of 7.2% in children and adolescents aged 18 and below (Thomas et al., 2015). Early research into symptom trajectories identified broad patterns of decline in ADHD symptoms with age, such that prevalence rates would gradually reduce to almost zero as fewer and fewer children met diagnostic criteria (Hill & Schoener, 1996). More recent research has indicated a more complex picture, wherein certain symptoms do tend to subside with age for most children with ADHD, but by no means is this always the case (Willcutt, 2012). On a symptom level, follow-up studies have identified differences in longitudinal trajectories of specific symptom groups from childhood into adolescence. Namely, whereas hyperactivity/impulsivity symptoms tend to show a pattern of decline over time, inattention appears to remain at similar levels as children approach adolescence (Hinshaw et al., 2006; Klassen et al., 2010; Larsson et al., 2006). This pattern of decline has been found not to differ by gender (Monuteaux et al., 2010). ADHD symptomatology also subsides to varying extents for different people. Latent class analyses have identified distinct symptom trajectories in different patient groups, with some children experiencing an almost complete decline in symptoms by late adolescence, while others show a more stable pattern of symptoms, and indeed a small group shows worsening or new onset of symptoms during adolescence (Shaw & Sudre, 2021). Such findings have contributed to a more complex view of ADHD as not simply a disorder that remits after childhood, but one in which symptoms may ameliorate over time for some people, while for others, symptoms remain stable or can even worsen as time goes on.

Relatively recently, it has become clear that around a third of those diagnosed with ADHD in childhood will continue to meet full diagnostic criteria by early adulthood, and the majority (approximately 65%) will continue to experience significant and impairing symptoms of ADHD even if these fall below diagnostic thresholds (Faraone et al., 2006). In clinical populations, estimates of persistence have been even higher (van Lieshout et al., 2016). One meta-analytic review of 86 prevalence studies of children, and 11 studies of adults, reported pooled prevalences of 5.9-7.1% in childhood, and 5% in adulthood (Willcutt, 2012). A recent systematic review and meta-analysis distinguished between syndromatic ADHD (i.e., that persisting from childhood) and symptomatic adult ADHD (i.e., meeting criteria in adulthood with no childhood history), reporting lower prevalence rates (2.58%) for syndromatic compared to symptomatic (6.76%) ADHD in adulthood (Song et al., 2021). There is also evidence that childhood ADHD persists or otherwise manifests at clinically significant levels in older adulthood, with a study of older adults (aged 60 to 94 years) reporting a syndromatic prevalence of 2.8% and a symptomatic prevalence of 4.2% (Michielsen et al., 2012). Notably, the authors reported that prevalence rates were higher in the younger group (aged 60 to 70 years), suggesting that there continues to be a decline in symptoms even into the latest ages. A large recent meta-analysis of 41,420 older adults with ADHD (aged 50 and over) reported a pooled prevalence estimate of 2.18% for symptomatic ADHD ascertained by research diagnosis (Dobrosavljevic et al., 2020). While they reported a much lower prevalence estimate of 0.23% for clinically diagnosed ADHD in this sample, this likely reflects underdiagnosis in older groups rather than a lower true rate of ADHD.

Notably, while childhood ADHD occurs at much higher rates in boys, with male to female ratios at or exceeding 2.2:1 (Cuffe et al., 2005; Danielson et al., 2018), sex differences have been shown to largely or entirely subside in adulthood (Cortese et al., 2016; Hinshaw et al., 2021). Male to female ratios in adult community samples typically fall below 2.2:1 and often reach 1:1, while in some high-risk samples (e.g., where participants are in clinical or disability care, incarcerated, or undergoing substance abuse treatment) higher rates of ADHD have been

reported in women (Williamson & Johnston, 2015). Rather than representing an age-related increase in ADHD symptomatology in women, some have suggested that the higher prevalence rates may instead reflect increased recognition and treatment seeking by women in adulthood, in the context of underrecognition of ADHD symptoms in girls by parents, teachers, and clinicians in childhood (Chronis-Tuscano, 2022; Kessler et al., 2006).

Highlighting the importance of the distinction between syndromatic and symptomatic definitions of ADHD, a series of longitudinal studies recently cast scientific doubt on the increasingly accepted notion that childhood ADHD usually persists into adulthood. The first was a landmark study of the Dunedin longitudinal cohort by Moffitt et al. (2015), who found that the overwhelming majority of those meeting diagnostic criteria for ADHD in childhood no longer met them in adulthood, and most of those meeting criteria in adulthood had not met them as children. Given their use of stringent research diagnoses in both childhood and adulthood in a well-known longitudinal cohort with low attrition rates, their findings of an almost complete lack of overlap constituted strong evidence that not only did childhood ADHD not usually persist into adulthood, but ADHD could newly occur in adulthood in lieu of a childhood history. Several replication studies then reported a similar lack of overlap between those meeting diagnostic criteria in childhood and adulthood in different cohorts (Agnew-Blais et al., 2016; Caye et al., 2016). Together, these studies called into question the validity of adult ADHD as it is currently diagnosed, i.e., as a continuation of the childhood neurodevelopmental disorder that has been thoroughly studied and successfully treated for decades.

Initial interpretations of these findings posited that child and adult ADHD could be aetiologically distinct conditions, with childhood ADHD being a traditional neurodevelopmental disorder while adult (or late-onset) ADHD relied on a separate set of genetic and environmental risk factors which only gave rise to manifest symptoms later in life (Castellanos, 2015; Moffitt et al., 2015). However, this explanation is difficult to reconcile with the large body of evidence for persistence of ADHD symptoms into at least early adulthood (Willcutt, 2012). A recent review by Asherson and Agnew-Blais (2019) assessed available evidence on age at onset to shed

light on whether late-onset ADHD could be a distinct condition. The authors noted that of the late-onset group who did met criteria in adulthood but not in childhood, many first met criteria between ages 12 and 16, and so would be better described as adolescent- or early-adult-onset cases. Furthermore, many in the late-onset group displayed subthreshold ADHD symptoms as children, or otherwise symptoms of comorbid externalising disorders such as ODD, or other neurodevelopmental indicators including mild IQ and language impairments. This suggests that a majority of late-onset cases are preceded by a profile of neurodevelopmental abnormalities resembling those seen in clinical cases of childhood ADHD. Thus, despite a later onset of clinically significant ADHD symptoms, the evidence does not support a distinct aetiological basis for adult ADHD symptomatology in most cases. Asherson and Agnew-Blais (2019) noted that this does not rule out a rarer aetiologically distinct form of ADHD, as there was evidence for a small late-onset group who did not show any early indicators. They also highlighted the dearth of studies following up with children beyond young adulthood, which precludes clear conclusions as to long-term persistence as well as whether there is a distinct form of adult-onset (rather than adolescent-onset) ADHD. Moreover, the lack of genetically sensitive cohort studies assessing ADHD in childhood through to adulthood currently preclude conclusions as to whether shared genetic and environmental risk factors explain the overlap between ADHD symptomatology in childhood and adulthood.

1.1.3. Comorbidity in ADHD

Alongside its core symptoms, ADHD is known to confer a heightened risk for a wide range of comorbid disorders in both childhood and adulthood (Gnanavel et al., 2019; Reale et al., 2017). Having at least one comorbid disorder is now recognised as being the rule rather than the exception in people with ADHD (Miller et al., 2007). While many studies have reported rates of psychiatric comorbidity in various populations and using various diagnostic criteria, a consistent finding has been that people who have ADHD but do not have any comorbid disorders are in the minority (Gnanavel et al., 2019; Jensen & Steinhausen, 2015). This non-

comorbid or ‘pure ADHD’ group has been estimated as comprising 0-40% of childhood ADHD cases in early studies (Gillberg et al., 2004; Jensen et al., 1997; Kadesjö & Gillberg, 2001), with more recent clinical and epidemiological studies (some of which also include adolescents) estimating the non-comorbid presentation as comprising anywhere from 13% to 32.3% of cases (Ghanizadeh, 2009; Kraut et al., 2013; Larson et al., 2011). Rates of childhood comorbidity tend to be higher in clinical populations and in children with more severe core ADHD symptoms, as well as in those with the combined type of ADHD (Gnanavel et al., 2019; Reale et al., 2017; Soendergaard et al., 2016). However, even based on the lower estimates from population studies, the evidence to date suggests that at least 60% of children with ADHD will also meet criteria for at least one comorbid disorder, either concurrently or at some point during childhood. Rates of comorbidity are similar or even slightly higher in adulthood, and again are shown to be higher in adults with more severe core ADHD symptoms (Fayyad et al., 2007). An early review of research on adult psychiatric comorbidities of ADHD suggested that 65-89% of adults with ADHD had at least one comorbid disorder during their lifespan (Sobanski, 2006). More recent studies have similarly estimated the lifespan prevalence of at least one comorbidity at 83% (Rucklidge et al., 2016), with a recent expert consensus statement reporting the rate at somewhere between 60% and 80% (Kooij et al., 2019).

The specific comorbidities seen in ADHD encompass a wide range of psychiatric, developmental and behavioural disorders. There is substantial heterogeneity in symptom presentations, and patterns of comorbidity have been shown to vary by age and gender. During childhood and early adolescence, the most commonly reported comorbidities of ADHD are other neurodevelopmental disorders such as autism spectrum disorder (ASD) and developmental coordination disorder (Antshel et al., 2013; Gnanavel et al., 2019; Jensen & Steinhausen, 2015; Larson et al., 2011), other externalising disorders, namely conduct disorder (CD) (Larson et al., 2011) and oppositional defiant disorder (ODD) (Gillberg et al., 2004; Jensen & Steinhausen, 2015; Reale et al., 2017), learning disorders (Gnanavel et al., 2019; Jensen & Steinhausen, 2015; Larson et al., 2011; Reale et al., 2017), sleep disorders

(Gnanavel et al., 2019; Reale et al., 2017), tic disorders (Gnanavel et al., 2019), internalising disorders including anxiety and depression (Gair et al., 2021; Kadesjö & Gillberg, 2001; Reale et al., 2017), as well as some evidence for comorbidity with obsessive-compulsive disorder (OCD) and bipolar disorder (Gillberg et al., 2004; Gnanavel et al., 2019). Notably, girls with ADHD have been shown to have lower rates of comorbid neurodevelopmental and externalising disorders and higher rates of internalising disorders, eating disorders, and language impairments compared to boys with ADHD (Jensen & Steinhausen, 2015; Tung et al., 2016). However, girls' relative odds of having an externalising disorder if they have ADHD are higher than that for internalising disorders (Tung et al., 2016). That is, while girls with ADHD are more likely to have internalising disorders than girls without ADHD, they are comparatively far more likely to have externalising disorders compared to girls without ADHD. This may be because typically developing girls already have relatively high rates of internalising disorders but have much lower rates of externalising disorders than typically developing boys. As such, it is perhaps not surprising that girls with ADHD have only somewhat higher rates of internalising disorders than typically developing girls, but much higher rates of externalising disorders, perhaps reflecting the shared genetic overlap between ADHD and other externalising disorders (discussed in section 1.2.2.2.).

In later adolescence and adulthood, people with ADHD are similarly at increased risk of developing a range of later-onset disorders. The most common comorbidities reported in late adolescence and adulthood for individuals with ADHD include major depressive disorder (Rucklidge et al., 2016; Solberg et al., 2018), anxiety disorders (Groß-Lesch et al., 2016; Rucklidge et al., 2016), alcohol and other substance use disorders (Katzman et al., 2017; Rucklidge et al., 2016), ASD (Hayashi et al., 2022; Leitner, 2014), personality disorders including antisocial personality disorder (seen as an adulthood continuation of CD) (Katzman et al., 2017; Solberg et al., 2018; Storebø & Simonsen, 2016), bipolar disorder (Klassen et al., 2010; Schiweck et al., 2021), and eating disorders (Groß-Lesch et al., 2016). While gender differences in the prevalence and core symptoms of ADHD tend to be less prominent by

adulthood, there is evidence for gender differences in patterns of comorbidity as well as the relative risk of comorbidity that ADHD confers for men and women, particularly from studies using larger samples. For example, a study of 910 adults with ADHD (452 of them women) found that women with ADHD had relatively higher rates of mood, anxiety and eating disorders, while men with ADHD had relatively higher rates of substance use disorders (Groß-Lesch et al., 2016). The authors noted that this pattern reflects gender differences in psychiatric disorders seen in the general population, which would suggest that ADHD may increase the global risk of comorbid disorders via a transdiagnostic mechanism such as emotional regulation, with specific presentations reflecting heterogeneity already present in the population. Recently, a very large population study of 40,103 adults with ADHD (17,815 of them women), similarly found that women with ADHD were at relatively higher risk of anxiety, depression, bipolar and personality disorders compared to men with ADHD, whereas men were at relatively higher risk of substance use disorders and schizophrenia (Solberg et al., 2018). Importantly, while both men and women with ADHD had a substantially higher prevalence of all assessed disorders than the non-ADHD group, the authors highlighted that having ADHD was associated with substantially higher prevalence differences for all comorbid disorders for women as opposed to men. That is, while men with ADHD had higher prevalences of comorbid disorders than men without ADHD, women with ADHD had comparatively far higher prevalences of comorbid disorders than women without ADHD.

There remains a need for a better understanding of comorbidity in ADHD, as comorbid disorders have a bearing on the overall functioning of people with ADHD as well as on diagnosis and treatment. The presence of comorbid disorders has been shown to predict greater functional impairment and worse longer-term outcomes in those with ADHD (Booster et al., 2012; Larson et al., 2011). Symptoms of comorbid disorders may also mask core ADHD symptoms in both children and adults, hindering appropriate diagnosis and treatment (Gillberg et al., 2004; Kooij et al., 2010). This may be particularly so in adulthood and especially for women, whose overall symptom presentation may lead clinicians to focus on the often more

obvious symptoms of internalising disorders such as depression and anxiety disorders (Young et al., 2020). There is also some evidence that certain comorbidities (namely CD and borderline personality disorder) may account for the increased severity of substance use seen in adults with ADHD, suggesting that certain comorbidities of ADHD may account for the increased risk of other comorbidities (Torok et al., 2012). Such findings can themselves inform treatment approaches for ADHD where more than one comorbid disorder is also present. While there is not a large body of research directly assessing the relative efficacy of interventions for ADHD that are tailored to specific patterns of comorbidity, the studies that do exist suggest that response to specific therapeutic modalities (i.e., pharmacological, behavioural and psychological treatments) can differ based on one's pattern of comorbidity. One of the earliest such studies, by Jensen et al. (2001), used data on 579 children from the Multimodal Treatment Study of Children with ADHD (MTA). They found that children with ADHD and only comorbid anxiety disorders, those with only comorbid ODD/CD, and those with both comorbid anxiety and ODD/CD, showed distinct response patterns to pharmacological and behavioural treatments. Namely, those with comorbid anxiety alone responded equally well to pharmacological and behavioural treatments, those with comorbid ODD/CD alone responded best to pharmacological treatments (regardless of whether they received combined behavioural treatments), and those with both comorbid anxiety and ODD/CD responded best to combined pharmacological and behavioural treatments. A much more recent multicentre 1-year follow-up study of 1,919 children with ADHD (1,269 of whom had at least one comorbid disorder) found that children and adolescents with ADHD and comorbid disorders showed greater improvement in a clinical outcome measure of global functioning when treated with combined therapies, i.e., those including pharmacological and either behavioural or psychological treatments, as opposed to pharmacological therapy alone (Reale et al., 2017). Echoing much earlier suggestions (Gillberg et al., 2004), Reale et al. (2017) noted that there remains a dearth of research guiding the treatment of ADHD with specific reference to patterns of comorbidity.

In addition, understanding the aetiological overlap between ADHD and common comorbid disorders can inform preventative measures targeting early risk factors. While there are overlapping neurobiological mechanisms and genetic risk factors that may independently increase the risk of several disorders simultaneously, ADHD may also predispose to, elicit, or increase the subsequent risk of developing other disorders over time. As discussed in section 1.2.1., the early onset and pervasive impairments in behavioural, emotional and attentional regulation seen in ADHD may situate ADHD as a potential early risk-modifying factor for developing a range of disorders. As discussed in section 1.3.1., ADHD may also increase the risk for exposure to a set of adverse environmental exposures which may serve as risk factors for comorbid disorders. An important context for these environmental exposures, and for the early development of ADHD and commonly co-occurring disorders, is the family environment. The following section will discuss the role of parental ADHD symptomatology in shaping this environment, as well as how parent and child ADHD symptoms may interact to jointly create an environment that may increase the risk of both more negative behaviours in parents, and potentially more negative outcomes in children who inherit genetic risk for ADHD from their parents.

1.1.4. ADHD in parents; Moving from 'Families of children with ADHD' to 'Families with ADHD'

The recognition that ADHD can persist into adulthood has led to a shift in family research on ADHD, specifically with regard to the potential effects of adult ADHD on parenting and the broader rearing environment parents provide for children. As ADHD was previously believed not to occur in adults, studies investigating parent and family characteristics in relation to ADHD had focused mainly on the problems associated with 'having a child with ADHD' (Johnston & Mash, 2001). Therein, parents of children with ADHD were found to report poorer mental health and more family dysfunction than parents of children without ADHD, including higher rates of depression, social isolation, parenting stress, negative parent-child interactions, alcohol use, low parenting self-efficacy, and self-blame (Brown & Pacini, 1989;

Fischer, 1990; Johnston & Mash, 2001; Mash & Johnston, 1990; Molina et al., 1997). As parents themselves were assumed to differ only by whether or not their child had ADHD (and/or associated comorbid disorders), any differences between families were attributed to differences in child behaviour. Indeed, much of this literature explicitly assumed the cause of parental and wider family problems to be the child's symptoms of ADHD and/or comorbid disruptive disorders, positioning findings as evidence for the effect, impact, or burden, that having a child with ADHD has on parents and families (Hankin, 2001; Harpin, 2005). Illustrating the prominence of this assumption, a measurement scale termed the Family Strain Index was constructed to assess the burden children with ADHD were causing, including items asking parents how often their child "Made you feel stressed or worried" and "Caused conflict or tension within the family" (Riley et al., 2006). The role of parents' own behaviour and proneness to parenting stress and conflict was largely ignored, and the role of ADHD-related impairments and psychopathologies in parents as primary drivers of family dysfunction, rather than consequences of exposure to the ADHD child, was not considered.

A key empirical development has arisen from findings that at least one parent of a child with ADHD typically either meets diagnostic criteria for ADHD themselves or otherwise met criteria or were diagnosed with ADHD as children (Johnston et al., 2012). Early indicative evidence for this came from findings that parents who were diagnosed with ADHD during childhood had high rates of children who were diagnosed with ADHD (Biederman et al., 1995). Separately, mothers and fathers of children with ADHD retrospectively reported experiencing more symptoms of ADHD as children (Chronis et al., 2003). Early estimates of the prevalence of ADHD in parents of children with ADHD found that, of families where at least one child had ADHD, 49-65% had at least one parent with a lifetime diagnosis of ADHD depending on whether children also had comorbid CD or ODD (Smalley et al., 2000). Later, it was found that 41% of families with a child with ADHD had at least one parent who concurrently met criteria for ADHD based on the Adult Self-Report Scale (ASRS), and children whose parents met criteria had more severe ADHD symptomatology (Takeda et al., 2010). A more recent study

found that in a clinically referred sample of children undergoing treatment for ADHD after an ICD-10 diagnosis, 44% were found to have at least one parent who concurrently met criteria for ADHD based on DSM-5 oriented cut-offs on the ADHS-Self-Report tool (Starck et al., 2016).

These findings have direct implications for family research on ADHD. Firstly, they suggest that many of the parent and family difficulties previously seen as consequences of having a child with ADHD at least partly reflect symptoms of ADHD and/or associated problems in parents themselves (Johnston & Lee-Flynn, 2011). Secondly, they highlight the possibility that parents with elevated ADHD symptomatology may provide rearing environments that affect their offspring's ADHD-related developmental trajectories (Park et al., 2017). Parents' elevated risk for comorbid disorders may also have additional indirect effects on their parenting. For example, parental anxiety has been associated with controlling and overprotective parenting while parental depression has been associated with inconsistent parenting (Mulraney et al., 2019). Children at genetic risk for ADHD may be exposed to these additional parenting behaviours depending on their parents' specific pattern of comorbid symptomatology.

Research on the potential effects of adult ADHD on parenting has revealed a range of parenting impairments or otherwise suboptimal parent or family characteristics associated with ADHD diagnosis or elevated ADHD symptoms in parents (Johnston et al., 2012; Park et al., 2017). Studies focusing on parental control, discipline, and negative parenting during childhood have reported impairments including lax and overreactive parenting (Arnold et al., 1997; Banks et al., 2008; Harvey et al., 2003; Johnston et al., 2004), high levels of criticism and corporal punishment (Chronis-Tuscano et al., 2008), inconsistent discipline (Chen & Johnston, 2007; Chronis-Tuscano et al., 2008; Mokrova et al., 2010; Murray & Johnston, 2006), low child monitoring (Murray & Johnston, 2006), higher parent-child conflict (Harvey et al., 2003), wider family conflict and reduced cohesion (Biederman et al., 2002; Pressman et al., 2006), and high levels of home chaos (Mokrova et al., 2010). Increased negative and overreactive parenting tended to be specific to parental hyperactive-impulsive symptoms

(Johnston et al., 2004), while increased inconsistent or lax parenting were found to be specific to parental inattentive symptoms in some studies (Chen & Johnston, 2007; Harvey et al., 2003) but not in others (Johnston et al., 2004).

Other studies have assessed associations between parental ADHD and positive parenting and emotional responsiveness. Those focusing on parenting during infancy have found evidence for impairments including lower responsiveness to infants' distress and negative emotion despite infant behaviour not differing significantly from that of infants whose parents did not have ADHD (Landau et al., 2010), maternal insensitivity and higher intrusiveness and expressed negative regard towards infants (Semple et al., 2011), and decreased length of mothers' verbal utterances towards infants (Kryski et al., 2010). Others have assessed positive parenting in childhood, providing somewhat mixed findings. Several studies have found no associations between parental ADHD symptoms and positive parenting behaviour towards children (Johnston et al., 2002; Mokrova et al., 2010; Murray & Johnston, 2006), while these and other studies have reported associations with unsupportive parenting (Mokrova et al., 2010) and lower child involvement (Chen & Johnston, 2007; Ellis & Nigg, 2009; Mokrova et al., 2010). In one study, mothers rated more highly on ADHD symptomatology by other informants were observed to engage in more positive parenting with children during a play task, suggesting that parental ADHD symptomatology may confer some benefits for specific aspects of parenting (Chronis-Tuscano et al., 2008). A recent meta-analysis of research on parenting impairments associated with parental ADHD symptomatology found a very small overall association with positive parenting compared to associations with harsh and lax parenting, suggesting that parents with elevated ADHD symptoms may not be impaired in all domains (Park et al., 2017).

There is also evidence that ADHD-related parenting behaviours interact with children's symptoms of ADHD, comorbid disorders, and disruptive behaviours, driving more negative responses in some cases but more positive responses in others. In one study, mothers' self-reported ADHD symptoms were associated with lower child involvement, but this association

was not significant after accounting for children's comorbid ODD symptoms (Chronis-Tuscano et al., 2008). Another found that mothers with elevated ADHD symptoms responded with more hostility and reactivity towards infants, but only when they reported seeing infants as 'difficult' (Watkins & Mash, 2009). Several studies have investigated the interaction between parent and child ADHD symptoms in the context of the similarity-fit hypothesis, which posits that parents and children with similar levels of ADHD symptoms are likely to have less conflict, perhaps due to increased behavioural and/or cognitive compatibility, or increased empathy from more similar parents (Johnston et al., 2018). A pair of related studies tested this hypothesis with regard to positive and negative parenting, producing somewhat differing findings. The first found that maternal ADHD symptoms were independently associated with more expressed negative emotion towards children, and mothers with low ADHD symptoms reported less positive parenting towards children with high ADHD symptoms (Psychogiou et al., 2008). However, when both mothers and children had high ADHD symptoms, mothers reported more positive parenting, supporting the similarity-fit hypothesis. The second study extended these findings to a sample of mothers and fathers while focusing on negative parenting behaviours. They found that both mothers and fathers reported more negative parenting towards children with high ADHD symptoms (Psychogiou et al., 2007). However, high ADHD symptoms in mothers ameliorated these negative parenting responses, again supporting a similarity-fit hypothesis. Conversely, high ADHD symptoms in fathers worsened negative responses to children with high ADHD symptoms, supporting a similarity-misfit hypothesis. Further support for the similarity-fit hypothesis for mothers comes from findings that mothers with elevated ADHD symptoms displayed lower observed irritability towards children if their child had ADHD, but not if their child did not have ADHD (Griggs & Mikami, 2011).

In summary, there is consistent evidence for higher rates of negative or suboptimal disciplinary parenting behaviours in parents with elevated ADHD symptoms. Evidence for a lack of positive parenting behaviours is less consistent, with some indications of an increase in certain positive

behaviours. It is also clear that parental ADHD symptoms interact with children's own ADHD symptoms and related behaviours, potentially affecting both positive and negative parenting behaviours depending on children's levels of disruptive behaviour and their similarity with mothers and fathers. As a whole, this body of research indicates a substantial role for ADHD-related parenting impairments in shaping children's rearing environment. It follows that for children who inherit genetic risk for ADHD from parents, their own development does not occur in isolation from heritable ADHD-related parental behaviours. Equally, parental mental health, parenting stress and wider family functioning are likely to be driven in large part by parents' own ADHD-related problems, which then interact with children's ADHD symptoms. In other words, it is clear that shared genetic risk for ADHD concurrently drives both parent and child behaviours which jointly shape the family environment (Johnston et al., 2012)

Discouragingly, studies continue to be published that adopt the traditional model of child-imposed burden on families without accounting for parental ADHD and/or comorbid disorder symptoms. These still report the 'effects' or 'impacts' of having a child with ADHD on various parent outcomes, including parent separation, sleep problems, low health-related quality of life, lower work performance, and job firings (Kousgaard et al., 2018; Peasgood et al., 2021; Si et al., 2020; Zhao et al., 2019). As discussed previously, all of these problems have been shown to occur at higher rates in adults with ADHD. The continued publication of such findings without reference to potential ADHD symptomatology in parents demonstrates the need to more firmly establish the notion that families of children with ADHD will typically have at least one parent who is at high genetic risk for ADHD and a range of common comorbid disorders.

More broadly, there is a need for a conceptual shift away from the traditional framework focusing on ways in which child ADHD affects families, towards one that focuses on ways in which ADHD symptomatology in multiple family members can affect overall family interaction and functioning. In other words, where research was previously aimed at 'families *of children* with ADHD', a more appropriate approach would be to study 'families *with* ADHD'. This approach is better suited to understanding child development in the context of the wider family

environment, and to constructing family-level interventions that can optimally improve parent and child outcomes by targeting both parent and child ADHD-related behaviours (Johnston et al., 2012). However, a key remaining question concerns the extent to which specific parenting impairments affect different aspects of children's development, including their ADHD-related developmental trajectories. It is plausible that the intergenerational transmission of ADHD and common comorbid disorders relies not only on transmitted genetic risk, but on a complex interaction of children's inherited risk factors and their environmental exposure to heritable ADHD-related parenting behaviours. As discussed in section 1.2.3., a range of studies have set out to assess whether various parenting behaviours predict or are associated with child ADHD and/or comorbid disorder symptomatology. However, much of the existing research suffers from major limitations, and there remains a need for more research on the extent to which specific parent behaviours predict ADHD and comorbid symptomatology in children.

1.2. Aetiological influences on ADHD and comorbidity with related disorders

1.2.1. Neurobiological underpinnings

The aetiology of ADHD is multifactorial, relying on a complex interplay of genetic and environmental influences which in combination affect the onset, presentation, and persistence of ADHD symptomatology (Faraone & Larsson, 2019; Luo et al., 2019). To contextualise and best understand the aetiology of ADHD and the potential mechanisms behind its comorbidity with other disorders, it is important to understand its pathophysiology, i.e., the neurobiological basis of the core executive deficits seen in ADHD, and how this manifests in a profile of symptoms that would lead a person to meet diagnostic criteria.

1.2.1.1. Neurobiology of ADHD

As with most psychiatric disorders, early drug trials informed some of the first scientific inferences as to the neurobiological underpinnings of ADHD. Stimulant medications, which act primarily as combined dopamine and noradrenaline reuptake inhibitors, are the most frequently prescribed and have shown to be the most efficacious medications available for

ADHD (Cortese et al., 2018; Lenzi et al., 2018). Put simply, these increase the availability and therefore binding of dopamine and noradrenaline molecules (neurotransmitters) to their respective receptors on neurons, enhancing the activity of dopaminergic brain pathways that underpin executive functions including motivated attention and behavioural self-regulation, and of noradrenergic pathways that underpin alertness (Stahl, 2021). Less frequently, non-stimulant medications are used, which act primarily on noradrenergic but not dopaminergic receptors. Based on the efficacy of stimulant medications, early researchers hypothesised that a deficiency of dopamine and/or noradrenaline in the brain may explain the pathophysiology of ADHD (Swanson et al., 2007), just as a deficiency of serotonin and an excess of dopamine were speculated to underlie depression and schizophrenia respectively. However, as for other disorders, it has become clear that the pathophysiology of ADHD cannot be encapsulated by a simple deficit of any given neurotransmitter. Instead, it relies on a complex and long-term disruption in normal brain development which results in a wide array of observable changes in brain structure and function (discussed below).

An extensive body of neuroimaging research has documented a range of structural abnormalities associated with ADHD, including reduced grey and white matter in various brain regions and reduced overall cortical thickness (Arnsten & Rubia, 2012; Hart et al., 2013; Kooij et al., 2019; Shaw et al., 2007). While many of these abnormalities overlap with other disorders (as discussed below), the distinguishing neurobiological feature of ADHD is disrupted development of frontal brain regions, known broadly as the frontal cortex (Banaschewski et al., 2005). Frontal brain regions are responsible for various cognitive and executive functions, and act by consolidating and regulating neural signals from other parts of the brain that process basic and complex sensory input, motor and behavioural impulses, and basic emotional responses (Stahl, 2021). The frontal regions receive these crude and disparate neural impulses and process them into cohesive experiences, complex emotions, cognitions, judgements, decisions, and plans. Frontal regions also send signals back to other brain regions, driving top-down regulation of emotional impulses and underpinning effective

execution of planned, motivated behaviour (Arnsten & Rubia, 2012). In ADHD, the development of these frontal regions is disrupted, causing differences in their structure and their functional connectivity with other brain areas (Tomasi & Volkow, 2012). The most prominent disruptions in functional connectivity are seen in fronto-striatal pathways, which connect with reward regions responsible for neurochemical reward responses that drive motivated behaviour, and fronto-cortical pathways, which connect to other cortical regions responsible for a variety of functions including sensory and motor regulation (Cubillo et al., 2012). In addition, there is increasing evidence for disrupted development of the default mode network, a pathway from frontal regions to several midbrain regions, in both children and adults with ADHD (Querne et al., 2017; Wilson et al., 2013). This pathway is broadly responsible for states of rest such as daydreaming or mind-wandering and is deactivated during conscious self-awareness, attention-requiring tasks, and goal-directed behaviour (Liddle et al., 2011; Uddin et al., 2008). In ADHD, this deactivation of the default mode network has been shown to be impaired during tasks requiring sustained attention unless they are underpinned by high motivational incentives (Liddle et al., 2011). There is also evidence for a disruption in fronto-cerebellar pathways, which underpin timing of behavioural responses and time-related expectations (Durston et al., 2011). In combination, these disruptions cause age-inappropriate deficits in the ability to engage in adaptive, motivated, self-regulated behaviour in the presence of competing behavioural impulses (for example impulses to move and talk when it may not be appropriate), as well as to pay attention to specific information in one's immediate environment while inhibiting responses to a range of potentially distracting sensory stimuli.

These complex and long-term structural and functional abnormalities result in (but may also be partially driven by) the relative underactivity of dopaminergic and noradrenergic pathways that is the target of ADHD medications. By artificially increasing the activation of dopamine and/or noradrenaline receptors on the neurons making up these pathways, ADHD medications normalise their activity such that it more closely resembles that seen in healthy (or

developmentally typical) people (Liddle et al., 2011; Rubia et al., 2014). However, they do not reverse or necessarily result in full remission of ADHD symptoms and associated impairments (Safren et al., 2010). In other words, medications largely treat the downstream consequences of earlier developmental disruptions. They do not correct the abnormalities in structure and connectivity between brain areas, though there is some evidence that medication-enhanced activity of these areas may cause some maturational improvements in structure and/or function over time (Pretus et al., 2017; Schweren et al., 2013). The non-specific way in which these medications increase the activity of dopaminergic and noradrenergic receptors across various brain regions (rather than only the regions and pathways specifically disrupted in ADHD) can explain common side effects such as decreased appetite, insomnia, elevated heart rate and blood pressure, sweating, and agitation, which are regulated by dopaminergic and noradrenergic neurons in other parts of the brain (Jaeschke et al., 2021; Kis et al., 2020). Clearly, while pharmacological interventions are the most efficacious option available, they do not fully explain nor address the core pathophysiology of ADHD.

The neurobiological basis of ADHD can inform the understanding of its aetiology, that is, the development of ADHD in the context of genetic and environmental risk factors. There is a high degree of heterogeneity in symptom presentations and functional impairments in people with ADHD (Luo et al., 2019). However, understanding that the executive deficits seen in ADHD may be underpinned by a range of mechanisms which ultimately coalesce on long-term disruptions in the development of frontal brain regions and connecting pathways, suggests that the genetic and environmental factors that cause ADHD should be capable of causing these long-term disruptions. Given the progression from sensitive periods of brain development in infancy and early childhood to relatively lower neuroplasticity at later ages, it is perhaps not surprising that ADHD has been most consistently shown to rely on genetic and early environmental risk factors. Arguably, environmental exposures during later childhood, adolescence, and adulthood would need to be relatively extreme to cause a long-term disruption (or worsening of existing disruption) in brain function. However, long-term exposure

to environments that either scaffold or hinder the ongoing development of executive functioning across development may well play an important role in longer-term trajectories of ADHD symptoms (Claussen et al., 2022; Johnston et al., 2012).

1.2.1.2. Neurobiological overlap between ADHD and other disorders

The neurobiological underpinnings of ADHD can also inform theory as to its overlap with common comorbid disorders. This is a complex topic, as given the wide range of disorders associated with ADHD and the heterogeneity in presentations of ADHD itself, the underpinnings of comorbidity between ADHD and other disorders are likely to differ (Steinberg & Drabick, 2015). A complicating factor is that symptoms of ADHD often overlap with those of other disorders, and indeed a range of neurodevelopmental and psychiatric disorders feature impaired behavioural, attentional and emotional regulation (Cludius et al., 2020; Keller et al., 2019; Swann et al., 2009). For example, impulsivity and excessive motor activity are features of manic and hypomanic episodes in bipolar disorder, while difficulties with regulating attention and behaviour are also seen in ASD. While the DSM-5 and ICD-11 note that these and other ADHD-like symptoms tend to present differently when they occur as part of other disorders (American Psychiatric Association, 2013; World Health Organization, 2018), there is some evidence that some of the executive impairments seen in other disorders are underpinned by overlapping dysfunction of frontal regions to those seen in ADHD (Arnsten & Rubia, 2012; Gallo & Posner, 2016). However, differences in specific abnormalities have also been noted between conditions, for example a progressive and more specific reduction in grey matter in frontal, temporal and parietal brain regions in schizophrenia, as opposed to a stable pattern of lower grey and white matter in these brain regions in ADHD (Banaschewski et al., 2005). Additionally, a recent study provided evidence that neurobiological overlap between neurodevelopmental disorders can be expressed in distinct disruptions in functional connectivity in specific pathways (Park et al., 2018). Namely, it found differential patterns of disrupted connectivity of the default mode network in ADHD and ASD, in the ventral attention

network in ADHD and schizophrenia, and in the fronto-parietal and limbic networks in ASD and schizophrenia.

Importantly, overlapping symptoms and neurobiological abnormalities between any two disorders do not necessarily indicate common aetiological risk factors or mechanisms. Disorders with similar neurobiological abnormalities differ by genetic and environmental influences, the developmental primacy of conditions (i.e., the typical age at exposure to relevant risk factors, and age at onset of symptoms), as well as the stable, progressive, or indeed in some cases temporary, nature of the underlying pathophysiology. For example, substance use can cause symptoms closely resembling those of ADHD by causing similar disruptions in brain function, most prominently of fronto-striatal pathways underpinning reward and motivation (Klugah-Brown et al., 2020; Koob & Volkow, 2016). However, the temporary nature of these disruptions suggests that substance use cannot be said to cause or increase the risk for developing ADHD, unless it is capable of causing long-term dysfunction in these areas that persists even after substance use has subsided.

Some have suggested that there may be interactive effects between ADHD and certain comorbid disorders such as anxiety (Schatz & Rostain, 2006). It is not implausible that impairing or distressing symptoms of anxiety or other disorders could place additional strain on executive functioning and thereby worsen existing ADHD symptoms. However, the developmental primacy of ADHD would suggest that it is likely to be a stable modifying factor that contributes to more severe symptom expressions of other disorders (Taurines et al., 2010). Several neurobiological explanations could be put forward for how this could occur for different disorders. Brain-based executive deficits in ADHD could increase people's susceptibility to experiencing a range of psychiatric symptoms more frequently and/or intensely, thereby moderating an individual's existing risk for meeting diagnostic criteria for certain disorders (Gallo & Posner, 2016; Steinberg & Drabick, 2015). For example, early-onset deficits in attentional, emotional and behavioural regulation seen in ADHD may serve as transdiagnostic risk factors for fixating excessively on negative stimuli due to deficits in

attentional disengagement, for experiencing the resulting negative or distressing emotions more intensely, and for failing to develop adaptive coping strategies that underlie mental health and resilience to environmental challenges. These hindrances could directly increase the risk of experiencing clinically significant symptoms of internalising disorders, personality disorders and others, in the context of pre-existing genetic and environmental risk for those disorders. As discussed in section 1.2.2.2., such an explanation is supported by findings of genetic overlap between inattentive (but not hyperactive-impulsive) symptoms of ADHD and anxiety. Neurobiological deficits in inhibitory control could also directly increase the risk of exhibiting clinically significant levels of aggressive or antisocial behaviour seen in other externalising disorders. Similarly, high levels of impulsivity and sensation-seeking in ADHD may increase the risk for the early initiation and subsequent maintenance of substance use, while deficits in reward pathways in the brain may additionally increase susceptibility to developing the neural adaptations underlying substance addiction, increasing the risk of developing substance use disorders (Swanson et al., 2007). Finally, an important potential explanation for a wider array of comorbid disorders is that heritable deficits in brain-based executive functions could cause people with ADHD to behave in ways that elicit adverse responses from others, particularly parents and other family members, which then serve as additional environmental risk factors for developing comorbid disorders. This and other examples of gene-environment interplay will be discussed in section 1.3. First, the following sections will summarise the extant research on the genetic and environmental influences on ADHD and its overlap with comorbid disorders.

1.2.2. Genetic influences

1.2.2.1. Genetics of ADHD

Several decades of quantitative genetic research have consistently shown ADHD to be among the most heritable disorders in psychiatry (Faraone & Larsson, 2019). Alongside family studies, a wide range of twin studies have been carried out on ADHD at various ages, using

both binary measures of clinical diagnostic status and dimensional measures of ADHD as rated by children, parents, teachers, and researchers or clinicians. A recent review estimated the mean heritability across 37 twin studies of children and adolescents at 74% (Faraone & Larsson, 2019). Many individual estimates exceed 80%, and even the lowest estimates, some as low as 51% (Spatola et al., 2007), nonetheless suggest substantial heritability of ADHD.

In adulthood, findings on the heritability of ADHD have been somewhat mixed, with early studies finding heritability to be substantially lower compared to that in childhood. However, this appears to be because early research on adult ADHD used self-report measures of ADHD symptoms, which have been shown to produce lower heritability estimates in childhood and adolescence compared to parent, teacher and clinician reports (Kan et al., 2014; Merwood et al., 2013; Schultz et al., 2006). When combined parent- and self-reports or clinical diagnoses of adult ADHD are used, heritability estimates remain substantial and comparable to those in childhood. For example, the adult subset of the Swedish twin study by Larsson et al. (2014), which included 37,714 twins (mean age 23 years), all of whom were diagnosed with ADHD at age 18 or later, estimated heritability of clinically diagnosed adult ADHD at 72%. Others have published similar or even higher estimates when incorporating parent symptom reports, and have separately estimated heritable components driving stability (or persistence) and change in ADHD symptoms from childhood through adolescence and into young adulthood. For example, Chang et al. (2013) estimated the heritability of a combined parent-report and self-report measure of ADHD symptoms at ages 19-20 at 78%. They also found that a core heritable component drove stability in ADHD symptomatology from ages 8-9 onwards, while new heritable components explaining additional variance in symptoms were introduced at ages 13-14, 16-17, and 19-20, supporting similar earlier findings by other authors (Kuntsi et al., 2005; Larsson et al., 2006). Such findings suggest that childhood and adult ADHD symptomatology is driven in part by the same aetiological factors, while distinct genetic factors may also be responsible for remission of symptoms with age. Notably, in contrast to the observed sex differences in prevalence rates and symptom presentations of ADHD, a large

Swedish twin study of 59,514 twins (including children, adolescents and young adults) found no significant sex differences in genetic and environmental influences on ADHD (Larsson et al., 2014).

While quantitative genetic findings have established the high heritability of ADHD, somewhat slower progress has been made in molecular genetic research aimed at identifying the specific genetic risk factors involved and their potential mechanisms. Most of the genetic variation in the population is in single base pair differences in genetic sequence known as single nucleotide polymorphisms (SNPs) (Knopik et al., 2017). However, around 13% of genetic variation is in copy number variations (CNVs), larger changes in genetic structure wherein stretches of 50 or more base pairs of the genetic sequence are omitted (deletions), repeated (duplications), encoded in the wrong region (translocations) or broken and rearranged (inversions) during genetic recombination or replication (Hawi et al., 2015). ADHD has been shown to rely on the combined effects of many SNPs, each explaining a small proportion of trait variance, but also on multiple base pair variants including CNVs, particularly rare, large CNVs spanning 100,000 or more base pairs (Pierce et al., 2020; Thapar, 2018). These can cause loss or over-expression of genes which can exert substantial effects on development (Hawi et al., 2015). As such, rare, large CNVs have often been implicated in neurodevelopmental disorders such as ASD and schizophrenia (Takumi & Tamada, 2018), particularly in more severe cases accompanied by physical abnormalities or severe cognitive impairment (Cook Jr & Scherer, 2008), or highly penetrant presentations of disorders within specific families (Gibson, 2012).

Early studies on SNPs in ADHD relied on candidate gene methods, which assessed associations between ADHD symptoms and specific genetic variants hypothesised to be involved in ADHD. These studies prominently featured dopamine-regulating genes including DRD4, DRD5, and DAT1 (Sciberras et al., 2017), and some of their potential mechanisms were supported by *in vivo* and *in vitro* findings that they were involved in neurotransmission and related neural regulatory processes that might plausibly affect the function of

dopaminergic and other neuronal pathways (Hawi et al., 2015). However, the selective study of candidate genes based on *a priori* hypotheses about their likely role in a given disorder has since been recognised as empirically unsound, with resulting findings being prone to reporting bias and p-hacking (Dick et al., 2015; Hewitt, 2012). Reflecting this, candidate gene approaches tend to display a pattern of an initial study finding a promising association which subsequent studies fail to replicate (Gizer et al., 2009). Some early progress was also made on the role of CNVs in ADHD, using family linkage studies to identify genetic sequences shared by family members who had ADHD but not by those who did not have ADHD (Faraone & Larsson, 2019). These revealed that CNVs in several chromosomal regions, including 5p, 6q, and 11q, accounted for concordance within families (Elia & Devoto, 2007). However, family linkage studies typically require the participation and genotyping of large extended families, and are less suited to identifying smaller variations in genetic sequence including small deletions and insertions as well as SNPs, which ultimately account for most of the genetic variance in the population (Li et al., 2014). As such, as with other disorders, family linkage studies tended to identify CNVs that contribute to rare and family-specific presentations of ADHD occurring alongside other neurocognitive deficits, but which are not present in most cases of ADHD (Faraone & Larsson, 2019).

Genome-wide association studies (GWAS) and variants such as CNV-GWAS have now largely surpassed candidate gene and linkage approaches as a hypothesis-free method of assessing associations between a given trait and millions of genetic variants across the genome, in large samples of unrelated individuals. The SNP heritability of a trait can also be estimated by assessing the total trait variance explained by SNP variation in the sample (Knopik et al., 2017). However, in contrast to GWAS of schizophrenia and other conditions (Horwitz et al., 2019), GWAS of ADHD had not identified any significantly associated SNPs until very recently. Demontis et al. (2019) identified the first genome-wide significant loci for ADHD in a GWAS meta-analysis of 20,183 people with ADHD and 35,191 controls, reporting 12 loci associated with ADHD. They noted that these did not overlap with candidate genes

previously associated with ADHD symptomatology (Brookes et al., 2006). They also reported a substantial SNP heritability estimate of 22%, as well as assessing potential mechanisms of specific loci using functioning profiling tools. These tools use databases of experimental findings of increased transcription of certain genes in certain cells types, tissue types, and biological processes and pathways, to provide insight into the potential mechanisms by which specific genetic variants could be involved in a disorder (Guy & Mor, 2021; Huang et al., 2013). If there is a pattern of clustering of many genetic associations in one or more biological processes, this indicates that these genes are likely to be associated with the trait via their effects on these processes (Hawi et al., 2015). For example, if many genome-wide significant loci identified in an ADHD GWAS were found to be functionally implicated in neuroplasticity processes, this would implicate disrupted neuroplasticity as a potential genetically driven mechanism underpinning ADHD. Demontis et al. (2019) noted that several genes at or near the loci identified in their analysis were functionally implicated in synapse formation, regulation of neural development and neuroplasticity, and synaptic regulation of dopamine levels (a set of processes that includes dopamine reuptake).

The most recent GWAS of ADHD (currently available as a pre-print) used an expanded sample and identified 27 genome-wide significant loci (Demontis et al., 2022). Notably, only 6 of the original 12 loci from their earlier analysis were significant in this analysis. In addition, the SNP heritability estimate was lower, at 14%, which the authors attributed to differences in the additional cohorts used in the follow-up study. The authors highlighted several functional profiling findings, including several loci being functionally implicated in the regulation of early brain development, while others were preferentially expressed in specific brain regions and cell types, including the frontal cortex and midbrain (i.e., subcortical) dopaminergic neurons. They also constructed polygenic scores (PGS) for one of the cohorts in their study to investigate associations with neurocognitive measures available in that cohort. PGS are individualised scores of genetic risk or propensity for a trait constructed by summing the effect sizes of the most significant SNPs identified in a GWAS, such that individuals who have more

of the identified SNPs have higher PGS for the trait. Demontis et al. (2022) found that their ADHD PGS was associated with impairments in attention and working memory. Overall, these findings are consistent with the state of knowledge on the neurobiological underpinnings of ADHD, and suggest that common genetic variation may contribute to the disruptions in development and function of several implicated brain regions, and separately that polygenic risk for ADHD may contribute to the core symptom of inattention as well as the associated feature of working memory impairment seen in many people with ADHD.

CNV-GWAS have also been used to study ADHD. As opposed to family linkage studies, CNV-GWAS have the advantage of efficiently assessing associations between traits and a wide array of both rare and common CNVs in unrelated individuals (McCarroll, 2008). CNV-GWAS of ADHD have broadly supported previous family linkage findings, identifying CNVs associated with ADHD in chromosomal regions containing multiple glutamate receptor genes (Elia et al., 2012) and nicotinic receptor genes (Williams et al., 2012). However, it has been noted that CNV-GWAS still tend to identify largely person-specific variants that are not present in most individuals, and so are not likely to explain variance in ADHD across the wider population (Hawi et al., 2015). Nonetheless, the mechanisms through which these variants operate could provide insight into the mechanisms underlying ADHD in the wider population. A broader informative finding from CNV-GWAS is that people with ADHD have higher overall rates of rare, large CNVs (i.e., those spanning more than 100,000 base pairs) compared to controls, with rates being particularly high in those with intellectual disability (Williams et al., 2010). This suggests that while specific CNVs may exert relatively person-specific effects on ADHD (i.e., effects that may not explain variance in ADHD in others in the population), a higher overall load of large CNVs, which are capable of disrupting a wide variety of biological processes, confers a higher risk of meeting criteria for ADHD.

1.2.2.2. Genetic overlap between ADHD and other disorders

Alongside evidence for genetic influences on core ADHD symptomatology, quantitative and molecular genetic studies have also demonstrated that shared genetic influences explain substantial portions of the overlap seen between ADHD and various other disorders. Early research focused largely on overlap with other externalising disorders (particularly CD in childhood and antisocial personality disorder and substance use disorders in adulthood). Based on findings of high clustering of these comorbid disorders in some families with ADHD, some posited that ADHD with comorbid CD or antisocial personality disorder could be an aetiologically distinct subtype of ADHD (Faraone et al., 2000). Family studies showed that siblings of people with this presentation were found to have higher rates of psychopathology than the siblings of people with non-antisocial presentations of ADHD (Faraone et al., 1998), suggesting that genetic influences on ADHD within these families may also drive the risk for other externalising disorders. However, it was also clear from early twin studies that a significant portion of the variance in externalising problems such as CD was explained by shared environmental effects (Thapar et al., 2001). Furthermore, bivariate twin analyses showed that while the heritable component of CD could be fully accounted for by overlapping genetic effects on ADHD, CD-specific shared and non-shared environmental components were necessary to explain variance in CD, and indeed, only a small portion of variance in CD was explained by overlapping non-shared effects on ADHD (Thapar et al., 2001). Such findings suggested that rather than representing an aetiologically distinct form of ADHD, the comorbid presentation of ADHD with CD (or, in adulthood, antisocial personality disorder) may reflect environmental conditions in certain families. Indeed, several early studies highlighted specific associations between CD and environmental adversity and family conflict, and between ADHD and neurodevelopmental and learning impairments, while those with both ADHD and CD shared associated features of both disorders (Leung et al., 1996; Schachar & Tannock, 1995).

The early focus on comorbid presentations of ADHD and other externalising disorders established an early evidence base on the genetic overlap between these disorders. Since

then, a range of twin studies has demonstrated that overlapping genetic influences explain symptomatic overlap between ADHD and various other disorders, including ASD and developmental coordination disorder (Lichtenstein et al., 2010; Ronald et al., 2010; Ronald et al., 2008), depression (Chen et al., 2016; Cole et al., 2009; Spatola et al., 2007), tic disorders (Lichtenstein et al., 2010), anxiety disorders (Chen et al., 2016; Spatola et al., 2007), learning disorders (Lichtenstein et al., 2010), alcohol use disorder (Capusan et al., 2015), and binge eating in women (Capusan et al., 2017). Family studies have also shown evidence for genetic overlap with schizophrenia and bipolar disorders (Larsson et al., 2013), and self-harm, suicidal behaviour and completed suicide (Ljung et al., 2014). With the exceptions of ASD, tic disorders, and depression, which appear to share particularly high genetic overlap with ADHD (Cole et al., 2009; Lichtenstein et al., 2010), the genetic overlap between ADHD and symptoms of other disorders appears to be moderate and relatively evenly distributed. A recent meta-analysis of twin studies reported comparable pooled estimates of genetic overlap between symptoms of ADHD and broad dimensions of neurodevelopmental (r_G = .56), internalising (r_G = .50), and externalising (r_G = .49) symptoms (Andersson et al., 2020). Estimates were highest for genetic overlap between ADHD and ASD symptoms (r_G = .59), reflecting the shared early onset and neurodevelopmental underpinnings of these highly co-occurring phenotypes.

A notable finding in the meta-analysis by Andersson et al. (2020) was that pooled estimates of overall genetic overlap between symptoms of ADHD and other disorders were only slightly higher in childhood (r_G = .53) than in adulthood (r_G = .51), suggesting that genetic contributions to overall comorbidity between ADHD and other disorders do not subside or weaken with age. Given its early onset compared to most other disorders, these findings situate ADHD as an early risk-modifying factor that may moderate or mediate the risk for experiencing symptoms of a range of typically later-onset disorders across both childhood and adulthood, with individual patterns of comorbidity depending on more specific genetic and environmental risk factors for other disorders. One argument against this view could be that the genetic

contribution to risk for such a wide range of disorders is not specific to ADHD, but simply reflects a shared genetic liability across all neuropsychiatric disorders. Some support for this explanation has come from studies decomposing genetic risk for various disorders into latent general and specific factors. For example, in a community sample of 1,571 twin pairs aged 9 to 17, a latent general genetic factor accounted for variance across a range of internalising and externalising symptoms (including hyperactivity-impulsivity and inattention) (Lahey et al., 2011). However, this general factor explained relatively little variance in hyperactive-impulsive (24%) and inattentive (32%) symptoms compared to, for example, 94% for major depressive disorder and 98% for generalised anxiety disorder symptoms. Similar findings were reported for clinical diagnoses using a Swedish national registry study of 3,475,112 adults, wherein a latent general genetic factor explained substantial variance across a range of psychiatric disorders including ADHD, major depressive disorder, anxiety, schizophrenia and schizoaffective disorder, bipolar disorder, alcohol and substance use disorders, as well as criminal behaviour (Pettersson et al., 2016). However, out of all disorders in the study, the general factor explained the least variance in ADHD (31%), compared to 58% and 55% for schizophrenia and schizoaffective disorder, 41% and 35% for bipolar and major depressive disorders, 38% for anxiety, and 60% and 46% for substance and alcohol use disorders.

In combination, these findings suggest that while a general genetic factor may explain some of the overlap between ADHD and other neuropsychiatric disorders, both symptoms and diagnoses of ADHD are not as well accounted for by this factor as are those of other disorders. It follows that the particularly wide range of comorbidities seen in ADHD is not likely to simply reflect a shared general genetic liability across all disorders. Instead, overlap with specific disorders may rely on genetic influences that are more specific to certain disorder groups, reflecting shared developmental pathways, neurocognitive features, or symptoms. For example, shared genetic influences could account for overlapping disruptions in functional connectivity of specific brain pathways seen in ADHD, ASD, and schizophrenia (Park et al., 2018). On the symptom level, a large Swedish population-based twin study of 16,734 twins

reported that a shared latent factor explaining variance on the hyperactivity, impulsivity, and inattention dimensions of ADHD was highly genetically overlapping (r_G = .80-.88 in independent groups aged 9 and 12) with a latent factor explaining variance on the social impairment, communication impairment, and restricted/repetitive behaviours and interests dimensions of ASD (Ronald et al., 2014). Shared genetic influences on emotional, attentional, and motivational regulation could explain overlap between ADHD, depressive and anxiety disorders. There is some support for this explanation with regard to anxiety, from twin findings that the genetic overlap between symptoms of ADHD and anxiety was explained by inattentive (but not hyperactive-impulsive) symptoms (Michelini et al., 2015). This suggests that disruptions in attentional regulation (and/or related neurocognitive processes that are not related to hyperactivity-impulsivity) are a common genetically driven feature increasing risk for both ADHD and anxiety. Similarly, genetic influences on impulsivity may explain the overlap between ADHD and alcohol and substance use disorders. This explanation is supported by findings that hyperactivity-impulsivity and CD symptoms accounted for prospective associations between ADHD and initiation of all substance use as well as nicotine and cannabis dependence by age 18, while inattention contributed only to minor residual risk for nicotine dependence (Elkins et al., 2007). All of these findings support the notion that the genetic underpinnings of comorbidity between ADHD and other disorders do not reflect a shared general genetic liability cutting across all disorders, but act via specific effects on neurocognitive processes that are directly implicated in ADHD.

Molecular genetic research has supported quantitative findings on the genetic overlap between ADHD and other disorders. For example, consistent with family findings on the genetic overlap between ADHD, schizophrenia and bipolar disorder (Larsson et al., 2013), a relatively early study based on a schizophrenia GWAS reported that alleles over-represented in adults with schizophrenia were also seen more often in children with ADHD (Hamshere et al., 2013). Authors further showed that childhood ADHD cases could be discriminated from controls using these schizophrenia risk alleles, and that improved discriminative power could

be attained using alleles that were also over-represented in adults with bipolar disorder. Similarly, a cross-disorder GWAS assessing SNP-based genetic overlap between several psychiatric disorders reported a common SNP-based genetic correlation between ADHD and major depressive disorder (Lee et al., 2013). It should be noted that at the time of publishing of both of these studies, no genome-wide significant SNPs for ADHD itself had been identified. A more recent GWAS meta-analysis reported substantial SNP-based genetic correlations between ADHD and bipolar disorder, with two genome-wide significant SNPs explaining some of the covariance between the two disorders (van Hulzen et al., 2017).

The first GWAS to identify genome-wide significant SNPs for ADHD, by Demontis et al. (2019), also assessed bivariate genetic correlations between polygenic risk for ADHD and a range of traits, including various psychiatric disorders, physical health indicators such as BMI, wellbeing, sleep problems, and educational outcomes. Of assessed correlations with 219 phenotypes, 93 were significant. Two of the largest correlations were with major depressive disorder and depressive symptoms, supporting previous findings of particularly high genetic overlap between ADHD and depression (Cole et al., 2009). Other notable genetic correlations were with insomnia, schizophrenia, low subjective wellbeing, neuroticism, low birth weight, cigarette smoking and lung cancer, type 2 diabetes, overweight and obesity, mother's and father's younger age at death, low intelligence and educational attainment, younger age at first birth, and number of children born. Somewhat surprising findings included a non-significant ($p = .08$) genetic correlation with bipolar disorder, a positive genetic correlation with asthma, and a negative genetic correlation with anorexia nervosa. The pre-print follow-up study by Demontis et al. (2022), which identified a larger number of genome-wide significant SNPs of which only 6 overlapped with those found in the previous study, similarly assessed genetic correlations with a range of phenotypes. While many of these overlapped with those above, additional genetic correlations were found with ASD (which was among the largest but not larger than the correlation with depressive symptoms), bipolar disorder, cannabis use disorder, and younger age at menarche. This range of genetic correlations suggests that

common SNP variation explains significant portions of the overlap between ADHD and a range of psychiatric, personality, functional, health, and obstetric factors that have previously been identified as comorbidities or associated features of ADHD. As discussed in the following section, some of these features, such as low birth weight, have been traditionally seen as environmental risk factors for ADHD. Others, such as maternal and paternal young age at death, may reflect the consequences of ADHD-related risk factors for early mortality in the parents of those at high polygenic risk for ADHD.

A recent follow-up of the cross-disorder GWAS by Lee et al. (2013), using a much larger sample which included the ADHD GWAS from Demontis et al. (2019), reported significant genetic correlations between several psychiatric disorders, including ADHD, ASD, major depressive disorder, bipolar disorder, schizophrenia, OCD, Tourette's syndrome and anorexia nervosa (Lee et al., 2019). ADHD was positively genetically correlated with all other disorders with the exception of anorexia nervosa and OCD, which were negatively genetically correlated with ADHD (the correlation with OCD being non-significant). The authors identified several clusters of genetic correlations between specific disorders; alongside a very large genetic correlation between schizophrenia and bipolar, and a cluster of genetic correlations between anorexia nervosa, OCD and Tourette's syndrome, they found a cluster of genetic correlations between ADHD, ASD, and major depressive disorder (Lee et al., 2019). This supports the aforementioned findings on the particularly high genetic overlaps seen between ADHD and ASD, and between ADHD and depression, and indicates that shared SNP variation contributes to these overlaps. The results also further refute the notion that the co-occurrence of ADHD with a wide range of other disorders can simply be attributed to a shared general genetic liability across all disorders. While ADHD was associated with most other disorders, Lee et al. (2019) demonstrate that even SNP-based genetic overlap tends to cluster in groups roughly according to the type of disorder, most notably psychotic disorders, compulsive disorders, and a clustering of childhood-onset neurodevelopmental disorders with depression. The negative genetic correlation with anorexia nervosa further suggests that comorbidity differs by disorder

rather than being general, and is consistent with the recent findings that polygenic risk for ADHD was negatively genetically correlated with anorexia nervosa (Demontis et al., 2022; Demontis et al., 2019). Discouragingly, anxiety disorders were not included in these cross-disorder analyses, likely due to the slower progress made in GWAS of anxiety until very recently (Purves et al., 2020).

Molecular genetic findings can also shed light on the phenotypic mediators of overlap between ADHD and other disorders. For example, PGS for ADHD ascertained from clinical samples were shown to predict pragmatic language difficulties (a feature of ASD) in a community sample (Martin et al., 2014). The genetic association was specifically attributable to 'inappropriate initiation' and 'conversational context' subscales, but not to 'coherence', 'stereotyped conversation', or 'conversational rapport' subscales. This is perhaps not surprising given that the former impairments could result from hyperactivity-impulsivity symptoms seen in ADHD, while the latter impairments are more specific to stereotyped behaviours and perspective-taking difficulties seen mainly in ASD. This finding is an example of the way in which genetic overlap between conditions can manifest via specific neurocognitive features which may be shared among them.

It is important to note that all of the above studies assess genetic overlap driven by common SNPs, but not that of larger variants including CNVs which could explain a larger portion of the overall genetic overlap with other disorders, particularly other neurodevelopmental disorders. Broadly supporting previous family linkage findings, several CNV-GWAS have also reported associations between ADHD and a higher number of CNVs in chromosomal regions previously implicated in ASD and schizophrenia (Jarick et al., 2014; Lionel et al., 2011; Williams et al., 2012; Williams et al., 2010). This suggests that, as with ADHD itself, the genetic underpinnings of comorbidity between ADHD and other disorders relies on both common SNP variation and the effects of larger variants including CNVs.

1.2.3. Environmental influences

1.2.3.1. Environmental influences on ADHD

While ADHD is highly heritable, environmental factors account for around 25% of the variance in ADHD symptomatology in childhood and adolescence, and for around 30% in adulthood (Faraone & Larsson, 2019). Domain-specific environmental factors have also been shown to act on hyperactivity, impulsivity, and inattention symptom dimensions (Ronald et al., 2014). This indicates a substantial role for environmental influences on ADHD symptomatology. Moreover, genetic factors do not act in isolation from environmental contexts, as development ultimately relies on an ongoing interplay between genetic and environmental factors. Studies estimating heritability while not accounting for this interplay may provide inaccurate representations of the importance of genetic and environmental risk factors (Rijsdijk & Sham, 2002; Young et al., 2018). More broadly, heritability estimates may not be informative as to the relative importance of genetic and environmental factors in underrepresented populations, an important point given the overrepresentation of participants who are white, well-educated, and of relatively high socioeconomic status in behavioural genetic research.

A striking example of adverse environmental conditions exerting large effects on development in the absence of specific genetic risk comes from the Romanian orphanage studies, which reported that a substantial portion of orphaned children exposed to extreme institutional deprivation displayed syndromes of executive dysfunction closely resembling ADHD (Thapar et al., 2013). The children in these studies came from a range of families likely to reflect a normal distribution of genetic risk for ADHD in the population. This syndrome, termed ‘deprivation-related ADHD’, has since been shown to follow a similar pattern of persistence into adulthood, including a predominantly inattentive symptom presentation and almost equal rates in men and women, as well as elevation of common comorbid symptomatology, most notably symptoms of ASD (Kennedy et al., 2016). While this is clearly a rare example of extreme environmental adversity exerting atypically disruptive effects on early development, it demonstrates that sufficiently adverse environmental conditions can elicit a symptom profile very much resembling that of ADHD in those not selected for high genetic risk. In the majority

of the population, the disruption in brain development seen in ADHD relies on an interplay of genetic factors with various environmental factors over the course of development (Faraone et al., 2021). Crucially, however, while inherited genetic factors are immutable, environmental exposures constitute key targets for early interventions, arguably especially so for those at high genetic risk for ADHD and the range of associated comorbid disorders.

Recent population registry studies have reported that wider contextual factors such as parental unemployment, income, relative poverty, housing instability, and other indicators of socioeconomic disadvantage, appear to be risk factors for ADHD in children (Björkenstam et al., 2018; Carlsson et al., 2021; Keilow et al., 2020; Rowland et al., 2018). However, rather than exerting direct effects on child development, these broader factors are likely to act indirectly, for example through the effects of financial instability and resulting stress on parenting behaviours. Most studies on environmental risk factors for ADHD have focused on these and other more direct factors, including maternal health during pregnancy, specific parenting behaviours, parental psychopathology, and features of the home environment (Carlsson et al., 2021; Claussen et al., 2022; Sciberras et al., 2017). These studies can be broadly partitioned into those focusing on perinatal factors (exposures before and around the time of birth) and on postnatal factors (exposures occurring after the perinatal period). Perinatal risk factors may affect the onset and severity of early ADHD symptomatology in children at genetic risk, while later postnatal factors may exert ongoing effects on symptom severity and on longer-term developmental trajectories (Claussen et al., 2022).

Perinatal risk factors for ADHD are natural targets for research given the prominent role of the intrauterine environment in foetal development. They are also relatively easy to measure, many being a standard part of prenatal screening and birth records. One of the most well-studied perinatal risk factors associated with childhood ADHD is maternal smoking during pregnancy (He et al., 2020). However, it is increasingly clear that previously reported associations between maternal smoking during pregnancy and child ADHD symptomatology are not likely to be causal, but are better explained by overlapping genetic risk. Indeed, a

recent review of the literature on a range of perinatal risk factors for ADHD noted that maternal smoking during pregnancy, along with most other putative perinatal risk factors for ADHD, could not be said to exert a causal effect on the development of ADHD in children (Sciberras et al., 2017). Reviewing a wide range of established perinatal risk factors, they found that only premature birth and, to a lesser extent, low birth weight have relatively robust associations with child ADHD. The authors noted that these obstetric factors might be expected to increase risk for ADHD alongside a range of other conditions, as they reflect globally disrupted or limited foetal development. For all other factors, the authors concluded that there is insufficient evidence for robust associations with child ADHD, with many associations being shown to be accounted for by familial confounding when using genetically sensitive methodologies (further discussed in section 1.3.).

In the postnatal period, the accumulating number of potentially important environmental factors can further hinder inferences as to whether any given environmental exposure is likely to exert a causal effect on the development of ADHD. After children are born they encounter an ever-growing variety of environmental contexts containing many individual exposures, interacting with various early caregivers, playmates, technologies, and later a widening net of peers, teachers and institutions. This introduces more potential for findings to be affected by the omitted variable problem, wherein the association between a putative environmental risk factor and a given phenotype could be mediated or moderated by one or more unobserved environmental variables, such as other protective and risk factors (Scheres & Hamaker, 2010). With the exception of extreme adverse events, the effect of each individual exposure is less likely to cause large developmental changes in the context of the many other exposures that accumulate over time. Therefore, research on postnatal risk factors typically focuses on trait-like behaviours in parents, such as child-directed hostility or inconsistent discipline, which form an ongoing and relatively stable part of children's early environment. However, the behaviour of family members can vary greatly in frequency and intensity across even short periods of time, and researchers largely rely on retrospective parent reports of the presence or frequency

of parental or other family characteristics over a given time period. These retrospective reports are themselves subject to recall and reporting biases (Faraone & Larsson, 2019). Furthermore, most research on environmental risk factors for ADHD has relied on maternal reports of both their children's ADHD symptomatology and their own parenting behaviours or mental health (Deault, 2010). This can introduce rater effects such as shared rater bias, wherein characteristics of a reporter can affect their perception of their own and others' behaviour, resulting in potentially misleading associations that reflect the rater's subjective perception of their own and others' behaviours, rather than associations between actual behaviours (Hartman et al., 2007). More broadly, the use of single reporters increases the contextual specificity of measures, as different aspects of children's ADHD symptomatology could manifest to different extents around mothers as opposed to fathers, teachers and clinicians, who are themselves likely to focus on different aspects of children's behaviour (Freitag et al., 2010). Using multiple reporters addresses these potential rater effects and increases the likelihood of capturing all relevant aspects of overall ADHD symptomatology.

A major remaining issue is the predominant use of cross-sectional data, which is not informative as to the direction of potential effects (Deault, 2010). For example, parents of children with ADHD have been found to report more parenting stress and family dysfunction (Modesto-Lowe et al., 2008; Mofokeng & van der Wath, 2017), more overprotective and controlling parenting styles (Gau & Chang, 2013), and more inconsistent and hostile parenting including greater use of corporal punishment (Alizadeh et al., 2007; Bhide et al., 2019; Cussen et al., 2012). However, all of these behaviours could be evoked responses to children's ADHD symptomatology. Equally, long-term exposure to adverse parenting behaviours could also exert causal effects on children's ADHD symptomatology (whether or not these behaviours were evoked by earlier child behaviour). Longitudinal designs are a way of establishing the direction of associations, including bidirectional relationships where both parent and child behaviours may predict one another across time. Longitudinal studies have shown that a range of parent and family characteristics prospectively predict child ADHD symptomatology.

Predictors of either severity or persistence of child ADHD symptoms include parental depression (Elgar et al., 2003; Huhdanpää et al., 2021; Romano et al., 2006) and anxiety (Clavarino et al., 2010), overall parental psychopathology (Wüstner et al., 2019), child-directed hostility (Mulraney et al., 2019; Romano et al., 2006), physical abuse and child maltreatment (Claussen et al., 2022; González et al., 2019), inconsistent discipline and low parental involvement (Ellis & Nigg, 2009; Hawes et al., 2013), authoritarian parenting style (Huhdanpää et al., 2021), low maternal sensitivity (Choenni et al., 2019), paternal displays of rejection (Lifford et al., 2008), and negative family atmosphere (i.e., high levels of parental conflict and low levels of safety and harmony) (Huhdanpää et al., 2021).

Longitudinal studies have also demonstrated that certain parental behaviours can be evoked responses to children's ADHD-related behaviour. For example, Lifford et al. (2008), found that maternal displays of rejection were evoked by earlier child ADHD symptoms. A later study found that children's ADHD symptoms prospectively predicted parents' perceived powerlessness over their child's behaviour two years later, which in turn prospectively predicted higher coldness and rejection and lower warmth towards children another two years later (Glatz et al., 2011). However, this study did not assess whether parental behaviour in turn prospectively predicted child ADHD symptoms. Two recent longitudinal studies have reported unidirectional as well as bidirectional relationships. The first showed bidirectional predictions between children's ADHD symptoms and parental child-directed anger across three waves, when children were aged 4-5, 6-7, and 8-9 (Demmer et al., 2018). Children's ADHD symptoms at both earlier waves predicted more child-directed anger in mothers and/or fathers at both later waves. However, child-directed anger from one or both parents at both earlier waves also predicted higher child ADHD symptoms at both later waves. These findings suggest bidirectional influences between child ADHD symptomatology and negative parenting behaviours across childhood, wherein child ADHD symptomatology evokes more negative parenting from both parents, but negative parenting also predicts children's later ADHD symptomatology. A more recent study found that maternal overreactive parenting and life

stress when children were aged 3 predicted child ADHD symptoms at age 6, and child ADHD symptoms at age 3 predicted maternal depressive symptoms, life stress and lower warmth towards children by age 6 (Breaux & Harvey, 2019). Notably, this study controlled for maternal ADHD symptoms, suggesting that these associations were independent of the potential effects of ADHD symptomatology on mothers' depressive symptoms and life stress.

It is important to note that even longitudinal associations between well-measured phenotypes do not demonstrate causality, as any longitudinal association could still be caused by unobserved confounding variables. With this in mind, it is notable that most of the predictors of child ADHD symptomatology summarised above are behaviours that are associated with ADHD symptomatology in parents (as previously discussed in section 1.1.4.), although most of the above studies did not assess parental ADHD symptoms. This highlights the possibility that many of the predictions from parent behaviours and psychopathologies to children's ADHD symptoms could be accounted for by shared genetic risk for ADHD affecting both parents' behaviour and psychopathology and children's ADHD symptomatology. The issue of genetic confounding, and extant findings from studies that have used genetically sensitive designs to address these confounds and distinguish genetic from environmental influences, are later discussed in detail in section 1.3.

1.2.3.2. Environmental research on comorbidity between ADHD and other disorders

Environmental factors have been shown to account for some of the overlap between ADHD and other disorders, including some of the most heritable and strongly genetically related comorbidities of ADHD. Such findings are not new; an early bivariate twin analysis by Thapar et al. (2001) showed that a significant portion of variance in CD symptoms was explained by overlapping non-shared environmental influences on ADHD. A later monozygotic (MZ) twin differences study reported that MZ twins with ADHD had significantly higher depressive symptoms compared to their co-twins without ADHD (Piek et al., 2007). Since MZ twins differ

only by their non-shared environment (i.e., their individual environmental exposures, excluding those they share in their family environment), this finding provided particularly robust evidence for non-shared environmental effects on comorbidity between ADHD and depressive symptomatology. More recently, the large bivariate twin analysis by Ronald et al. (2014) reported substantial correlations between non-shared environmental effects on latent factors for ADHD and ASD symptoms at ages 9 and 12 (rE = .27-.73). Similarly, Michelini et al. (2015) assessed overlap between ADHD symptoms and common anxiety disorders including social anxiety, obsessive-compulsive symptoms, generalised anxiety, panic/agoraphobia, and physical injury fears. They found that the phenotypic overlap between ADHD and all forms of anxiety was specific to attention problems rather than hyperactivity-impulsivity, and reported significant non-shared environmental correlations (rE = .26-.32) between attention problems and all anxiety symptom measures.

While it is clear that environmental factors explain some of the overlap between ADHD and other disorders, the specific environmental exposures and the mechanisms by which they explain comorbidity is not clear. In the context of an individual's wider genetic and environmental risk for developing a range of disorders, the presence of ADHD could confer additional risk in several ways. While some of the comorbidity between ADHD and other disorders could simply reflect shared risk factors that simultaneously increase the risk for both disorders, an important possibility is that the effects of ADHD itself, at the cognitive, emotional, and behavioural levels, may place people with ADHD at increased environmental risk for developing other disorders. Relatively strong evidence for a causal effect of ADHD symptoms themselves comes from recent findings that pharmacologically treating ADHD can reduce the risk of experiencing depression. This was shown in a large longitudinal Swedish population registry study of 38,752 children and adults (32% female) by Chang et al. (2016). They found that after controlling for other psychiatric disorders and sociodemographic factors, those receiving stimulant or non-stimulant ADHD medications had a 43% lower risk of being diagnosed with depression 3 years later than those not receiving medication. The reduction in

risk was similar whether or not people had previously experienced depression, and was greater for those who had been receiving medication for longer. Furthermore, within-person analyses showed that episodes of depression were 20% less common when people were receiving medication than when they were not, after adjusting for antidepressant medication.

These findings suggest that one or more aspects of ADHD symptomatology or related functional impairment increase the risk for depression and this risk can be moderated by pharmacologically treating ADHD. There are several possible explanations for these findings. Firstly, it could be that the dopaminergic effects of stimulant medications simply reduced the risk of experiencing overt symptoms of depression. This is not implausible given that key features of depression include anhedonia, an inability to experience normal reward, and a lack of motivation, both of which have been associated with deficient dopaminergic activity (Treadway & Zald, 2011). However, it should be noted that this would itself constitute an example of an environmental intervention moderating the association between ADHD and depression. Another explanation is that this protective effect, particularly the reduction in risk for depression at the 3-year follow-up, could be accounted for by the effects of ADHD medications on core symptoms and functional impairments which otherwise increase the risk for depression. For example, impulsivity, inattention and corresponding functional impairments could predispose those with ADHD to a stressful or ‘depressogenic’ life. This has been proposed as an explanation for the overlap between ADHD and depression, as chronically high rates of stressful experiences are increasingly recognised as a major risk factor for depression (Riglin et al., 2021). ADHD could increase daily stressful experiences through various mechanisms, for example by causing educational or occupational underperformance, impairing healthy coping responses, and reducing participation in health behaviours that reduce stress, for example exercise and regular sleep. In addition, ADHD may increase interpersonal stress and decrease access to social support. One study of 230 older adults (aged 60-94) found that those meeting diagnostic criteria for ADHD reported higher rates of serious conflicts and higher depressive symptoms compared to those without ADHD, and that

serious conflicts partly mediated the association between ADHD and depressive symptoms (Semeijn et al., 2015). This suggests that higher rates of interpersonal stress experienced by people with ADHD may increase their risk for depression.

Another important possibility is that the executive deficits in ADHD moderate the effects of environmental risk factors for other disorders. The early onset and pervasive nature of ADHD-related executive impairments means that they could affect the way in which people with ADHD respond to a range of environmental exposures. For example, emotional dysregulation has been highlighted as a potential transdiagnostic factor affecting the risk for a range of other disorders in people with ADHD (Shaw et al., 2014). Because emotional regulation is a core component of adaptive responses to adverse or stressful experiences and resulting negative emotions and thoughts (Zimmer-Gembeck & Skinner, 2016), it stands as an important moderator of risk across all disorders that depend substantively on responses to distressing environmental exposures. An inability to regulate negative or distressing thoughts and emotions is a feature of many psychiatric disorders, including depression (Newby et al., 2014), social and other anxiety disorders (Pile & Lau, 2020), OCD (Hezel & Simpson, 2019), eating disorders (Corstorphine et al., 2007), and alcohol and other substance use disorders (Mattingley et al., 2022). Deficits in emotional regulation have also been noted in ASD (Cai et al., 2018), ODD and CD (Schoorl et al., 2016), schizophrenia (Khoury & Lecomte, 2012), and bipolar disorder (Dodd et al., 2019). In the context of individual risk for these other disorders, ADHD could contribute additional risk for more severe symptoms by hindering effective emotional regulation of responses to negative experiences (Bodalski et al., 2019; Steinberg & Drabick, 2015).

As well as moderating the effects of environmental risk factors for other disorders, ADHD could also increase exposure to risk factors for certain disorders via its effects on behaviour. Interestingly, a large twin study found that while childhood ADHD symptomatology predicted early substance use (specifically alcohol and tobacco use), which itself relied on shared and non-shared environmental influences, the overlap between ADHD symptoms and early

substance use was accounted for entirely by genetic overlap with hyperactivity-impulsivity symptoms (Chang et al., 2012). These findings appear to suggest that while genetically driven impulsivity increases the risk for early initiation of substance use, ADHD as a whole does not modify or otherwise uniquely contribute additional environmental risk for early substance use. This genetically driven overlap between ADHD and later substance use could be seen as an example of active rGE, wherein people seek out or select environmental exposures based on their genetic propensities (Knopik et al., 2017). In this case, genetically driven impulsivity and/or associated sensation-seeking may have caused those with ADHD to use substances at an earlier age, potentially affecting their risk of developing comorbid substance use disorders. These genetic effects on environmental exposures, further discussed in section 1.3., may also explain an increasing proportion of the overlap between ADHD and other disorders later in life, as people move away from their family environments and their own genetic propensities increasingly shape their environmental exposures.

While the above mechanisms may moderate or increase exposure to environmental risk factors for comorbid disorders at the individual level, another important source of ADHD-related environmental risk is the family environment. As with research on ADHD itself, the roles of parental psychopathology, specific parenting behaviours, and other family characteristics have been investigated as risk factors for comorbid disorders. This research base suffers from the same limitations seen in research on environmental risk factors for ADHD itself, namely a lack of control for familial confounding, recall and reporter biases due to predominantly single-parent ratings, and the use of cross-sectional analyses to identify correlates rather than predictors of specific comorbid presentations in children with ADHD (Deault, 2010). Furthermore, most research has focused on comorbid CD and ODD, and many of the family factors shown to be associated with these comorbid presentations, such as harsh parenting, low warmth, maternal depression, and parent-child conflict (Chronis et al., 2007; Edwards et al., 2001; Johnston & Jassy, 2007), overlap with those found to be associated with ADHD itself. Finally, as with research on ADHD itself, it remains unclear whether parent

psychopathologies and specific parenting behaviours are unidirectional risk factors exerting causal effects on children's risk for different comorbid disorders, or whether some are also evoked responses to children's ADHD and/or comorbid disorder symptoms.

Longitudinal studies have supported a transactional model, wherein early ADHD symptomatology places increased strain on parents, increasing their risk for displaying inconsistent, unresponsive, and harsh parenting, which in turn increases children's risk for developing comorbid CD and/or ODD (Deault, 2010; Johnston & Jassy, 2007). This model may also explain the increased risk for internalising disorders. For example, a recent longitudinal study found that overprotective parenting at age 5 mediated relationships between ADHD symptoms at age 3 and anxiety symptoms at age 9 (Meyer et al., 2022). This may suggest that parents' responses to their children's ADHD-related difficulties could result in observational learning of anxious thoughts or behaviours by children. Another longitudinal study found that children's inattentive symptoms at age 5 predicted parent-child relationship problems at age 15, which in turn predicted children's later depressive symptoms at age 20 (Humphreys et al., 2013). When ODD symptoms were included in analyses these were also found to predict parent-child relationship problems, suggesting that additional externalising comorbidities may contribute to risk for later internalising comorbidities via their effects on the parent-child relationship. Similarly, a recent longitudinal study found that parenting stress due to dysfunctional mother-daughter interactions mediated associations between childhood ADHD status in girls aged 6 to 12 and their later externalising, internalising, and specifically depressive symptoms and non-suicidal self-injury at ages 16 to 22 (Gordon & Hinshaw, 2017).

These findings provide relatively robust support for a transactional model, implicating environmental risk factors in the family environment as mediators of the overlap between early ADHD and later comorbid symptomatology. However, as discussed in the next section, these associations could still be accounted for by unobserved confounding variables. Most notably, shared genetic risk for ADHD in parents and children could account for children's ADHD

symptoms, parents' susceptibility to stress and parent-child conflict, and children's later comorbid symptoms.

1.3. Distinguishing genetic from environmental influences on ADHD using genetically sensitive/quasi-experimental designs

In terms of establishing the causal effect of any factor on ADHD or its overlap with other disorders, the most serious and overarching methodological obstacle is that of confounding of associations by uncontrolled genetic or environmental factors. As previously described, while genetic and environmental influences do not act in isolation from one another, uncontrolled confounding obscures inferences regarding both the overall roles of genetic and environmental factors on trait variance or covariance, and the specific predictive role of any putative genetic or environmental risk factor. sections 1.3.1. and 1.3.2. will describe several forms of genetic and environmental interplay, with a focus on forms of confounding that obscure the roles of family-level aetiological influences on ADHD and comorbidity. They will also detail several quasi-experimental research designs that can be used to account for these confounds, enabling more robust inferences as to the causal roles of different genetic and environmental factors on development. Finally, these sections will provide examples of studies that have used these designs to investigate aetiological influences on ADHD and its overlap with comorbid disorders.

1.3.1. Genetic confounding of environmental effects; adoption studies, sibling/cousin control designs, MCoTS

Two well-established forms of gene-environment interplay are gene-environment interaction (GxE) and gene-environment correlation (rGE). In relation to research on environmental risk factors, GxE can be of interest because genetic factors may moderate responses to a wide range of environmental exposures (Assary et al., 2018). However, rGE is of particular importance for family and developmental research because it can have broader effects on the environmental factors that individuals are exposed to. There are three key types of rGE: 1)

Active rGE; 2) Evocative rGE; and 3) Passive rGE. Active rGE occurs when the genetic propensities of an individual cause them to select or seek out environments that are congruent with their abilities or interests (Knopik et al., 2017). Traditional examples of active rGE are positive, for example a child with a genetic propensity towards reading ability choosing to spend more time reading, which may then exert a positive environmental effect on their reading ability. However, active rGE may also increase exposure to harmful environmental influences. For example, an adolescent with a genetic propensity towards sensation-seeking may seek out alcohol or other substances at an earlier age, and may be more likely to affiliate with peers with similar interests, which may then increase their risk of developing substance use disorders (Hill et al., 2008). Evocative rGE occurs when an individual's genetically driven behaviour evokes or elicits certain responses from other people. For example, a child with genetically driven hyperactivity could elicit peer rejection from other children, which may increase their risk for developing anxiety and delinquent behaviours (Mrug et al., 2012). Interestingly, a recent study found evidence for evocative rGE by showing that children's PGSs for ADHD were associated with higher levels of household chaos over and above the effects of mothers' PGSs for ADHD (Agnew-Blais et al., 2022). Evoked responses could also have protective effects. For example, children with genetically driven reading or other learning impairments may elicit more supportive responses from teachers and parents, increasing their likelihood of receiving interventions that stand to improve their learning outcomes.

While active and evocative rGE refer to genetically driven behaviours affecting an individual's exposure to certain environments, passive rGE occurs when a person's genotype is correlated with the environment they are born into. Family environments can be heavily influenced by the genetic propensities of each family member, potentially creating a problematic form of confounding in developmental research wherein any phenotypic association between two family members could be accounted for by their shared genetic risk for exhibiting both phenotypes. For example, as discussed previously, negative parenting behaviours have been shown to predict elevated symptoms of ADHD and comorbid disorders, but have also been

shown to be predicted by children's earlier symptoms, supporting a transactional model implicating evoked negative parenting behaviours as risk factors for children's later ADHD-related outcomes (Deault, 2010; Gordon & Hinshaw, 2017; Humphreys et al., 2013; Johnston & Jassy, 2007; Meyer et al., 2022). However, as these studies have not controlled for passive rGE, all of these associations could be explained by shared genetic risk for ADHD. This shared risk could simultaneously account for parents' elevated ADHD symptomatology, their associated risk for exhibiting a range of suboptimal parenting behaviours, and children's early-onset symptoms of ADHD and other externalising disorders, as well as their risk for developing (or experiencing more severe symptoms of) a range of disorders in adolescence and adulthood. Therefore, studies aiming to make causal inferences as to the role of any putative environmental risk factor for ADHD need to use genetically sensitive, quasi-experimental designs capable of accounting for genetic confounding (Liu & Neiderhiser, 2017).

The discordant sibling pair design is one example of a genetically sensitive design, and is particularly useful for determining whether the putative effects of prenatal risk factors could be explained by genetic or other familial confounding (Thapar & Rutter, 2019). These designs compare phenotypic outcomes for pairs of siblings who are discordant for an exposure (or differentially exposed). A prominent example is maternal smoking during pregnancy and children's risk for ADHD; discordant sibling pair studies have shown that while children whose mothers smoked during pregnancy are at increased risk of ADHD, the same is true for their siblings even if mothers did not smoke during pregnancy (Rice et al., 2018). This suggests that genetic or wider familial confounding, rather than a causal effect of intrauterine exposure to maternal smoking, explains the association. More broadly, if an association between a putative risk factor and a child phenotype is shown to be attenuated when comparing sibling or cousin pairs, this suggests that familial confounding was at least partially driving the association seen in a full sample (Sciberras et al., 2017). For postnatal exposures, comparison of MZ twin pairs allows for full control of genetic and shared environmental confounding on associations (Thapar & Rutter, 2019). Another method is the in vitro fertilisation (IVF) design,

in which children who are conceived via IVF may be exposed to an intrauterine environment of a genetically unrelated surrogate or their genetically related mother. If associations between a prenatal risk factor and child phenotype are seen even in children born to surrogate mothers, this indicates a causal effect of the environmental exposure (Thapar & Rutter, 2019). However, if associations are stronger in children born to their biological mothers, it suggests that they are at least partially explained by familial confounding.

In the perinatal risk literature, genetically sensitive studies using sibling and cousin pair comparison designs have revealed that many putative perinatal risk factors for ADHD are likely to be explained by familial confounding. The review of research on perinatal risk factors for ADHD by Sciberras et al. (2017) outlined a range of recent findings from studies using large population-based cohorts with linked medical records and, where available, relatedness data enabling sibling and cousin pair comparisons. Their review covered a range of risk factors including premature birth, low birth weight, other obstetric complications such as pre-eclampsia, maternal age at childbirth, maternal use of alcohol, tobacco, illicit drugs, anti-depressants, and paracetamol during pregnancy, foetal exposure to toxins, maternal stress during pregnancy, life events, history of depression, and BMI. The authors concluded that there was not sufficient evidence for a causal role for any of these risk factors, with many associations showing to be either fully or partially accounted for by familial confounding when studies used sibling and/or cousin pair comparisons. While premature birth and low birth weight were found to most strongly predict children's later risk for ADHD, the authors noted that most studies reporting these associations did not control for other risk factors, such as alcohol use or smoking during pregnancy (and indeed, no studies used sibling or cousin comparisons to control for familial confounding). For other factors, such as parental history of alcohol abuse and maternal paracetamol use during pregnancy, there were studies showing that these predicted children's later risk for ADHD, with the latter doing so in a dose-response fashion where associations were strongest for mothers who used the most paracetamol (Liew et al., 2014; Sundquist et al., 2014). However, as these did not control for familial confounding,

these associations could be explained by shared genetic risk for ADHD in parents and children. For example, ADHD symptomatology in parents could have increased their risk for having a history of alcohol abuse. ADHD has also been associated with increased experiences of disruptive and chronic pain, and reduced pain threshold and tolerance which are attenuated with ADHD medication (Asztély et al., 2019; Stickley et al., 2016; Treister et al., 2015). Therefore, the effects of ADHD symptomatology on pain processing in mothers may have explained their increased use of paracetamol during pregnancy. Where studies did control for familial confounding, most associations between prenatal risk factors and ADHD were partly or completely attenuated. A range of large population registry studies demonstrated full attenuation when comparing siblings discordant for maternal smoking during pregnancy (Skoglund et al., 2014), maternal antidepressant use during pregnancy (Laugesen et al., 2013), maternal overweight before pregnancy (Chen et al., 2014), and maternal age at first birth (Chang et al., 2014). These analyses suggest that rather than exerting causal effects on the risk of ADHD in offspring via effects on intrauterine conditions, these factors are proxies for mothers' own ADHD symptoms. While certain maternal phenotypes may be genetically driven while simultaneously affecting risk for offspring ADHD, the above research demonstrates the importance of controlling for familial confounding for establishing the presence of a putative causal effect of a prenatal or perinatal exposure on children's ADHD symptomatology.

Genetically sensitive studies have also shown that associations between postnatal exposures and child ADHD symptomatology are often at least partially attenuated after controlling for familial confounding. For example, a large Swedish co-twin control study of 8,192 twins (3,578 being MZ twins) found significant associations between child maltreatment, defined by parent reports of children experiencing either emotional abuse/neglect, physical neglect, physical abuse, or sexual abuse, and children's ADHD and ASD symptoms at age 9 (Dinkler et al., 2017). However, associations were highly attenuated in co-twin comparisons, with maltreatment being associated with only modest and specific increases in risk for ADHD in

boys and for ASD in girls. Since associations were not fully attenuated, these findings do provide relatively robust evidence for a small causal effect of maltreatment on the risk for ADHD in boys and ASD in girls. However, it is notable that the most endorsed type of maltreatment was emotional abuse/neglect, and since data were collected cross-sectionally, parent reports of overall maltreatment up to the age of 9 may have reflected evoked parental responses to twins' earlier ADHD and/or ASD symptoms. Another large Swedish co-twin control study of 18,168 twins (aged 20-46) found that retrospective reports of childhood maltreatment were associated with higher ADHD symptomatology in adulthood (Capusan et al., 2016). Associations were only slightly attenuated after controlling for familial confounding by comparing MZ and DZ co-twins. However, the study relied on retrospective self-reports of exposure to child maltreatment, a potential limitation given evidence that ADHD symptomatology in adulthood can confer a negative memory bias (Vrijsen et al., 2018) and a meta-analysis showing that prospectively collected measures of child maltreatment show low concordance with retrospective reports in adulthood, particularly those collected with questionnaires rather than interviews (Baldwin et al., 2019). Indeed, the lack of longitudinal data in this study means it remains unclear whether childhood maltreatment prospectively predicted ADHD symptomatology by adulthood, and/or if those who had higher ADHD symptoms in childhood evoked more adverse responses from parents.

One recent study attempted to both address familial confounding and assess directionality by conducting longitudinal analyses and supplementing findings with separate, cross-sectional MZ twin pair comparisons. Stern et al. (2018) used data from 2,040 twins from the Environmental Risk (E-Risk) Longitudinal Twin Study, investigating associations between various forms of victimisation and ADHD across childhood and young adulthood. Victimisation included measures of exposure to abuse/neglect (including physical, sexual and emotional abuse and physical and emotional neglect by an adult), bullying by peers, and domestic violence. While they found various associations between victimisation and risk for ADHD in childhood and adulthood, evidence for a causal role of victimisation was less clear when

comparing MZ twin pairs and, separately, assessing longitudinal relationships. Some of the strongest associations, between poly-victimisation and ADHD symptomatology in childhood, were fully attenuated when comparing MZ twin pairs. Equivalent associations in young adulthood were only very modestly attenuated, suggesting that while genetic confounding completely accounted for associations in childhood, associations in young adulthood could be attributed mainly to the environmental effects. However, while poly-victimisation may have exerted a causal effect on children's risk for ADHD, it is also possible that differences in ADHD symptomatology between twins evoked higher individual rates of victimisation. Indeed, longitudinal analyses (which did not compare MZ twin pairs due to sample size limitations) showed that abuse/neglect in childhood did not prospectively predict ADHD symptoms in young adulthood. Conversely, ADHD symptoms in childhood did prospectively predict abuse/neglect in young adulthood, even after accounting for individuals' earlier childhood abuse/neglect and ADHD symptoms. Furthermore, after controlling for CD, childhood ADHD symptoms were no longer associated with abuse/neglect in childhood and did not prospectively predict abuse/neglect in young adulthood, leaving only a concurrent association between the two in young adulthood. Stern et al. (2018) highlighted that their study emphasised the complexity of establishing causality, and noted that they did not assess parental ADHD symptomatology in their analyses. Studies using longitudinal designs while also controlling for familial confounding (and other covariates) are needed to make inferences about causality as well as the directionality of any environmentally driven associations.

Adoption designs are another way of separating genetic and environmental influences. When children are adopted by genetically unrelated parents at or shortly after birth, their adoptive family environment is not shaped by genetically related family members. This excludes passive rGE as an explanation for associations between parent or family factors and child phenotypes (Thapar & Rutter, 2019). While evocative rGE could still explain these associations, as children's genetically driven characteristics may evoke certain responses in adoptive family members, this itself can be assessed using data collected from children's birth

parents (Harold et al., 2013). If a birth parent measure predicts a behaviour in children's adoptive parents (despite birth parents sharing no or very little contact with children or the adoptive parents), this would indicate evocative rGE whereby one or more genetically driven characteristics of adopted children evoked a response from adoptive parents. Longitudinal adoption studies can provide particularly strong evidence for both causal effects of specific parent behaviours on later child outcomes, and evocative effects of earlier child behaviours on parent behaviour.

A series of longitudinal adoption studies have recently investigated associations between parenting behaviours and children's symptoms of ADHD and several comorbid disorders and functional outcomes. These used data from the Early Growth and Development Study (EGDS), a US-based longitudinal adoption-at-birth cohort (Leve et al., 2019). In the first study, Harold et al. (2013) found that birth mother ADHD symptoms predicted children's early ADHD-like behaviours (impulsivity and behavioural activation) at age 4.5 years, which predicted concurrent child-directed hostility from adoptive mothers, which in turn predicted children's ADHD symptoms at age 6 as reported by fathers. These findings indicated a direct environmental effect of early maternal hostility on children's ADHD symptomatology by mid-childhood, but also for an evocative rGE effect on hostility by children's genetically driven early ADHD-like symptoms. A key limitation of this study was that both measures were rated by adoptive mothers so were prone to shared rater bias, complicates inferences as to whether early ADHD-like behaviours in children actually evoked maternal hostility. Several follow-up studies using the EGDS cohort have since investigated subsequent relationships between parental hostility and child comorbid symptomatology and functional outcomes. One study again found that maternal hostility when children were aged 4.5 was evoked by children's concurrent ADHD-like symptoms, and that this hostility predicted children's father-rated aggression at age 6 (Sellers et al., 2020). Another study found that both maternal and paternal child-directed hostility when children were aged 4.5 were evoked by children's concurrent ADHD-like symptoms, and hostility in both parents predicted lower mathematic (but not

reading) ability by age 7 via its effects on ADHD symptoms at age 6 (Sellers et al., 2019). One limitation across all three of these studies is their inference of evocative effects of children's ADHD-like symptoms to parental hostility despite these being measured concurrently, at age 4.5. Arguably, more robust inferences as to evocative effects could be made if a children's symptoms prospectively predicted parental hostility at later waves. Longitudinal adoption studies using consistent repeated measures to assess prospective predictions while accounting for earlier scores could enable such robust inferences to be made.

The Children-of-Twins (CoT) design is a quantitative genetic method of decomposing associations between parent and child phenotypes into genetic, extended family environmental, and direct phenotypic exposure components (McAdams et al., 2014). This is achieved by leveraging the different proportions of genes and environments shared between children of twins. Namely, children of MZ twins share 50% of their genes with both their parent and with their aunt or uncle but share a rearing environment only with their parent, and children of dizygotic (DZ) twins share 50% of their genes with parents but only 25% with their aunt or uncle. Based on these differences, inferences can be made as to the genetic and environmental underpinnings of phenotypic associations in samples of extended families that include pairs of twins and their children. For example, if phenotypic correlations between children and their aunt or uncle (avuncular correlations) were found to be equal to parent-child correlations in MZ twin families (and half as large as parent-child correlations in DZ twin families), this would suggest that phenotypic parent-child associations were accounted for by genetic factors (passive rGE). If parent-child correlations were found to be higher than avuncular correlations in MZ twin families (or more than twice as high as avuncular correlations in DZ twin families), this would suggest that phenotypic parent-child associations were additionally driven at least in part by direct environmental exposure to the parent phenotype (and/or that the parent phenotype was evoked by the child phenotype). Overlapping shared environmental effects on parent phenotypes can also be estimated, and their effects on child phenotypes can be estimated to assess the role of extended family

environmental effects. Extensions such as Multiple-Children-of-Twins-and-Siblings (MCoTS) can additionally include siblings, half-siblings and cousins at both the parent and child levels (McAdams et al., 2018). This allows for increased sample sizes and improves power to estimate extended family environmental effects due to the additional degrees of genetic relatedness between relatives.

CoT studies have been used to assess parental risk factors for children's ADHD symptomatology. For example, one found that associations between maternal alcohol use disorder and child ADHD were explained primarily by genetic transmission (Knopik et al., 2006). Children were significantly more likely to meet criteria for ADHD if their mother had an alcohol use disorder or was a discordant MZ twin of someone with an alcohol use disorder, as compared to control children whose mother and their MZ twin did not have an alcohol use disorder. A later study demonstrated the same pattern for paternal alcohol use disorders, but found that covarying for maternal variables such as alcohol use, ADHD, and smoking during pregnancy, attenuated the genetically driven association between paternal alcohol use and child ADHD (Knopik et al., 2009). This was interpreted as suggesting that the environmental effects of maternal behaviour may be more important contributors to children's risk for ADHD. However, the effects of these maternal covariates (which were not decomposed into genetic and environmental paths) could well have captured maternal genetic risk transmitted to children rather than an environmental effect of maternal behaviour. A recent MCoTS study showed that mothers' and fathers' lower educational attainment was associated with increased ADHD symptomatology in children, and that these associations were explained primarily by genetic transmission, but also substantially by direct phenotypic exposure (Torvik et al., 2020). Associations with fathers' educational attainment were also explained in small part by extended family environmental effects. Another MCoTS study found that associations between maternal prenatal depression and children's ADHD symptomatology were explained primarily by genetic transmission, though there was a small residual effect of direct phenotypic exposure (Eilertsen, Hannigan, et al., 2021). These studies demonstrate the utility in using

quasi-experimental designs to assess whether exposure to a given parental phenotype exerts and environmentally driven effect on children after accounting for genetic confounding.

1.3.2. Environmental confounding of genetic effects; extended GCTA

Where GxE and rGE are well known sources of potential confounding in the environmental literature, research on genetic effects is prone to confounding by genetic nurture effects. Genetic nurture occurs when an individual's phenotype is affected not only by their own genotype but also by the indirect effects of their relatives' genotypes on their environment (Kong et al., 2018). There is some overlap between genetic nurture and passive rGE, as both refer to the effects of family members' genes on an individual's environment. However, genetic nurture refers to the indirect effects of genes that are transmitted from parents and those that are not transmitted (or not shared with siblings and other relatives). The estimated effect of an individual's genotype on their phenotypic expression can consist of both direct genetic effects on the individual level (e.g., biological or behavioural effects), and the indirect effects of the same genes in relatives (as well as the effects of non-shared genes). Genetic nurture effects, if unmeasured, can confound estimates of direct genetic effects. Genetic nurture effects are also informative in themselves, as they are quantifications of the environmental effect of parents' or other relatives' genetically driven behaviours on a given phenotype.

Genetic nurture effects have recently been investigated with several methods that use SNP data from parents and children. One method is to assess whether parental PGSs predict a child phenotype over and above the effects of children's own PGS for that phenotype. For example, using a genotyped sample of 11,262 mothers and their children, a recent study (currently available as a pre-print) found that, when modelling child, maternal, and paternal PGS effects jointly, children's ADHD symptoms at age 8 were predicted only by their own PGS for ADHD, but were also predicted by maternal PGSs for ASD and neuroticism (Pingault et al., 2021). This suggests that while children's ADHD symptoms relied primarily on their own inherited genetic risk, their mothers' genetic risk for ASD and neuroticism exerted additional

genetic nurture effects on children's ADHD symptoms. It is important to note that parental PGSs for ADHD only capture the effects of SNPs included in the PGS and which predict their own ADHD symptoms. This means the genetic nurture effects of any other SNPs would not be captured in estimates. Another method of estimating genetic nurture effects addresses this limitation, using an extension of genome-wide complex trait analysis (GCTA) to estimate the total indirect genetic effects of all common SNPs in parents and children on a given phenotype. For example, trio-GCTA can jointly model the total effect of maternal, paternal, and child genotypes on a given phenotype (Eilertsen, Jami, et al., 2021). If maternal or paternal genotypes are found to explain variance in a child phenotype over and above the effects of their own genotype, this indicates a genetic nurture effect. As trio GCTA and related methodologies do not measure a specific parental behaviour or phenotype, estimates of indirect genetic effects provide a quantification of the total effect of all parent behaviours and characteristics tagged by common SNPs on a child phenotype up to the time of measurement (Cheesman et al., 2020). A recent trio-GCTA study found evidence of combined parental indirect genetic effects on children's inattention, hyperactivity-impulsivity, and CD symptoms (but not ODD symptoms) at age 8 (Eilertsen et al., 2022). These effects accounted for around one third as much variance in children's symptoms as did the direct effects of their own genotype, suggesting substantive parental genetic nurture effects on these symptoms. While genetic nurture effects have only recently become a focus in research on psychiatric and behavioural phenotypes in humans, the above findings demonstrate the potential for better understanding the role of environmentally mediated indirect genetic effects on children's ADHD and related outcomes.

1.4. Aims, research questions and structure of this thesis

In this thesis, I use genetically sensitive designs to investigate relationships between different parental genetic and environmental factors and symptoms of ADHD and several common comorbid disorders in children. While the methodologies differ, the overarching aim of all three studies is to better characterise the role these parental factors play in the aetiology of

childhood ADHD and common comorbid disorders. Study 1 uses an MCoTS design to assess whether maternal adult ADHD symptoms share similar genetic overlap with children's mid-childhood symptoms of ADHD, ODD, conduct disorder, anxiety, and depression, as children's own ADHD symptoms in early childhood. Study 2 uses a trio GCTA design to assess whether there are environmentally mediated indirect genetic effects (i.e., genetic nurture) of maternal and paternal genotypes on children's mid-childhood ADHD symptoms. Study 3 uses an adoption-at-birth design to assess whether maternal and paternal hostility mediates associations between children's early symptoms of ADHD and their later symptoms of ODD and anxiety, two of the most common childhood comorbidities of ADHD.

1.5. References

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2. Evidence for strong aetiological overlap between child and adult attention-deficit hyperactivity disorder symptomatology using an extended family design.

This chapter is a manuscript that will soon be submitted for peer-review. Supplementary materials for this chapter, as detailed in the text, are included in Appendix 1 (page 196).

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2.1. Abstract

Background: Several longitudinal studies have suggested that child and adult attention-deficit hyperactivity disorder (ADHD) could be aetiologically distinct disorders. However, very few studies have directly evaluated aetiological overlap between child and adult ADHD, partly due to a lack of genetically sensitive data extending into adulthood. We circumvent this problem by exploring genetic overlap between maternal (adult) and offspring (child) ADHD and comorbid symptoms in an extended family cohort.

Methods: Data were drawn from the Norwegian Mother, Father, and Child Cohort Study (MoBa), a Norwegian birth registry cohort of 114,500 children and their parents. Data from the Medical Birth Registry of Norway (MBRN) were used to link extended families. Mothers self-reported their own ADHD symptoms when children (51% male) were aged 3, and subsequently reported children's ADHD symptoms at age 5, and children's ADHD, oppositional-defiant disorder (ODD), conduct disorder (CD), anxiety, and depression symptoms at age 8. Genetic correlations were derived using Multiple-Children-of-Twins-and-Siblings (MCoTS) and extended bivariate twin models.

Results: Correlations between adult ADHD symptoms and child ADHD, ODD, CD, anxiety, and depression symptoms at age 8 were all underpinned by medium to large genetic correlations. These cross-generational adult-child genetic correlations were of a comparable magnitude to equivalent child-child genetic correlations with ADHD symptoms at age 5.

Conclusions: Our findings provide genetically sensitive evidence that ADHD symptoms in adulthood share a common genetic architecture with symptoms of ADHD and four comorbid disorders at age 8.

2.2. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a highly heritable neurodevelopmental disorder featuring impairing core symptoms of hyperactivity, impulsivity, and inattention. The past decade has seen a shift towards widespread recognition that ADHD can affect adults as well as children, and a general consensus that most cases of childhood ADHD persist into at least young adulthood (Kooij et al., 2019). However, studies of several longitudinal cohorts have reported that a majority of participants who met diagnostic criteria for ADHD in adulthood did not meet criteria in childhood, and vice versa (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015). As these studies used high-quality longitudinal cohorts with low attrition rates and stringent definitions of child and adult ADHD, their findings represented a challenge to the notion of ADHD as an aetiologically consistent condition across the lifespan. They also renewed longstanding doubts as to whether putative cases of ADHD observed in adulthood should be as readily assumed to represent undiagnosed or later-onset presentations of the neurodevelopmental disorder that has long been studied and treated in children (Castellanos, 2015). Such doubts have important implications for the diagnosis and treatment of adults presenting with impairing symptoms of ADHD, as evidence for the efficacy of pharmacological treatments for ADHD continues to rely largely on clinical trials in children (Cortese et al., 2018). Therefore, clinical decisions to diagnose and prescribe such treatments to adults rest on the reasoned assumption that their symptoms are caused by the same neurodevelopmental mechanisms that cause symptoms in children, either going undiagnosed in childhood or having a later onset (Waite & Ramsay, 2010).

Since the initial studies suggesting the distinctiveness of childhood and adult ADHD first surfaced, various studies have sought to shed light on the topic (Faraone & Biederman, 2016; Sibley et al., 2018). However, the evidence base on lifespan trajectories of ADHD remains quite limited. A recent review of longitudinal research by Asherson and Agnew-Blais (2019) found evidence for a late-onset group who met diagnostic criteria for ADHD by early adulthood despite not having met criteria in childhood (Asherson & Agnew-Blais, 2019). In many of these

cases, symptoms occurred exclusively in the context of other disorders, broadly supporting suggestions that adult-onset ADHD symptoms could be better explained by other disorders or environmental factors, including substance use disorders (Taylor et al., 2021). However, refuting the notion of overall aetiological distinction, Asherson and Agnew-Blais (2019) noted that many late-onset cases displayed subthreshold symptoms of ADHD as children, or met criteria for common comorbid disorders, particularly oppositional-defiant disorder (ODD). They also suggested that most late-onset cases could more accurately be classified as 'adolescent-onset', with symptoms first emerging at ages 12-16. Among their conclusions, they posited that there may be variation in age of onset for ADHD similar to that seen in other neurodevelopmental disorders such as schizophrenia. This would suggest that most putative cases of ADHD in adults do in fact represent continuations (or otherwise later-onset presentations) of the neurodevelopmental disorder of ADHD seen in childhood.

However, Asherson and Agnew-Blais (2019) also highlighted several important gaps in extant research which preclude clear conclusions as to the overall continuity of ADHD symptoms from childhood to adulthood. Key among them was that most longitudinal childhood cohorts extend only to late adolescence or young adulthood, with a marked lack of data extending further into adulthood. Therefore, while it has been shown that most children with ADHD will still meet diagnostic criteria by early adulthood, it remains unclear whether they will continue to do so across adulthood. Furthermore, the lack of genetically informative cohort data spanning this longer period prevents the assessment of aetiological overlap between ADHD symptomatology in childhood and across adulthood. This gap in data is a key obstacle to drawing clear conclusions about whether ADHD in adulthood represents the same aetiological entity as childhood ADHD.

Recent genomic research has attempted to bridge this gap, providing some evidence for genetic overlap between ADHD in childhood and adulthood. Rovira et al. (2020) reported a high correlation (r_G = .81) between polygenic scores (PGSs) for ADHD ascertained in children (mean age = 10.14, SD = 3.24) and adults (mean age = 33.46 years, SD = 9.76). They also

found significant correlations between child and adult ADHD PGSs and related phenotypes including smoking, early pregnancy, academic performance, and intelligence. An important caveat is that genomic findings continue to suffer from the missing heritability problem, explaining only a small portion (~4%) of ADHD's heritability compared to quantitative genetic estimates (Li & He, 2021). Therefore, further research using methods capable of capturing all genetic variance in ADHD is also needed.

Another important indicator of overall aetiological overlap between adult and child ADHD is whether adult ADHD shares genetic underpinnings with a range of comorbid conditions commonly associated with childhood ADHD. In childhood, overlapping genetic influences partly explain high rates of comorbidity between ADHD and other externalizing conditions such as conduct disorder and oppositional defiant disorder, and internalizing conditions such as mood and anxiety disorders (Gustavson et al., 2021; Michelini et al., 2015; Tuvblad et al., 2009). Adults with ADHD also have high rates of comorbid disorders, but it is unclear whether this comorbidity relies on the same aetiological underpinnings that drive childhood comorbidity (Kooij et al., 2019). Assessing this overlap would provide a broader indication of whether ADHD in childhood and adulthood share a common genetic architecture.

Very few studies currently exist that can directly address the above questions by following people from childhood to adulthood. One way to circumvent this problem is to use intergenerational family data to estimate genetic covariance between adult and child ADHD across generations. In the present article, we use this novel extended family approach to empirically address whether child and adult ADHD are aetiologically distinct, by assessing the extent to which adult ADHD symptoms in mothers are genetically related to symptoms of ADHD and several common comorbid disorders in their offspring. We do this using the Norwegian Mother, Father, and Child Cohort Study (MoBa), a large dataset of related parents and their children. A substantial degree of genetic overlap between maternal ADHD symptoms and children's ADHD and comorbid symptoms would suggest that child and adult ADHD share

a common genetic architecture. In contrast, a marked lack of genetic overlap would suggest that adult ADHD symptoms represented a distinct aetiological entity.

2.3. Methods and materials

2.3.1. Sample

MoBa is a prospective population-based birth registry cohort of 114,500 children, 95,200 birth mothers and 75,200 birth fathers in Norway (Magnus et al., 2016). Data collection covered pregnancies across all of Norway from 1999 to 2008, with 40.6% of eligible pregnant women consenting to participate in the study. The current study is based on version 12 of the quality-assured data files released for research in January 2019. Using pedigree linkage data from the Medical Birth Registry of Norway (MBRN), a national health registry containing information about all births in Norway, we grouped MoBa participants into extended families of twins, siblings, half-siblings, and cousins in both the parent and child generations. This analytic sample consisted of a total of 25,469 mothers who reported their own ADHD symptoms and/or at least one child measure for 30,833 of their children (51% male). Mothers were aged 17 to 45 years when children were born (mean = 29.97 years, SD = 4.21). Supplementary Table S1 displays frequencies of mothers and children stratified by maternal relatedness groups and child relatedness groups.

2.3.2. Ethics

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics.

2.3.3. Measures

Internal consistency indices for all measures are displayed in Supplementary Table S2. For all adult and child symptom scales (detailed below), mean composites were computed when mothers responded to at least one item on a given scale. Of mothers who responded to at least one item on a given scale, 99.8% – 100% responded to at least half of all items, and 96.1% – 99.1% responded to all items. There were no notable differences in sample means, standard deviations, nor normality between the full sample and subsamples including only those who responded to at least half, or all, items.

2.3.3.1. Adult ADHD symptoms (reported by mothers when children were aged 3)

Mothers reported on their own ADHD symptoms by completing the Adult Self-Report Scale (ASRS), a self-report screening tool for ADHD in adults which has high levels of concordance (AUC = .90) with clinical diagnoses (Kessler et al., 2007). It includes 6 items measuring the frequency of problems with sustained attention, task initiation and completion, organisation, and age-appropriate indicators of hyperactivity (e.g., fidgeting when sitting still for prolonged periods). Mothers were 20-48 years of age when reporting their ADHD symptoms (mean = 32.95 years, SD = 4.17).

2.3.3.2. Child ADHD symptoms at age 5

Mothers reported children's ADHD symptoms at age 5 using the Conners Parent Rating Scale-Revised (CPRS-R) Short Form, a well-validated measure of parent-reported child ADHD symptoms, including 12 items covering a range of hyperactive, impulsive, and inattentive symptoms in children (Conners et al., 1998).

2.3.3.3. Child ADHD and comorbid symptoms at age 8

Mothers reported children's ADHD, ODD, and conduct disorder (CD) symptoms at age 8 using the Parent/Teacher Rating Scale for Disruptive Behavior (RS-DBD). This measure includes 18 ADHD items, 8 ODD items, and 8 CD items based on DSM-IV criteria (Silva et al., 2005).

Mothers reported children's anxiety symptoms using the short version of the Screen for Child Anxiety Related Disorders (SCARED), a measure covering symptoms of several DSM-IV anxiety disorders. The 5-item short version has similar psychometric properties to the full 41-item scale (Birmaher et al., 1999). Finally, mothers reported children's depression symptoms using the Short Moods and Feelings Questionnaire (sMFQ), a 13-item measure of recent feelings, thoughts, and behaviors related to low mood based on the DSM-III-TR criteria of depression (Messer et al., 1995).

2.3.4. Analyses

We set out to evaluate genetic overlap between adult (maternal) ADHD symptoms, and child (offspring) symptoms of ADHD and several comorbid disorders in mid-childhood. Mothers reported on their own ADHD symptoms several years prior to reporting on their children's symptoms of ADHD, ODD, CD, anxiety, and depression (i.e., when children were aged 3 vs. 8), reducing the risk of time-specific shared rater bias affecting our results. To contextualize our findings on adult ADHD, we also assessed associations between the above child symptoms at age 8 and children's own earlier ADHD symptoms at age 5. ADHD symptoms at 5 and 8 were assessed using distinct measures (see above).

Two sets of analyses were conducted, each using the OpenMx 2.18.1 package (Neale et al., 2016) in R Statistics 4.0.3. First, five Multiple-Children-of-Twins-and-Siblings (MCoTS) models assessed genetic relationships between mothers' adult ADHD symptoms and child ADHD, ODD, CD, anxiety, and depression symptoms at age 8. Second, five extended bivariate twin models assessed genetic relationships between children's early ADHD symptoms at age 5 and their later ADHD, ODD, CD, anxiety, and depression symptoms at age 8. We adapted these bivariate twin models to account for the additional degrees of genetic relatedness between siblings (50%), half-siblings (25%), and cousins (12.5%), and to constrain the shared environmental effect in cousins and paternal half-siblings to zero (as most cousins and paternal half-siblings do not share a household).

MCoTS analyses are an extension of the Children-of-Twins (CoT) design, a quasi-experimental method of determining the extent to which a parent-offspring association is attributable to shared genetic influences (McAdams et al., 2018). Where bivariate twin models can estimate genetic influences on covariance between phenotypes across twins, CoT models can estimate genetic influences on covariance between phenotypes across parents and children. Using extended families of twin parents and children, these models derive their power from the comparison of parent-offspring correlations and avuncular correlations (those between children and their aunt/uncle). Namely, children of identical twins share the same proportion of genes with their parent as they do with their aunt or uncle, but share a rearing environment only with their own parent. This separation of genetic and environmental influences allows for inferences as to the extent to which covariance between parents and their offspring is explained by shared genetic influences, with any excess parent-offspring similarity suggesting direct phenotypic transmission through exposure to the parent phenotype. The MCoTS design extends CoT analyses to include sibling, half-sibling and cousin parents, and multiple children per parent. This allows for larger datasets of extended families to be used, increasing statistical power. The full MCoTS model specification is shown in Supplementary Figure S3, while the extended bivariate twin model specification is shown in Supplementary Figure S4.

In all analyses we controlled for the effects of maternal age, parity (mothers' number of previous births), and children's year of birth on all variables, and the effects of child sex on child measures.

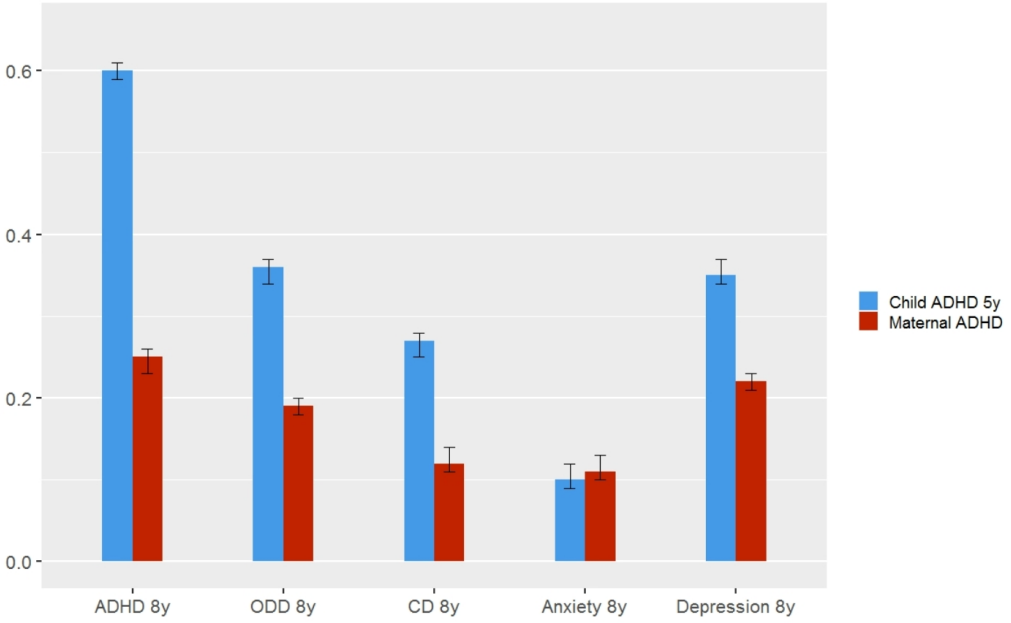
D.W. conducted all data preparation on raw item-level phenotypic data from MoBa. T.M., L.H., Y.A., D.W., and I.B. jointly created scripts for identifying and grouping extended families in MoBa by kinship group. D.W. adapted standard CoT and bivariate twin scripts (jointly written by T.M., L.H., and F.R.) and conducted all MCoTS and extended bivariate twin analyses.

2.4. Results

Descriptive statistics of all measures are shown in Supplementary Table S5. Log-likelihood significance tests output as standard by the OpenMx package were used to determine whether constraining shared environmental and genetic effects to zero resulted in a significant worsening of model fit compared to full models. Model fit comparisons and standardised parameter estimates from preliminary univariate models, testing the significance of genetic and shared environmental effects on adult ADHD symptoms, are shown in Supplementary Tables S6a and S6b. Formal model fit comparisons from MCoTS and extended bivariate twin models, testing genetic effects on covariance between adult and early child ADHD symptoms and each child symptom measure at age 8, are shown in Supplementary Tables S7 and S8. Standardized parameter estimates from these adult ADHD models and early child ADHD comparison models are shown in Supplementary Table S9.

Comparisons of results from adult ADHD (MCoTS) and child ADHD (extended bivariate twin) models are shown in Figures 1 and 2. Phenotypic correlations followed an expected pattern, with twin child-child correlations being larger than intergenerational adult-child correlations. Genetic influences on adult ADHD symptoms were correlated with genetic influences on children's ADHD (r_G = .55), ODD (r_G = .80), CD (r_G =.44), anxiety (r_G =.72), and depression (r_G = 1) symptoms at age 8. Similarly, genetic influences on child ADHD symptoms at age 5 were correlated with genetic influences on child ADHD (r_G = .84), ODD (r_G = .70), CD (r_G =.43), anxiety (r_G =.41), and depression (r_G = .64) symptoms at age 8.

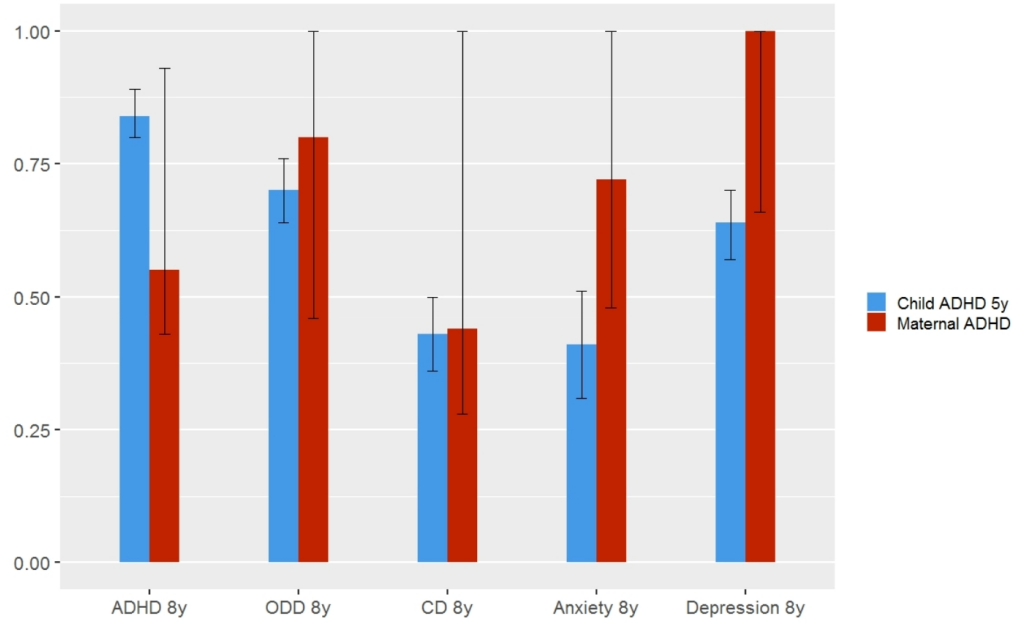
Figure 1. Bar plots of phenotypic correlations from MCoTS and extended bivariate twin models



Bar heights show estimates (95% CI) of phenotypic correlations between each child symptom measure at age 8 (on X axis) and early child ADHD (blue bars) and adult ADHD (red bars).

Children's ADHD and comorbid symptoms at age 8 shared roughly equal genetic overlap with adult ADHD symptoms and child ADHD symptoms at age 5 (Figure 2). Notably, for child ODD, CD, anxiety, and depression symptoms, point estimates of genetic correlations with adult ADHD symptoms were higher than those of correlations with child ADHD symptoms at age 5. However, confidence intervals were markedly wider for adult ADHD estimates (with some upper bounds reaching 1), likely due to the lower power to estimate intergenerational genetic correlations in MCoTS models compared to twin genetic correlations in bivariate twin models (McAdams et al., 2018). Importantly, none of the lower bounds of genetic correlations were close to zero, suggesting confidence in the genetic associations observed. Overall, confidence intervals of all adult ADHD genetic correlations were overlapping with their equivalent child ADHD correlations.

Figure 2. Bar plots of genetic correlations from MCoTS and extended bivariate twin models



Bar heights show estimates (95% CI) of genetic correlations between each child symptom measure at age 8 (on X axis) and early child ADHD (blue bars) and adult ADHD (red bars).

2.5. Discussion

We set out to address a gap in research regarding the aetiological overlap between ADHD symptoms in childhood and adulthood. We did this by assessing the extent to which mothers' adult ADHD symptoms, and children's own early ADHD symptoms at age 5, were genetically correlated with children's mid-childhood symptoms of ADHD and several common comorbid disorders at age 8. At the phenotypic level, children's own early ADHD symptoms were unsurprisingly more highly correlated with their later ADHD and comorbid symptoms by mid-childhood, as compared to mothers' adult ADHD symptoms. However, genetic influences on both adult ADHD symptoms and early child ADHD symptoms shared similarly high correlations with genetic influences on children's ADHD and comorbid symptoms in mid-childhood.

Our findings provide novel evidence for a shared genetic architecture between ADHD symptoms in childhood and adulthood, insofar as the genetic influences on ADHD symptoms in mothers were highly correlated with genetic influences on ADHD symptoms in their children at age 8. While past twin research has provided evidence for overlap between ADHD symptoms in childhood and late adolescence to early adulthood, no research to date has directly assessed genetic overlap between ADHD symptoms in childhood and across a broader age range in adulthood (i.e., beyond young adulthood).

More broadly, while there has been research on genetic overlap between ADHD and comorbid disorders in childhood (Michelini et al., 2015; Tuvblad et al., 2009) we are not aware of any research assessing the extent to which ADHD symptoms in adults share genetic overlap with children's symptoms of comorbid disorders. Our results demonstrate a very similar pattern of genetic overlap between ADHD symptoms measured at a range of ages in adulthood, and symptoms of ADHD and several common comorbid disorders in mid-childhood. This suggests that genetic influences on ADHD symptomatology in adulthood substantially overlap with those on symptoms of ADHD and comorbid disorders in mid-childhood. In other words, it is unlikely that adult ADHD symptoms in our sample represent a distinct aetiological entity from child ADHD symptoms. Our results do not directly address nor rule out the possibility of a late-onset form of ADHD. However, if an aetiologically distinct later-onset form of ADHD exists in some adults, our findings suggest that it is quite rare in our sample, since it did not drastically impact our estimates of genetic overlap with children's ADHD and comorbid symptoms.

It is also notable that in a large sample of mothers and children not selected for clinically significant ADHD (most of whom would not meet diagnostic cut-offs), genetically driven correlations were found between mothers' adult ADHD symptoms and children's ADHD and comorbid symptoms. This suggests that even if their symptoms are at sub-clinical levels, mothers transmit to their children genetic risk factors for the wider array of symptomatology that co-occurs with ADHD in clinically significant cases. In other words, mothers with mildly elevated hyperactivity, inattention, etc., may pass on genetic risk for mildly elevated

impulsivity, oppositionality, anxiety, etc., in children. This is in line with growing evidence that psychiatric and neurodevelopmental disorders represent the extreme ends of normally distributed traits in the population, and co-occur as a rule, rather than being discrete and non-overlapping categories of severe disorder only present among those with specific risk factors (Kotov et al., 2018).

2.5.1. Strengths and limitations

We investigated our hypotheses using a large representative national birth registry cohort including longitudinal child and parent data at a range of ages. Linking this dataset by extended family relationships with birth registry data allowed us to estimate genetic correlations between adult and child traits. This novel approach enabled us to bridge the gap in genetically sensitive data on ADHD and comorbid symptomatology extending from childhood into adulthood. Another key strength of the study was that mothers reported their ADHD symptoms well into adulthood, with the youngest being aged 20 and the oldest aged 48 at the time of self-report.

A potential limitation of our analyses was that mothers reported both their own and children's symptoms. While maternal ratings of child symptoms are likely valid (as mothers typically spend the most time with children), shared method bias could cause mothers' self and child ratings to be excessively correlated due to their own attitudes or traits (Deault, 2010). However, this is unlikely to have inflated our estimates of genetic overlap, as these rely on avuncular correlations, i.e., between an aunt's self-rated ADHD symptoms and their niece or nephew's mother-rated symptoms. Additionally, mothers reported their own ADHD symptoms and children's earlier and later symptoms several years apart (when children were aged 3, 5 and 8 respectively) reducing the likelihood of time-specific reporting biases. Systematic and/or heritable biases could still inflate estimates of genetic overlap, for instance if both mothers in an extended family had higher ADHD symptoms, so tended to be less attentive to children's symptoms and therefore consistently underreported these. However, several studies have

reported a lack of evidence that maternal ADHD symptoms bias their reports of children's ADHD symptoms (Faraone et al., 2003; Jassy, 2009).

2.5.2. Conclusions

Our analyses address a lack of genetically sensitive research assessing aetiological overlap between ADHD symptoms in childhood and throughout adulthood, as well as overlap with comorbid symptoms. Our findings add to the evidence base for the continuity of childhood ADHD symptomatology into and across adulthood, by demonstrating a genetically driven co-occurrence of adult ADHD symptoms in mothers, and a typical pattern of ADHD-related symptomatology in their children. In sum, our results suggest that ADHD symptoms in childhood and adulthood share a common genetic architecture and are not aetiologically distinct.

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3. Direct and indirect genetic effects on child ADHD symptoms: Trio-GCTA analyses in a large Norwegian birth registry cohort.

This chapter is a manuscript that will soon be submitted for peer-review. Supplementary materials for this chapter, as detailed in the text, are included in Appendix 2 (page 202).

Wechsler, D. L., Eilertsen, E. M., Ahmadzadeh, Y. I., Cheesman, R., Adamo, N., Hannigan, L. J., Ystrom, E., McAdams, T. A. (in prep.). Direct and indirect genetic effects on child ADHD symptoms: Trio-GCTA analyses in a large Norwegian birth registry cohort.

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3.1. Abstract

Background: Indirect genetic effects of family members may exert an environmental influence on children's ADHD symptomatology. These effects may be subsumed within estimates of the effects of children's own genotypes on their ADHD symptoms, potentially biasing our understanding of genetic influence. Estimates of genetic nurture can themselves also be informative regarding family environmental influences on development. We set out to quantify the indirect genetic effects of parents' genotypes on children's ADHD symptoms as measured in early and mid-childhood.

Methods: We analysed data from genotyped trios of children, mothers, and fathers from the Norwegian Mother, Father and Child Cohort Study (MoBa) birth cohort. Child ADHD data were available for 11,538 trios at age 5 (children 51.4% male), and 11,526 trios at age 8 (children 50.5% male). Trio-GCTA was used to jointly estimate direct genetic effects of children's genotype and indirect effects of mothers' and fathers' genotypes on children's ADHD symptoms at each age.

Results: At age 5, maternal (but not paternal) indirect genetic effects explained a substantial portion of variance in children's ADHD symptoms while child direct genetic effects were minimal. At age 8, child direct genetic effects were largest, while the joint indirect effects of maternal and paternal genotypes explained around a third of the genetic variance in ADHD symptoms. Notably, simultaneously estimating direct and indirect genetic effects (which had negative covariances) yielded a higher estimate of direct genetic effects in mid-childhood.

Conclusions: We find evidence for genetic nurture effects on child ADHD symptomatology in early and mid-childhood, suggesting that maternal and, later, paternal genotypes exert indirect effects on children's symptoms after accounting for any direct effects of their own genotype. In mid-childhood, these indirect effects appeared to act in an opposing direction to child direct genetic effects, potentially reflecting a regulating role of parents.

3.2. Introduction

ADHD is a neurodevelopmental disorder comprising developmentally inappropriate and impairing symptoms of inattention, hyperactivity and/or impulsivity (Faraone et al., 2021). Symptoms typically have a childhood onset and persist at clinically severe or subthreshold levels into at least young adulthood (Nigg et al., 2020). A wide range of twin studies have shown that ADHD is highly heritable, with 60-90% of variance in ADHD being explained by genetic factors and 10-40% explained by environmental factors (Sciberras et al., 2017). However, genetic and environmental influences do not operate independently, and estimates of genetic and environmental effects can be inaccurate if the methods used to obtain them do not adequately account for gene-environment interplay (Rijsdijk & Sham, 2002). While genetic research is often implicitly focused on understanding direct genetic effects—the direct influence of an individual's genotype on their own phenotype—several recent studies have emphasised that phenotypes are also subject to the indirect genetic effects of other peoples' genotypes via the environment (Kong et al., 2018; Young et al., 2018). For example, a child's household environment is in part shaped by the genetically driven behaviours of parents and siblings, which can exert genetic nurture effects on children's behaviour, physical health, and other developmental processes (Kong et al., 2018). Genetic nurture effects can correlate with direct genetic effects (a form of passive gene-environment correlation; rGE), and thus potentially bias estimates of direct genetic effects. Genetic nurture effects are also interesting in their own right as they can provide a broad indication of the impact of family members on children's development.

Recently, several approaches have been used to estimate genetic nurture effects on a focal individual's phenotype using genotype data from their family members. One approach uses polygenic scores (PGSs), individualised scores of genetic liability for a phenotype constructed using the weighted effect sizes of single-nucleotide polymorphisms (SNPs) found to account for phenotypic variance in genome-wide association studies (GWAS) (Rosenberg et al., 2019). When individual PGSs are constructed for children and their parents, and their effects

modelled jointly, genetic nurture effects can be inferred when parental PGSs predict child phenotypes after accounting for the effects of child genotype (Balbona et al., 2021). Taking this approach, a recent study by Pingault et al. (2021) (currently available as a pre-print) found that mothers' PGSs for autism spectrum disorder (ASD) and neuroticism (but not ADHD) predicted children's ADHD symptoms over and above their own PGS for ADHD. This provides evidence for maternal genetic nurture effects children's symptoms, but that these were driven by mothers' genetic risk for ASD and neuroticism rather than ADHD itself. Another study by de Zeeuw et al. (2020) found that children's ADHD symptoms were associated with their own PGSs for adult ADHD and educational attainment, but not with PGSs constructed from the 50% of non-transmitted SNPs from each parent. This was interpreted as indicating a lack of genetic nurture effects on child ADHD symptomatology. However, it should be noted that PGS-based studies only estimate the effects of SNPs that are included in each PGS, which represent only a fraction of overall genetic variance, namely that specifically associated with the measured phenotype.

Genetic nurture effects can also be estimated using extensions of SNP heritability methods such as genome-wide complex trait analysis (GCTA), a method of estimating the portion of phenotypic variance accounted for by variance in common SNPs (Yang et al., 2011). While conventional GCTA aims to estimate direct genetic effects, it does not account for the fact that the phenotypic variance accounted for by any given SNP in an individual could be due in part to genetic nurture effects, i.e., by affecting the behaviour of family members who share the same SNP (Young et al., 2018). For example, SNPs exerting direct genetic effects on children's ADHD symptoms may, in parents, affect the harshness or consistency of their parenting, which may exert additional effects on children's ADHD symptoms (Johnston et al., 2012; Park et al., 2017). These effects can be quantified by jointly modelling the indirect effects of parent genotypes alongside the direct genetic effects of the child genotype. For example, maternal GCTA (Eaves et al., 2014) and trio-GCTA (Eilertsen et al., 2021) can estimate child, maternal, and paternal genetic effects separately, while Relatedness Disequilibrium

Regression (RDR) estimates child genetic effects alongside a combined parental genetic effect (Young et al., 2018). Notably, for RDR and trio-GCTA, the availability of genetic data from both parents allows for the unbiased estimation of SNP heritability (i.e., direct child genetic effects) while accounting for genetic nurture effects and any effects of population stratification and assortative mating.

A key strength of trio-GCTA and related methods is that they capture the cumulative contribution of all heritable characteristics of family members on a child phenotype up to the time of measurement, without needing to measure specific characteristics (Cheesman et al., 2020; Eilertsen et al., 2021). This can complement and inform existing research efforts to assess the importance of family-level influences on child development. For example, observational researchers have sought to establish the effects of parenting on children's ADHD symptomatology, typically relying on retrospective parent reports of engaging in specific behaviours over a certain time period, which are hindered by recall and rater biases (Claussen et al., 2022; Deault, 2010; Putnick, 2019). To date, a small number of genetically sensitive studies have demonstrated that certain parental risk factors, such as child-directed hostility and abuse/neglect, predict or are associated with child ADHD symptomatology (Harold et al., 2013; Stern et al., 2018). However, the relative importance of specific parent behaviours in the development of ADHD is difficult to discern among the wide range of inter-correlated behaviours and parent-child interactions that occur across development. While it is virtually impossible to simultaneously measure all child exposures that may impact ADHD, trio-GCTA provides an opportunity to estimate the cumulative impact of all heritable parent behaviours and characteristics up to a given age.

Recently, Eilertsen et al. (2022) used trio-GCTA to assess direct and indirect genetic effects on several child externalising phenotypes in 9,675 trios of children and parents from the Norwegian Mother, Father and Child Cohort Study (MoBa) birth cohort. They reported substantial indirect genetic effects of parents' combined genotype on children's conduct, inattention, and hyperactivity symptoms (but not oppositional defiant symptoms) at age 8,

alongside the larger direct genetic effects of children's own genotype on all measures. While some portion of these indirect effects could be due to assortative mating and residual population stratification, these results provide evidence for genetic nurture effects on several externalising phenotypes in mid-childhood, including the two main symptom clusters of ADHD.

Trio-GCTA could also help to better understand the relative importance of genetic and environmental effects on ADHD symptoms across development. Twin research on ADHD has shown a slight increase in the heritability of ADHD from early to mid-childhood, with non-shared environmental effects explaining the remaining variance (Kuntsi et al., 2005). Genetic effects have also been shown to account for most of the stability of ADHD symptoms across childhood, adolescence, and early adulthood, although newly arising genetic and non-shared environmental factors do account for additional variance at later ages (Chang et al., 2013; Kuntsi et al., 2005). As discussed previously, however, estimates of genetic and environmental effects may be biased by passive rGE including unmeasured genetic nurture effects. Trio-GCTA can shed light on age-related aetiological differences in ADHD by quantifying the relative importance of direct and indirect genetic effects at different ages. However, to date, no studies have explored developmental change in ADHD using methods that can distinguish direct and indirect genetic effects.

Here, we set out to assess direct and indirect genetic effects on children's ADHD symptomatology using trios of children and their parents from the MoBa cohort. We were interested in whether there were genetic nurture effects on children's symptoms in early childhood, and whether there were age-related changes in the relative importance of direct and indirect effects on children's symptoms by mid-childhood. We use clinically oriented measures of ADHD symptoms constructed to discriminate clinical cases from community controls.

3.3. Methods

3.3.1. Sample

MoBa is a prospective population-based birth registry cohort of 114,500 children, 95,200 birth mothers and 75,200 birth fathers in Norway (Magnus et al., 2016). Data collection for MoBa covered pregnancies across all of Norway from 1999 to 2008, with 40.6% of eligible pregnant women consenting to participate in the study. The current study is based on version 12 of the quality-assured data files released for research in January 2019.

After genetic quality control and selection of measures, our analytic sample consisted of 11,538 genotyped trios where child ADHD data were available at age 5, and 11,526 trios where data were available at age 8. These subsamples were largely overlapping, with 8,123 trios with child ADHD data available at both ages. There was a roughly equal number of boys and girls at both ages (51.4% and 50.5% male at ages 5 and 8 respectively).

3.3.2. Ethics

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics.

3.3.3. Measures

Mothers reported children's ADHD symptoms at age 5 years using the Conners Parent Rating Scale-Revised (CPRS-R) Short Form. The CPRS-R is a well-validated measure of parent-reported child ADHD symptoms, constructed from items found to best discriminate clinically diagnosed children from community controls matched for age, sex, and ethnicity (Conners et al., 1998). It includes 12 items assessing children's inattentive, impulsive and hyperactive symptoms. Mothers reported children's ADHD symptoms at age 8 years using the Revised Short Form of the Parent/Teacher Rating Scale for Disruptive Behavior (RS-DBD). The RS-DBD is a measure of parent-reported child ADHD symptoms which includes 18 items assessing children's inattentive, impulsive and hyperactive symptoms (Silva et al., 2005).

Scores on the CPRS-R and the RS-DBD have excellent internal consistency (Cronbach's alpha = .88; .91). For the overlapping set of 8,123 trios where child ADHD symptom measures were available at both ages 5 and 8, mothers' ratings of children's ADHD symptoms were moderately correlated (Pearson's *r* = .55). For both child ADHD scales, mean composites were computed when mothers responded to more than half of items on a scale. Of mothers who responded to more than half of items on the 5-year and 8-year ADHD scales, 96.1% and 96.6% respectively responded to all items. There were no notable differences in sample means, standard deviations, nor normality between the full sample and a subsample including only those who responded to all items.

3.3.4. Analyses

We controlled for the effects of maternal age, parity (mother's number of births), and child sex by regressing their effects out of child ADHD measures. In addition, to minimise the contribution of population stratification, principal components of genetic ancestry were computed for mothers and fathers using the –within and –pca-clusters commands in PLINK (Chang et al., 2015), based on an LD-pruned version of the final quality-controlled genotype data in MoBa. The effects of 40 principal components (the first 20 from each parent) were regressed out of child ADHD measures. Genotype batch groups were also regressed out to control for batch effects. We applied Box-Cox transformations (Osborne, 2010) on the resulting standardised residuals to reduce non-normality.

Genomic relatedness matrices (GRMs) were computed for all individuals (Yang et al., 2011) and pairs whose SNP-based genetic correlations exceeded 0.10 (who were not parent-child pairs) were excluded from analyses, to minimise the potential for confounding by passive rGE (e.g. whereby genetic relatedness correlates with environmental similarity). Trio-GCTA analyses were then conducted using the VCModels package (Eilertsen et al., 2021) in Julia 1.5.3. (Bezanson et al., 2017). Full models simultaneously estimated the direct effects of children's genotype and the indirect effects of maternal and paternal genotypes. Covariances

between these effects were also modelled, while all variance not accounted for by SNP variation was captured in a residual term (Eilertsen et al., 2021). Several nested models were tested, with Combined models constraining maternal and paternal effects to be equal, providing a combined parental indirect genetic effect, Direct models estimating only child direct genetic effects (equivalent to standard GCTA), and Null models constraining all genetic effects to zero. Standard log-likelihood significance tests were used to rule out nested models with significantly worse fit compared to Full models. Akaike's Information Criterion (AIC) was then used to compare the relative fit of Full models and any nested models that were not significantly worse fitting, favouring more parsimonious models with a lower AIC (Akaike, 2011).

D.W. conducted all data preparation on raw item-level phenotypic data from MoBa. E.E., Y.A., and D.W. jointly contributed to scripts for linking phenotypic data with SNP data from MoBa Genetics. R.C. conducted quality control on SNP data from MoBa Genetics and computed principal components of genetic ancestry for those data. E.E. created scripts for computing GRMs and conducting Trio-GCTA model fitting using the VCModels package for Julia. D.W., Y.A., and E.E. jointly adjusted and troubleshot these general scripts when computational or modelling issues arose. D.W. computed GRMs specific to the analytic sample in the current study and conducted all Trio-GCTA analyses.

3.4. Results

Descriptive statistics for the sample are displayed in Supplementary Table S1. Standardised parameter estimates and fit statistics for all models are displayed in Table 1. In the age 5 Full model, child direct genetic effects explained 0.6% of variance in child ADHD symptomatology while maternal indirect genetic effects explained 9.9% of variance. Paternal indirect genetic effects explained no variance, and the Combined model constraining maternal and paternal effects to be equal was a significantly worse fit to the data than the Full model. The Direct and Null models were not significantly worse fitting compared to the Full model, although the AIC

for the Full model was very similar, indicating comparable overall model fit. As statistical power was likely an issue, and the nested Direct and Null models forcibly attribute variance explained by the maternal genotype (the largest variance component) to child direct genetic effects or to the residual non-genetic component, we focus our interpretations mainly on the Full model.

Table 1. Standardised parameter estimates (SEs) and model fit statistics from age 5 and age 8 trio-GCTA analyses

Included are Full models estimating all genetic effects separately, Combined parental effects models constraining maternal and paternal genetic effects to be equal, Direct models constraining parental genetic effects to zero, and Null models constraining all genetic effects to zero.

Effects on child ADHD symptoms at 5 years											
Model	σ_o^2	σ_m^2	σ_p^2	σ_{om}	σ_{op}	σ_{mp}	σ_ϵ^2	*-2LL*	*AIC*	*df*	*p-value*
Full	.006 (.016)	.099 (.048)	.000 (.001)	.024 (.028)	.000 (.007)	-.001 (.028)	.871 (.041)	22,745.58	27,761.58	7	
Combined	.001 (.007)	.030 (.027)*		.003 (.018)*		-	.933 (.041)	27,753.73	27,763.73	4	0.043
Direct	.025 (.039)	-	-	-	-	-	.975 (.042)	27,756.32	27,762.32	2	0.057
Null	-	-	-	-	-	-	1 (0)	27,756.73	27,760.73	1	0.084
Effects on child ADHD symptoms at 8 years											
Model	σ_o^2	σ_m^2	σ_p^2	σ_{om}	σ_{op}	σ_{mp}	σ_ϵ^2	*-2LL*	*AIC*	*df*	*p-value*
Full	.174 (.078)	.077 (.045)	.081 (.053)	-.013 (.049)	-.079 (.056)	.064 (.040)	.761 (.057)	27,563.79	27,579.79	7	
Combined	.161 (.081)	.072 (.040)*		-.044 (.050)*		-	.783 (.057)	27,567.68	27,577.68	4	0.274
Direct	.148 (.041)	-	-	-	-	-	.852 (.042)	27,572.23	27,578.23	2	0.134
Null	-	-	-	-	-	-	1 (0)	27,585.96	27,589.96	1	0.001

σ_o^2, σ_m^2, σ_p^2 = Child, maternal and paternal genetic effects; σ_{om}, σ_{op}, σ_{mp} = Correlations between child, maternal and paternal genetic effects; σ_ϵ^2 = Variance not explained by genetic effects. *Combined models jointly estimate parental genetic effects (σ_{pp}^2) and correlations between child and parental genetic effects (σ_{opp}).

In the age 8 Full model, child direct genetic effects explained 17.4% of variance in children's ADHD symptomatology while maternal and paternal indirect genetic effects explained 7.7% and 8.1% of variance, respectively. The Combined model constraining maternal and paternal effects to be equal did not display significantly worse fit and had a lower AIC than the Full model, suggesting that modelling maternal and paternal effects separately did not substantively improve explanatory power. Parameter estimates from the Combined model were also similar, with child direct genetic effects explaining 16.1% of variance in child ADHD

symptomatology, while parental indirect genetic effects explained 7.2% of variance. Notably, while the Null model was a significantly worse fit to the data, the Direct model constraining parental effects to zero was not significantly worse fitting compared to Full nor Combined models. This suggests that explanatory power was not substantially reduced when excluding indirect genetic effects of parents. However, the AIC was lower for the Combined model, and excluding parental indirect effects resulted in a lower estimate of direct effects of children's genotype in the Direct model. Covariance between child direct and parent indirect genetic effects was negative in the Combined model, suggesting that indirect effects may have been suppressing estimates of direct effects when not modelled. As a result, we focus our interpretations mainly on the Combined model.

3.5. Discussion

We set out to assess whether maternal and paternal genotypes exerted indirect effects on children's ADHD symptomatology, over and above the direct effects of children's own genotype. We also assessed the potential for developmental change in the magnitude and relative proportions of direct and indirect genetic effects from early to mid-childhood. At age 5, we found that when estimating both direct and indirect genetic effects, maternal indirect effects were by far the largest while child direct genetic effects were minimal and paternal indirect genetic effects were zero. At age 8, however, there were substantial direct genetic effects and both maternal and paternal indirect genetic effects. Maternal and paternal effects in mid-childhood were equal and could be combined into a joint parental effect, explaining around half as much variance in child ADHD symptoms as direct genetic effects.

Broadly, our findings provide evidence for genetic nurture effects on children's ADHD symptomatology in early and mid-childhood, insofar as mothers' and/or fathers' genotypes accounted for variance in children's ADHD symptoms over and above the direct effect of children's own genotype. Previously, de Zeeuw et al. (2020) and Pingault et al. (2021) found no evidence for genetic nurture effects of parents' ADHD PGSs on children's ADHD

symptoms. This was despite the latter study using the same age 8 child ADHD measure as our study, also in a subset of the MoBa sample. The key distinction of PGS approaches is that their inferences of genetic nurture rely on parents' PGSs for specific phenotypes, which include only those SNPs that explain variance in that specific parental phenotype (itself typically measured at one point in time). Notably, Pingault et al. (2021) did find that child ADHD symptoms were predicted by mothers' PGSs for ASD and neuroticism. In contrast to PGS approaches, trio-GCTA captures the indirect effects of all genotyped parental SNPs on a child phenotype, maximising the chance of observing indirect genetic effects. Indeed, using trio-GCTA, Eilertsen et al. (2022) found evidence for substantial genetic nurture effects on three of the four externalising phenotypes they analysed, including inattention, hyperactivity, and conduct symptoms. It may be concluded, then, that there are genetic nurture effects on children's ADHD symptoms, but these do not appear to be caused by SNPs that raise parents' own risk for ADHD. It should be noted that estimates of indirect genetic effects from both trio-GCTA and PGS approaches can also include residual population stratification effects, i.e., the effects of environmental factors that are correlated with SNP variation in parents but are not caused by parent characteristics or behaviours. These could include social or other environmental effects associated with specific geographical regions or socioeconomic conditions.

The relative lack of direct genetic effects at age 5 when jointly modelling direct and indirect genetic effects was surprising, and appeared to suggest that children's common SNP variation had almost no effect on their ADHD symptomatology in early childhood above and beyond their mothers' indirect genetic effects. One explanation for this is that at earlier ages, mothers' ratings of their children's ADHD symptoms could more strongly reflect heritable rater biases, as maternal perceptions of children's developmental level largely rely on their observations of children's behaviour within the context of the home environment. This may mask children's underlying executive deficits relative to typically developing children of the same age. However, after children enter compulsory formal schooling (at age 6 in Norway), those with

higher ADHD symptomatology are likely to encounter various cognitive and behavioural demands that exceed their developmental level. Mothers' ratings of children's ADHD symptoms may then begin to reflect feedback from teachers and other parents about their children's issues with learning or disruptive behaviour (particularly if these are severe enough to warrant learning support or clinical intervention), and so may be more representative of their children's objective developmental level relative to other children. Indeed, there is some evidence that mother ratings of child ADHD symptoms and behaviour problems are prone to subjective biases based on contextual factors, mothers' attributions of the causes of children's behaviour, and mothers' parenting self-efficacy (Park et al., 2022; Sollie et al., 2013). In relation to our findings, such biases may have played less of a role after mothers received wider feedback on their children's behaviour outside the home environment.

Another notable finding was that in mid-childhood, estimates of direct genetic effects were higher when parental indirect genetic effects were estimated versus when they were not. This was surprising given that unmeasured indirect genetic effects are typically suggested to account for a portion of estimates of direct genetic effects (i.e., SNP heritability), thus inflating them if unmodelled (Kong et al., 2018). In turn, it is expected that modelling them should result in a smaller, though unbiased, estimate of direct genetic effects (Young et al., 2018). The opposite was the case in our analyses; modelling direct and indirect effects together revealed a stronger direct effect of children's own genotype. While this may seem counterintuitive, it can be explained by the negative covariances between direct and indirect genetic effects in mid-childhood. Negative covariances between direct and indirect genetic effects are a common finding in the animal literature (Lee, 2002), and have been reported in relation to gestational weight gain in humans (Warrington et al., 2018). Recent trio-GCTA studies have also reported negative covariances between direct and indirect genetic effects for psychiatric and behavioural phenotypes, including children's depression, conduct, and inattention symptoms (Cheesman et al., 2020; Eilertsen et al., 2022). Negative covariances can occur when child and parent genotypes contribute to phenotypic variance in opposing directions

(Cheesman et al., 2020; Eilertsen et al., 2022). For instance, where children's own genotype may contribute to their ADHD symptoms in one direction, their parents' genotypes could exert opposing or regulating effects. In our analyses, direct genetic effects in children could have been partially cancelled out by unmodelled opposing indirect genetic effects of parents, reducing the apparent overall genetic variance explained. Interestingly, in the trio GCTA analyses by Eilertsen et al. (2022), estimates of direct genetic effects on conduct and inattention symptoms were also smaller when models did not include negatively covarying indirect genetic effects. In contrast, for hyperactivity symptoms direct and indirect effects were positively covarying, and estimates of direct genetic effects were larger (i.e., inflated) in models that did not include indirect genetic effects. This highlights the possibility that genetic nurture effects can not only inflate estimates of direct genetic effects, but may deflate or suppress estimates if they act on the phenotype in an opposing direction to direct effects.

3.5.1. Strengths and limitations

We used a large, representative sample of genotyped child, mother and father trios combined with a novel methodology to assess the indirect effects of maternal and paternal genotypes on children's ADHD symptomatology in early and middle childhood, over and above the direct effects of children's own genotype. This allowed us to assess the cumulative effect of all parental behaviours, characteristics, and associated environmental exposures tagged by parental SNPs on children's ADHD symptoms up to ages 5 and 8. However, there were several limitations. First, our sample size likely resulted in inadequate power to detect small effects as evidenced by the large standard errors for many of our parameter estimates. This likely contributed to challenges in distinguishing best-fitting models. This issue will be addressed as larger samples of genotyped trios become available. Second, as discussed, children's ADHD symptoms were reported by mothers, so ratings could have been subject to rater biases and mothers' perceptions based largely on their own interactions with children. Father, teacher, and clinician ratings could be used in future to minimise rater bias and ensure measures capture children's ADHD symptomatology across a range of contexts.

3.5.2. Conclusions

Our findings provide evidence for genetic nurture effects on child ADHD symptomatology in early and mid-childhood, insofar as mothers' and fathers' genotypes exerted indirect effects on children's ADHD symptoms over and above the effects of children's own genotype. The cumulative contribution of all environmentally mediated indirect genetic effects was substantial in both early and mid-childhood. However, maternal genetic effects were the main source of genetically driven symptom variation in early childhood, while in mid-childhood the joint genetic effect of parents was around half as important as children's own genetic risk.

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4. Does parental hostility mediate associations between early ADHD symptoms and subsequent ODD and anxiety symptoms in early adolescence? A longitudinal adoption-at-birth investigation.

This chapter is a manuscript that will soon be submitted for peer-review. Supplementary materials for this chapter, as detailed in the text, are included in Appendix 3 (page 203).

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4.1. Abstract

Comorbid disorders are the norm in ADHD but the role of environmental risk factors for children's development of comorbid symptomatology remains unclear. We investigated whether associations between children's early ADHD symptoms and their later ODD and anxiety symptoms were mediated by evoked parental hostility. Our sample comprised 294 adopted children (57.2% male; 55.3% white) and their adoptive parents from the US-based Early Growth and Development Study. We assessed reciprocal relationships between adoptive parents' self-reported hostility and partner-rated child ADHD, ODD, and anxiety symptoms at ages 6, 8 and 11 using cross-lagged panel models (CLPMs). We compared results derived using several variants of the CLPM (the standard CLPM, the Random Intercept CLPM, and the CL2PM which contains 'lag-2' paths spanning more than two waves). We did not find evidence that evoked parental hostility mediated relationships between children's early ADHD symptoms and later ODD and anxiety symptoms. Instead, we found evidence for unidirectional effects wherein early paternal hostility predicted ODD and ADHD symptoms but not vice versa. These findings are discussed along with a critical comparison of results from the different CLPMs.

4.2. Background

Attention-deficit hyperactivity disorder (ADHD) is a highly heritable neurodevelopmental disorder characterised by elevated hyperactivity, impulsivity and inattention. Alongside these core symptoms, people with ADHD have high rates of comorbid disorders which account for a substantial portion of long-term functional impairment in key areas of life (Gordon et al., 2006). Common childhood comorbidities include oppositional defiant disorder (ODD), conduct disorder (CD), mood and anxiety disorders, autism spectrum disorder and intellectual disability (Kooij et al., 2010). The mechanisms behind these high rates of comorbidity are not yet clear, but likely comprise a complex interplay of genetic and environmental risk factors (Reale et al., 2017). For example, there is evidence for substantial genetic overlap between ADHD and

other externalising conditions such as ODD and CD (Tuvblad et al., 2009), and for some genetic overlap with mood and anxiety disorders (Du Rietz et al., 2017; Michelini et al., 2015). Some have also posited ways in which ADHD-related executive impairments may cause, or be caused by, some symptoms of commonly co-occurring disorders. In the context of established theories of ADHD, Schatz and Rostain (2006) outlined several potential mechanisms of comorbidity with anxiety. For instance, ADHD-related deficits in information processing speed may cause difficulty conforming to social norms or academic expectations, causing anxiety when environmental demands exceed cognitive processing ability. Separately, higher levels of anxiety may cause the disruptions in arousal, behavioural activation and sustained effort commonly seen in ADHD.

A relatively understudied area of research concerns environmental influences on comorbidity, particularly parenting factors. While parenting is hypothesised to play a substantial role in children's development from birth through to at least late adolescence, there is a lack of rigorous research on its role in the development of comorbid disorders in the context of ADHD. However, there are several indications that parenting may be important for children's ADHD-related developmental outcomes. Several negative or suboptimal parenting behaviours, such as child-directed hostility, reactive and inconsistent parenting, have been shown to associate with, and often prospectively predict, symptoms of ADHD and common comorbid disorders in children (Deault, 2010; Harold et al., 2013). These parenting behaviours have been shown to be more common in parents with ADHD (Johnston et al., 2012), and several studies have suggested that negative parenting behaviours such as corporal punishment and over-reactivity may mediate the intergenerational transmission of core ADHD symptoms from parent to child (Breaux et al., 2017; Moroney et al., 2017; Tung et al., 2015). Taken together, these findings suggest that children who inherit genetic risk for ADHD from their parents are also likely to be exposed to the environmental effects of ADHD-related differences in parenting. This highlights the possibility that the development of comorbid disorders (and

potentially the severity of core ADHD symptoms) may rely in part on adverse parenting behaviours that are more common in parents of children with ADHD.

The role of parenting in comorbidity in ADHD is difficult to study, and most research to date suffers from several important limitations. A systematic review by Deault (2010) summarised the most common limitations at the time of writing, which have seen varying degrees of recognition and rectification in research to date. An overarching issue is the lack of research on comorbid internalising disorders, which Deault attributed in part to the lack of attention to girls with ADHD, who report more internalising comorbidities than do boys (Rucklidge & Tannock, 2001). Despite a more recent research focus on girls with ADHD (Hinshaw et al., 2021; Young et al., 2020) and an associated increase in research on internalising comorbidities (Mphahlele et al., 2020), the majority of research remains focused on externalising comorbidities in samples consisting primarily of boys. Most studies have also relied on mother ratings of both their own behaviours and children's symptoms, which can introduce shared rater bias wherein parents' own traits may affect their perceptions of children's traits (Konold & Pianta, 2007). Deault also highlighted the need for more studies using longitudinal designs to identify prospective predictors of child symptoms over time, age-specific influences, and evocative effects wherein child behaviour may evoke adverse responses from parents. Despite a recent increase in the use of longitudinal designs, most of this research continues to assess relationships between parent and child measures rated by a single primary caregiver, usually the mother (Gair et al., 2021; McRae et al., 2020; Speyer et al., 2022).

Among the most problematic and persisting limitations highlighted by Deault (2010) is a lack of research using genetically sensitive designs that can account for passive gene-environment correlation (rGE). As parents and children share genetic risk for ADHD, this shared risk may manifest both as adverse parenting behaviours in adults and as ADHD and comorbid symptoms in their children. Therefore, any observed associations between child ADHD symptoms, parenting, and subsequent child comorbid symptoms could be explained entirely

or partially by genetic relatedness (Price & Jaffee, 2008). Genetically sensitive designs are needed to account for genetic confounds and assess the role of specific parent and child behaviours over and above shared genetic risk within families. A direct way of doing this is the adoption study, which leverages the fact that adopted children are reared by genetically unrelated adoptive parents (Thapar & Rutter, 2019). Therefore, associations between parent and child behaviours cannot be attributed to genetic relatedness (passive rGE).

Several genetically sensitive longitudinal studies have investigated reciprocal relationships between parenting and children's ADHD and comorbid symptoms using adoption-at-birth data from the Early Growth and Development Study (EGDS) (Leve et al., 2019). This sample includes both boys and girls, as well as including both adoptive mother and father ratings of their own and children's behaviour. The first study found that children's genetically influenced impulsivity at 4.5 years positively predicted concurrent levels of maternal hostility, which in turn positively predicted father-rated child ADHD symptoms at age 6 (Harold et al., 2013). A follow-up study found that maternal hostility at 4.5 years (as evoked by genetically influenced child impulsivity at 4.5 years) also predicted father-rated child aggression at age 6 (Sellers et al., 2020). Another study found that maternal and paternal hostility at 4.5 years (as evoked by genetically influenced child impulsivity at age 4.5) predicted impairments in mathematic (but not reading) ability at 7 years, via ADHD symptoms at 6 years (Sellers et al., 2019). These findings appear to indicate reciprocal relationships between children's early genetically influenced impulsivity, concurrent parental hostility, and children's later ADHD symptoms, comorbid symptoms, and ADHD-related functional impairments. However, one important assumption made in these studies was that children's genetically influenced impulsivity *evoked* parental hostility. While modelled as a prediction from child to parent, these measures were reported concurrently at 4.5 years, so it is possible that child impulsivity was influenced by concurrent or earlier parental hostility rather than evoking it.

Another potential issue regarding the interpretation of these prior studies concerns the methodology itself, namely the use of cross-lagged panel models (CLPMs). While these have

been widely used in developmental research, it has been pointed out that they do not separate stable between-person variance from within-person variance (Hamaker et al., 2015). As such, even longitudinal predictions in CLPMs could represent between-person covariance (i.e., stability). For example, if parental hostility prospectively predicted child anxiety symptoms in a CLPM, this could simply mean that families where parents were more hostile at one timepoint had children who were more anxious at a later timepoint (for a variety of possible reasons including genetic confounds and factors in the family environment). It would not necessarily indicate that parents increasing or decreasing their hostility levels would cause subsequent increases or decreases in children's anxiety, which is arguably the focus of most developmental research that aims to identify targets for interventions. Several variants of the CLPM have been suggested to better account for between-person covariance in different ways, but there is no clear consensus on which approach does this best (Hamaker et al., 2015; Lüdtke & Robitzsch, 2021).

In the present analyses, we sought to build upon the above findings while addressing limitations in previous work. We also compared findings derived from several variants of the CLPM that have been proposed to better account for between-person stability (further described below). Using data from the EGDS adoption sample spanning three waves from mid-childhood to early adolescence, we investigated whether evoked adoptive parent hostility mediated relationships between children's early ADHD symptoms and their later ODD and anxiety symptoms, over and above relationships with previous and concurrent symptoms. We selected ODD and anxiety as these are two of the most common comorbidities of ADHD, and symptoms of both are known to have an onset in early to mid-childhood (Boylan et al., 2007; Frick & Nigg, 2012; Hammerness et al., 2010). We hypothesised that children's early ADHD symptoms would prospectively predict adoptive parent hostility, and that this in turn would prospectively predict partner-rated child ODD and/or anxiety symptoms.

4.3. Method

4.3.1. Sample

Data were drawn from EGDS, a longitudinal US adoption-at-birth cohort of 561 children, their adoptive parents and birth parents (Leve et al., 2019). The study recruited from 45 adoption agencies in 15 states across the US, and as of 2019, individual EGDS participants resided across 46 states of the US as well as in 12 other countries. Selection criteria included adoptive families who had domestic adoption placements within 3 months of adoptive children's birth, who were biologically unrelated to adoptive children, and where the adopted child had no known major medical conditions. Data collection started shortly after birth and currently extends to child age 15 years. Median child age at adoption placement was 2 days (M = 5.58; *S.D.* = 11.32; range = 0-91 days). More than half of children in EGDS are male (57.2%), and more than half are White (55.3%), with most of the remaining children being either multi-ethnic (19.6%), Black or African American (13.2%), or Hispanic or Latinx (10.9%). Data from Cohort I (n = 361) in EGDS were used in the current study, as this cohort had consistent repeated measures at the ages we needed. Data from this cohort formed an analytic sample of 294 families after excluding families where responses were not available from both adoptive mothers and fathers. Within Cohort I, mean ages of birth mothers and fathers at child's birth were 24.1 and 25.4 years respectively, with most being White (birth mothers = 71%; birth fathers = 75%). Birth parents typically had up to a high school education with median annual household incomes of $25,000 or less. Mean ages of adoptive mothers and fathers were 37.8 and 38.4 years respectively, with most being White (adoptive mothers = 91.4%; adoptive fathers = 90.2%). Adoptive parents typically had college educations with median annual household incomes of $70-100k. These sociodemographic differences are those typically seen between birth and adoptive parents. Sampling biases that may have affected the representativeness of the sample were found to be minimal (Leve et al., 2013). Full sample characteristics are described elsewhere (Leve et al., 2019).

4.3.2. Ethics

After receiving a complete description of their participation, all parents provided written informed consent for themselves, and adoptive parents consented for their child. From child age 7 years and onwards, children also provided assent. Ethical approval was obtained from the institutional review boards for the universities involved in data collection.

4.3.3. Measures

Adoptive parent and adopted child measures were reported by adoptive mothers and fathers when children were aged 6, 8, and 11 years old. Using the hostility subscale of the Iowa Family Interaction Rating Scales (Melby & Conger, 2000), adoptive mothers and fathers reported the frequency of their hostile behaviours towards adopted children during the past month, on a 7-point Likert scale from “Never” to “Always”. The scale comprised 5 items, such as “Get angry at him/her”, “Criticize him/her or his/her ideas”, and “Hit, push, grab, or shove him/her”. The scale had good internal consistency (Cronbach’s alpha = 0.70 – 0.79). Mean composites of parental hostility were computed from item-level responses by the EGDS research team, and cases were excluded if adoptive parents did not respond to at least 4 of the 5 hostility items.

The DSM-V oriented subscales of the Child Behavior Checklist (CBCL) include measures of child ADHD, ODD and anxiety symptoms chosen to reflect DSM-V criteria (Achenbach & Rescorla, 2000). Using these subscales, adoptive mothers and fathers reported on whether various behaviours were true of their adopted child during the past 6 months, on a 3-point Likert scale from “Not true” to “Very true”. The ADHD, ODD, and anxiety problems subscales comprised 7, 5, and 9 items respectively and all had acceptable to good internal consistency, with respective Cronbach’s alphas of 0.76 – 0.84, 0.78 – 0.84, and 0.68 – 0.81. Raw scores were computed by the EGDS research team according to the Achenbach and Rescorla (2000) CBCL scoring manual, from which T-scores were computed such that scores of 50 to 64 correspond to the normal range defined by Achenbach and Rescorla (2000), and scores of 65 or above, and 70 or above, respectively, correspond to the borderline clinical and clinical

ranges. Cases were excluded if adoptive parents did not respond to at least 79 of the 99 items on the total CBCL scale.

4.3.3.1. Covariates

We controlled for the effects of several covariates across all analyses, including the effects of obstetric complications (Marceau et al., 2013) on all child measures, and the effects of child sex on all child and adoptive parent measures. Additionally, we controlled for adoption openness (the amount of contact children and adoptive parents have had with birth parents) to account for potential birth parent influences on child and adoptive parent behaviours. A combined measure of birth mother rated openness at 3-6 months and adoptive mother and father rated openness at 9 months was included as a control for all measures at 6 years, and adoptive mother and father rated openness at 8 and 11 years were included as controls for all measures at 8 and 11 years.

4.3.3.2. Missingness

Adoptive parent rated data were partially missing, with the most highly missing being fathers' responses at 8 years (42.2% missing). Families with partially missing data were included in models using full information maximum likelihood (FIML) in Mplus 8.3. FIML has been shown to produce the least biased estimates of even highly missing and non-normal data as compared to several common imputation methods (Li & Lomax, 2017).

4.3.4. Analyses

We explored relationships between adoptive mother and adoptive father hostility and child ADHD, ODD and anxiety symptoms across three waves from mid-childhood to early adolescence (ages 6, 8 and 11 years). To avoid inflation of associations due to shared-rater bias, we used a cross-rater method wherein each parent rated their own hostility while their partner rated children's symptoms. We fitted three types of model to the data using Mplus 8.3: CLPMs, CL2PMs and RI-CLPMs, described below.

The EGDS research team conducted data cleaning and preparation of raw item-level phenotypic data from EGDS (e.g., calculation of T-scores and mean composites). D.W. conducted minor additional data cleaning on scale-level measures (e.g., excluding one family discovered to have been mislabelled by the EGDS research team). D.W. computed the combined measure of adoption openness for inclusion as a covariate in analyses. D.W. wrote all scripts for fitting CLPM models and their variants in Mplus, and conducted all data analyses.

4.3.4.1. CLPM

To create the standard CLPM (Supplementary Figure S1a), first-wave correlations, autoregressive and cross-lagged paths were estimated between all four measures (parental hostility, child ADHD, ODD and anxiety symptoms) across the 3 waves of data. Within-wave correlations between the residual variances of all measures were also estimated at 8 and 11 years.

4.3.4.2. RI-CLPM

The random-intercept CLPM (RI-CLPM) uses random intercepts to model stable, trait-like variance in observed measures across time (Hamaker et al., 2015). The residual variance in variables then represent each individual's fluctuation around their own mean (intercept) at each timepoint. In RI-CLPMs (Supplementary Figure S1b), random intercepts were modelled for each of the four measures, estimating stable between-person differences that affected a person's scores equally across the three waves. Alongside these random intercepts, latent mean-centred variables were modelled for each observed measure, representing a person's fluctuation around their own mean score at each wave. These person-mean centred variables were then analysed in place of observed variables.

4.3.4.3. CL2PM

Recently, Lüdtke and Robitzsch (2021) highlighted limitations with RI-CLPMs and cautioned against dismissing findings from CLPMs in favour of those from RI-CLPMs, noting that CLPMs

may in fact more adequately capture the long-term processes that are of interest in developmental research. They also suggested that if the aim is to better control for stability, this can also be achieved using CLPMs that include 'lag-2' effects (which they called CL2PMs), which estimate prospective relationships between variables that are two or more waves apart (e.g., Time 1 to Time 3). In CL2PMs (Supplementary Figure S1c), in addition to the paths estimated in standard CLPMs, autoregressive and cross-lagged paths were estimated from each measure at age 6 to each other measure at age 11. In these models, lag-2 autoregressive paths represent long-term stability, while lag-2 cross-lagged paths represent direct long-term predictions spanning three waves.

4.4. Results

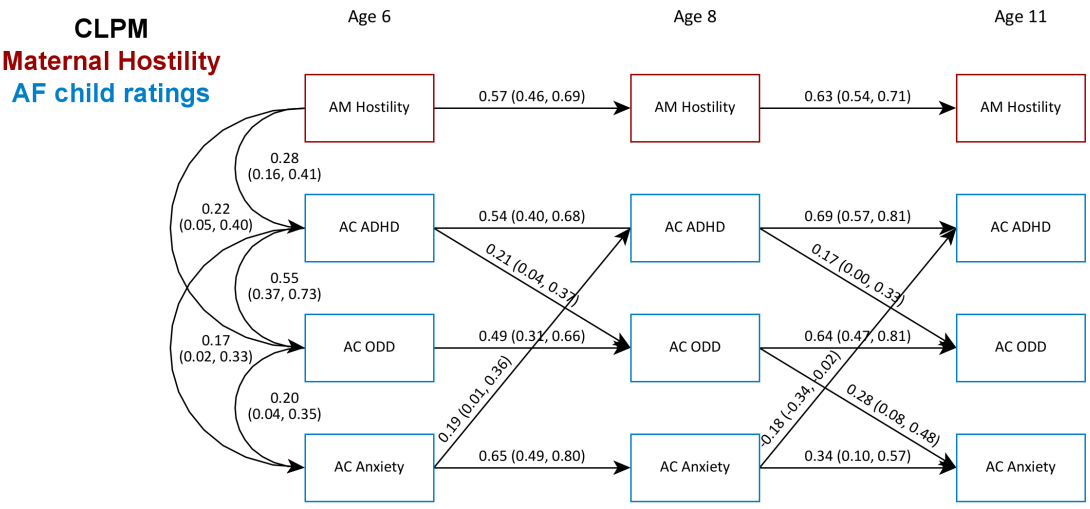
Descriptive statistics of all adoptive parent and adopted child measures are displayed in Supplementary Table S2. While the focus of the current study was not on identifying a best-fitting or most parsimonious model, several standard fit indices were used to establish adequate fit before different models were interpreted. Fit statistics for CLPMs, CL2PMs, and RI-CLPMs are displayed in Table 1. While all models demonstrated good fit to the data, CL2PMs demonstrated the best fit according to the standardised root mean square residual (SRMR), an absolute fit index that does not penalise for model complexity (Kline, 2015). However, RI-CLPMs achieved equal or better fit than CLPMs and CL2PMs according to the root mean square error of approximation (RMSEA), an absolute fit index that does penalise for model complexity (Kline, 2015). This broadly suggests that accounting for stability using the CL2PM and RI-CLPM methods produces models that more accurately represent our data, despite the complexity introduced by specifying additional parameters.

Table 1. Model fit comparisons of Maternal and Paternal Hostility CLPMs, CL2PMs, and RI-CLPMs

	Main analyses (partner ratings of child measures)					
	Maternal Hostility			Paternal Hostility		
	RMSEA (90% CI)	CFI	SRMR	RMSEA (90% CI)	CFI	SRMR
CLPM	0.044 (0.023, 0.063)	0.976	0.028	0.053 (0.034, 0.071)	0.970	0.031
CL2PM	0.037 (0.000, 0.061)	0.989	0.019	0.055 (0.033, 0.077)	0.978	0.024
RI-CLPM	0.037 (0.007, 0.057)	0.984	0.030	0.049 (0.027, 0.068)	0.978	0.030

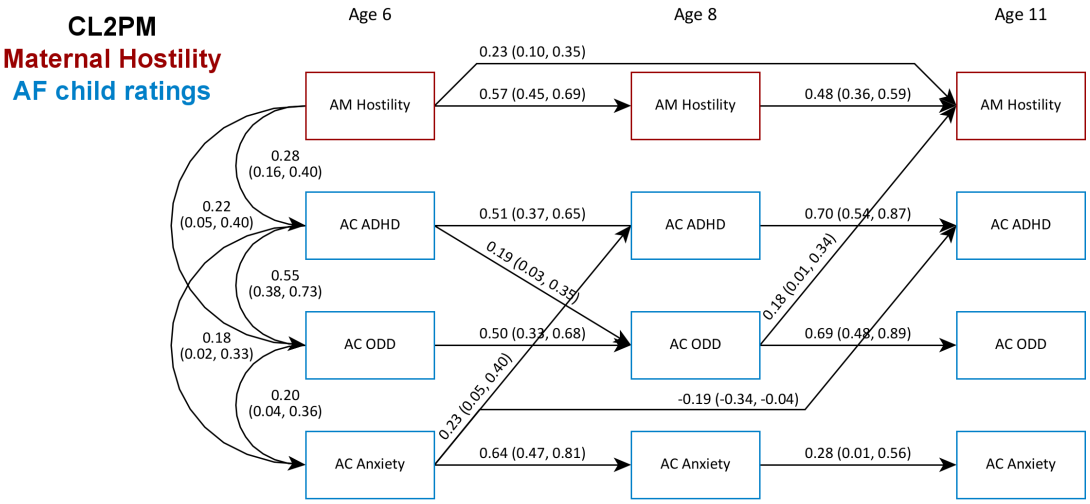
Path diagrams for Maternal Hostility CLPMs, CL2PMs, and RI-CLPMs are displayed in Figures 1 to 3, while equivalent path diagrams for Paternal Hostility models are displayed in Figures 4 to 6. For simplicity, non-significant paths and control variables are not shown in path diagrams, and residual correlations are not shown for CLPMs and CL2PMs, although none of these were fixed to zero. Fit statistics and path diagrams of sensitivity analyses, where the same parent rated both their own and their children's measures, are included in Supplementary Table S6 and Supplementary Figures S7 to S12.

Figure 1. Path diagram of the Maternal Hostility CLPM



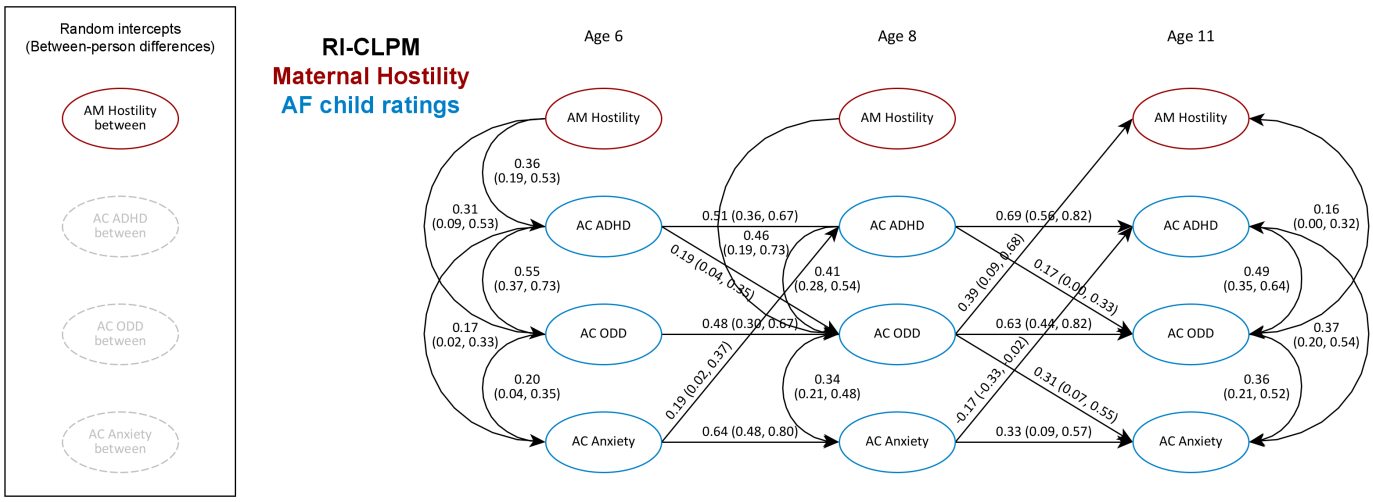
Child measures are father-rated. Included are standardised parameter estimates of all significant cross-lagged, autoregressive and first-wave correlation paths. *AM = adoptive mother; AC = adopted child.*

Figure 2. Path diagram of the Maternal Hostility CL2PM



Child measures are father-rated. Included are standardised parameter estimates of all significant cross-lagged, autoregressive and first-wave correlation paths. *AM = adoptive mother; AC = adopted child.*

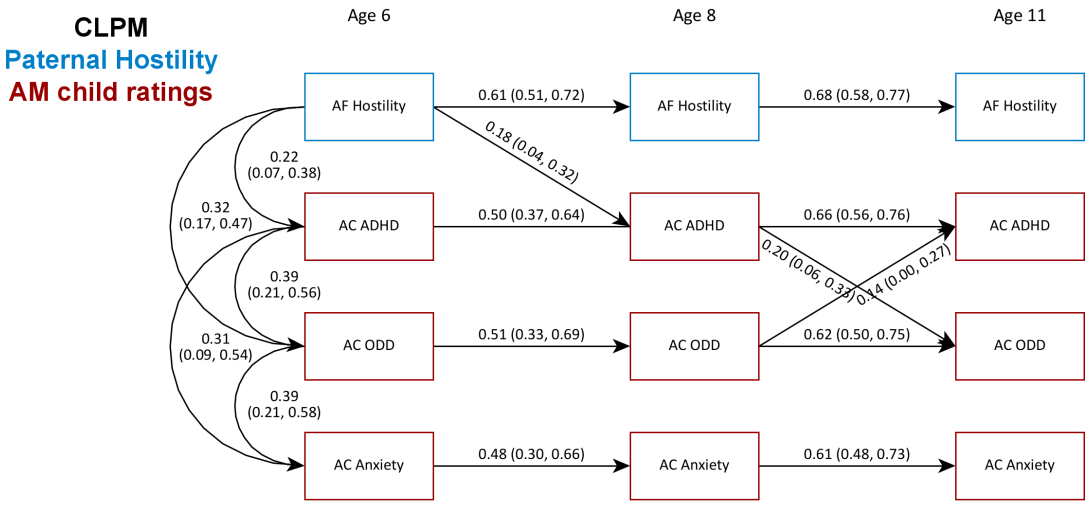
Figure 3. Path diagram of the Maternal Hostility RI-CLPM



Child measures are father-rated. Included are standardised parameter estimates of all significant cross-lagged, autoregressive and first-wave correlation paths. Random intercepts and any significant correlations between them are displayed on the left, with non-significant random intercepts greyed out. *AM = adoptive mother; AC = adopted child.*

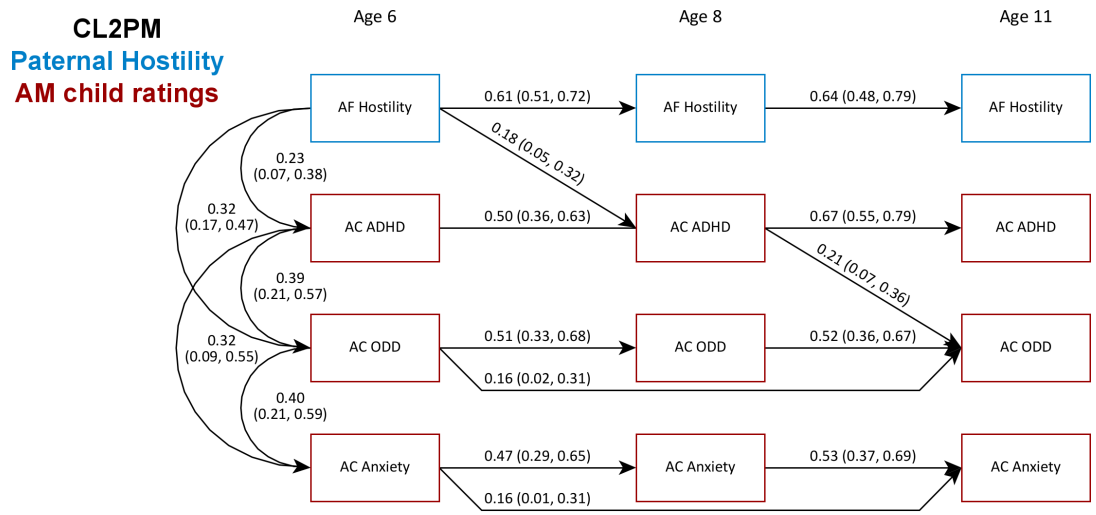
The results of Maternal Hostility models did not support the hypothesis that children's early ADHD symptoms would prospectively predict adoptive parent hostility, and that this in turn would prospectively predict partner-rated child ODD and/or anxiety symptoms. In the Maternal Hostility CLPM (Figure 1), early child ADHD symptoms did not prospectively predict maternal hostility, and maternal hostility in turn did not prospectively predict child ODD nor anxiety symptoms. These results did not differ by modelling approach, as these predictions were also not seen in the Maternal Hostility CL2PM (Figure 2) nor RI-CLPM (Figure 3). It should be noted that only the random intercept for maternal hostility was significant (Figure 3), suggesting a lack of stable between-person differences in children's father-rated ADHD, ODD and anxiety symptoms.

Figure 4. Path diagram of the Paternal Hostility CLPM



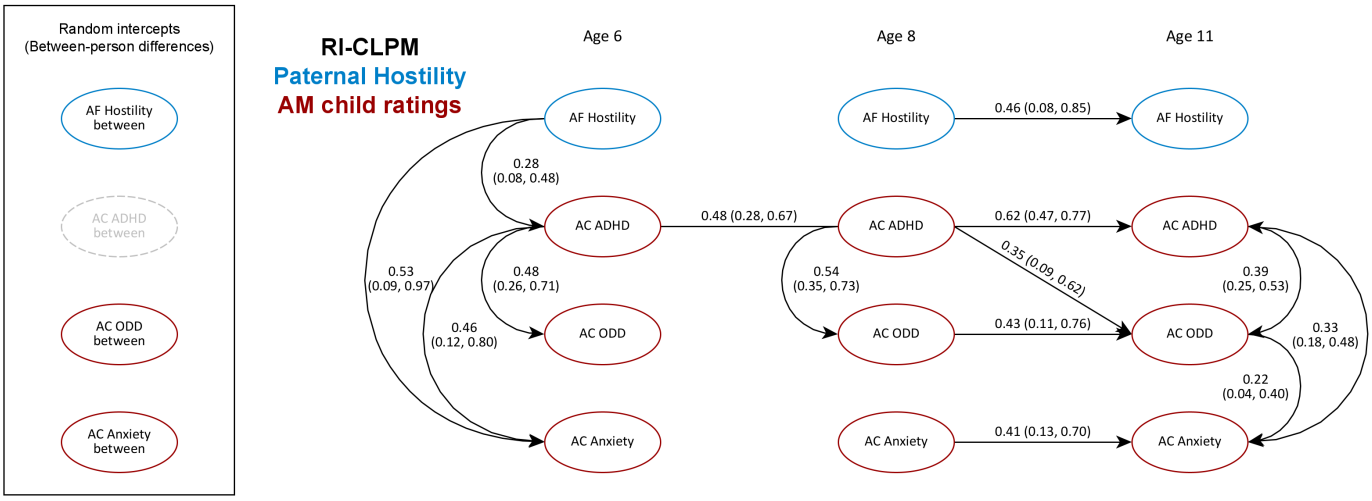
Child measures are mother-rated. Included are standardised parameter estimates of all significant cross-lagged, autoregressive and first-wave correlation paths. *AF = adoptive father; AC = adopted child.*

Figure 5. Path diagram of the Paternal Hostility CL2PM



Child measures are mother-rated. Included are standardised parameter estimates of all significant cross-lagged, autoregressive and first-wave correlation paths. *AF = adoptive father; AC = adopted child.*

Figure 6. Path diagram of the Paternal Hostility RI-CLPM



Child measures are mother-rated. Included are standardised parameter estimates of all significant cross-lagged, autoregressive and first-wave correlation paths. Random intercepts are displayed on the left, with non-significant random intercepts greyed out. Note: There were no significant correlations between random intercepts. *AF = adoptive father; AC = adopted child.*

The results of Paternal Hostility models did not support the hypothesis that children's early ADHD symptoms would prospectively predict adoptive parent hostility, and that this in turn would prospectively predict partner-rated child ODD and/or anxiety symptoms. In the Paternal Hostility CLPM (Figure 4), child ADHD symptoms did not prospectively predict paternal hostility. However, paternal hostility at age 6 did indirectly positively predict child ADHD and ODD symptoms at age 11 via its effect on child ADHD symptoms at age 8 (Supplementary Table S10). The same pattern of predictions was seen in the Paternal Hostility CL2PM (Figure 5), but not in the RI-CLPM (Figure 6). In the RI-CLPM, within-person fluctuations in paternal hostility at age 6 did not predict child ADHD symptoms at age 8 (nor, by extension, ADHD and ODD symptoms at age 11). Notably, the significant random intercepts for paternal hostility and mother-rated child ODD and anxiety symptoms were not correlated, indicating that distinct factors drove stable between-person differences in these measures.

4.5. Discussion

We set out to investigate whether associations between child ADHD and comorbid symptoms were mediated by parenting, whereby children's ADHD symptoms evoked hostility in parents which in turn predicted later comorbid symptoms in children. We did not find evidence for such mediation, instead finding only that paternal (but not maternal) hostility prospectively predicted child ADHD and ODD symptoms. These findings and several considerations regarding their interpretation are discussed below, followed by a discussion of how findings were affected by modelling approach.

4.5.1. Lack of evocative effects from child ADHD to parental hostility

Counter to our hypotheses, child ADHD symptoms did not evoke parental hostility. These findings are not consistent with reports from previous EGDS studies by Harold et al. (2013), Sellers et al. (2019) and Sellers et al. (2020), all of which reported that early ADHD-like behaviour (impulsivity) evoked parental hostility. A key reason for these studies drawing different conclusions to ours is likely to be a difference in modelling decisions. Namely, in all

three of these prior studies, within-wave associations between child ADHD-like symptoms at age 4.5 and concurrent parental hostility were assumed to represent evocative effects whereby child ADHD-like symptoms evoked parental hostility in the same wave. In the present study, we inferred evocative relationships only from cross-lagged paths between waves (i.e., where child measures prospectively predicted parent measures at subsequent waves). This somewhat stricter approach to inferring evocative effects may explain the lack of findings of evocative effects in our study, because while we did find concurrent associations between child ADHD symptoms and both maternal and paternal hostility at age 6, we did not find prospective predictions meeting our definition of evocative effects. We would suggest careful consideration of modelling decisions in longitudinal analyses where these stand to have meaningful implications for the interpretation of findings.

4.5.2. Predictions from parental hostility to child ADHD and ODD symptoms

While we did not find evidence that child ADHD symptoms evoked parental hostility, we did find evidence for prospective predictions from paternal hostility at age 6 to mother-rated ODD and ADHD symptoms at age 11 via ADHD symptoms at age 8. This suggests that early paternal hostility exerts a long-term influence on children's ODD and core ADHD symptomatology as rated by mothers several years later. Importantly, the use of an adoption sample means these predictions cannot be due to genetic relatedness between fathers and children. These findings contribute to a growing evidence base indicating that parenting behaviours (including behaviours associated with ADHD in parents) can have an environmental effect on children's ADHD and comorbid symptomatology (Breaux et al., 2017; Choenni et al., 2019; McRae et al., 2020; Moroney et al., 2017; Tung et al., 2015). This evidence base has begun to be incorporated into theoretical frameworks, for example that suggested by Caye et al. (2017), which posits that alongside stable genetic and neurobiological risk factors, non-stable environmental factors such as family interactions may affect inattention and hyperactivity-impulsivity symptoms. Parent training interventions targeting negative parenting behaviours have been shown to improve children's core ADHD

symptoms (Rimestad et al., 2019). However, there remains a need for more research on parent training interventions for child ADHD and comorbid outcomes, and particularly parent training for fathers, who have been largely excluded from randomised controlled trials for behavioural interventions (Fabiano, 2007). Our findings situate parental hostility as a target for such interventions, and highlight the importance of developing parent training for fathers as well as mothers.

In contrast to paternal hostility, maternal hostility did not prospectively predict any father-rated child measure. Prima facie, this may suggest that paternal hostility is simply more important for children's ADHD-related comorbid symptoms. The difference in prediction between maternal and paternal hostility is unlikely to be due to differences in reporting between mothers and fathers, as they had very similar scores on self-reported hostility as well as children's symptoms (Supplementary Table S2). The higher missingness of father-rated child measures may have limited statistical power to detect significant relationships with maternal hostility. However, sensitivity analyses wherein fathers rated their own and children's measures still yielded significant predictions from paternal hostility to children's later ODD symptoms (Supplementary Figures S7-9). This suggests that higher missingness on child symptoms alone would not account for a lack of power to detect predictions from maternal hostility to father-rated child measures. A possible explanation lies in context specificity, namely that the contexts in which parents interact with children may affect their ratings of child behaviour. Despite recent improvements in fathers' equal participation in parenting (Schoppe-Sullivan & Fagan, 2020), mothers nonetheless tend to spend more time with children across a wider variety of contexts. Therefore, they may be more likely to notice subtler behaviour as opposed to fathers, who may report only more overt or context-specific behaviour. This possibility is supported by our sensitivity analyses wherein parents rated both their own and children's symptoms. From these, it emerges that mothers' ratings of child symptoms were predicted by their own and fathers' prior hostility, whereas fathers' ratings were predicted only by their own hostility. Therefore, while it is possible that maternal hostility may simply not have been as

important, it is also plausible that mother ratings were more sensitive to subtler changes in children's behaviour compared to fathers, and/or that children did not display oppositional behaviours around fathers unless they were more hostile towards children.

4.5.3. Comparison of findings from CLPMs, CL2PMs and RI-CLPMs

One of our aims was to compare results from CLPMs with those from models using two recently proposed alternative modelling approaches. The first was the RI-CLPM, which models random intercepts that capture between-person differences, and person-mean centred variables that capture within-person fluctuations around an individual's intercept (Hamaker et al., 2015). The second was the CL2PM, a standard CLPM that additionally estimates 'lag-2' paths between measures two or more waves apart to account for between-person stability and longer-term effects (Lüdtke & Robitzsch, 2021).

There were no major differences between the results of CLPMs and CL2PMs. While several lag-2 paths were significant while some paths that were significant in CLPMs were not so in CL2PMs, there was no consistent pattern of informative changes in significant paths. Overall, findings related to our hypotheses were consistent across the two approaches such that our conclusions would not have differed depending on the approach used. However, the results of RI-CLPMs were markedly different. Some (but not most) measures were found to have significant random intercepts, indicating the presence of stable trait-like effects on those measures. Consequently, various significant paths from CLPMs and CL2PMs were not significant in equivalent RI-CLPMs. This has shown to be a common occurrence among RI-CLPM studies (Barzeva et al., 2020; Griffith et al., 2021; Keijsers, 2016; Long et al., 2019; Masselink et al., 2018), and is often interpreted as demonstrating that the significant paths from CLPMs were spurious, as they were simply due to uncontrolled between-person differences. However, while methodological rigor may motivate these conclusions, several recent papers have cautioned against overvaluing within-person effects at the expense of between-person effects, while noting wider limitations of the RI-CLPM.

A critique by Lüdtke and Robitzsch (2021) outlined several limitations of RI-CLPMs. Key among these was a fundamental theoretical limitation, namely that cross-lagged paths in RI-CLPMs only estimate relationships between temporary fluctuations around an individual's mean. They noted that this may not be the most appropriate approach for studying long-term developmental processes. Instead, they suggested that RI-CLPMs might be more useful for research with short time lags between measurements, such as intensive longitudinal designs where researchers are interested in short-term influences on someone's daily fluctuation around their mean on a given behaviour, emotion or experience (Bolger & Laurenceau, 2013). They argued that findings from CLPMs may be more informative if the research focus is on potential causes that make people different from others, in which case CL2PMs provide an alternative way of accounting for stability while also better controlling for unobserved confounding. In a similar vein, Rohrer and Murayama (2021) outlined why assessing within-person fluctuations is neither necessary nor sufficient for causal inference, and noted that time-varying confounders can also result in spurious within-person associations. They suggested that rather than trying to decide on the best modelling approach to establish causality, researchers should be clear on the types of causal effects they want to examine and take into account the assumptions and limitations of a given modelling approach.

With the above in mind, our study can be seen as an illustrative example of when an already strong design, dataset and research question might be better suited to a CLPM (or CL2PM) approach. Several key features of our study may have been better suited to CLPM than RI-CLPM approaches: 1) We do not focus on shorter-term fluctuations in behavior or experience, but on long-term developmental changes in behavioral measures two and three years apart; 2) We do not focus on relationships between behaviors within one individual, but assess relationships between parent and child measures across time; 3) We use adoption-at-birth data that eliminates, by design, a large part of the correlated stable trait-like factors likely to confound parent-child associations (i.e., overlapping genetic influences on parent and child traits). We posit that these features reduce the relative benefits of RI-CLPMs as far as

controlling for confounding by stable between-person differences, and that arguably, it is unlikely that fluctuations in one parent (or child) behavior would predict mere fluctuations in a child (or parent) behavior several years later. Indeed, we did not find any such predictions in any of our RI-CLPMs (including sensitivity analyses). A final issue with RI-CLPMs in our study was that certain measures did not have significant random intercepts, suggesting that there were no stable between-person differences acting on those measures. We followed modelling guidance by Mulder and Hamaker (2021) who suggest fixing the effects of non-significant random intercepts to zero. However, this results in models containing both person-mean centred variables (for measures with a significant random intercept) and standard variables. This complicates interpretation in cases where relationships are found between person-mean centred variables (representing fluctuations in a measure) and standard variables (representing basic scores on a measure).

4.5.4. Strengths and Limitations

We tested our hypotheses using a rigorous modelling approach, comparing findings between multi-wave CLPMs, RI-CLPMs, and CL2PMs, while using consistent parent measures and partner-rated child measures throughout. Importantly, the use of an adoption sample meant associations were not attributable to genetic relatedness between parents and children, allowing us to assess associations between parent behaviours and child symptoms unconfounded by passive rGE. Finally, our sample included an almost equal number of boys and girls, such that our findings are not only applicable to boys.

However, there were several limitations. First, the use of an adoption sample means that our findings may not generalise to biological families where parents and children share genetic risk for ADHD. In these families, one or both parents are likely to have elevated ADHD symptoms, and so may be more likely to react adversely to children's ADHD-related difficulties (Johnston et al., 2012; Park et al., 2017). In turn, children with higher ADHD symptoms may be more prone to developing symptoms of comorbid disorders in response to these and other

risk factors. Our findings would therefore benefit from replication in genetically sensitive research on biological families where parents, children, or both, have ADHD. Second, while our sample included both boys and girls, to avoid losing statistical power we opted not to run separate analyses for boys and girls. There remains a need for research explicitly accounting for sex differences in the presentation of ADHD and comorbid symptoms, and for differences in maternal and paternal parenting behaviours towards boys and girls (Hinshaw et al., 2021). Third, range restriction may have affected our findings, as levels of ADHD symptoms were low among adopted children in our sample, as were levels of parental hostility.

4.5.5. Conclusions and future directions

We did not find evidence that evoked parental hostility mediated associations between children's early ADHD symptoms and their later ODD and anxiety symptoms. Instead, our findings suggested unidirectional predictions from early paternal hostility to child ODD and ADHD symptoms by age 11 via child ADHD symptoms at age 8. Our findings add to an emerging body of research indicating that negative parenting behaviours such as child-directed hostility prospectively predict child ADHD and comorbid symptomatology throughout childhood and up to at least early adolescence. More genetically sensitive research is needed to determine whether these predictions generalise to families where parents and children share genetic risk for ADHD, and to elucidate the mechanisms by which parenting may influence ADHD and comorbid symptomatology. Such research could further inform interventions focused on preventing the worsening of ADHD and comorbid disorder symptoms throughout childhood.

Our findings also inform recent debate about the relative benefits of CLPM, CL2PM and RI-CLPM approaches for causal inference, supporting suggestions that caution is needed before dismissing significant findings from CLPMs if they are no longer significant in an equivalent RI-CLPM. Rather than dismiss the importance of between-person differences as a confound or as fundamentally separate from within-person processes, it seems sensible for

developmental researchers to adopt the approach that is best suited to the type of developmental process in question.

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5. Discussion

5.1. Synthesis of findings

In the studies contained within this thesis, I used genetically sensitive methodologies to investigate several types of parental influence on the aetiology of childhood ADHD and comorbid disorders. Specifically, I assessed the extent to which parents contributed to their children's ADHD and/or comorbid symptomatology via direct transmission of genetic risk, via environmentally mediated indirect genetic effects such as genetic nurture, and through the specific environmental effects of child-directed hostility. Broadly, my findings inform a conceptualisation of childhood ADHD and comorbid symptoms as depending in substantive part on the influence of parents, via a combination of genetic and environmental effects. These findings contribute to a body of literature on parenting and intergenerational transmission of risk that remains largely hindered by a lack of genetically sensitive methods, despite the highly familial nature of ADHD. The key findings and their theoretical implications are discussed below, along with suggestions for future research.

5.1.1. Shared genetic architecture between adult ADHD and child ADHD

The findings of Chapter 2 provide novel evidence for shared aetiological underpinnings between adult ADHD symptoms and childhood symptoms of ADHD and several common comorbid disorders. As discussed previously, it has become increasingly clear that at least one parent of a child with ADHD will also either meet criteria for ADHD or have elevated symptoms themselves (Park et al., 2017). However, my findings are the first to directly demonstrate that associations between symptoms of ADHD in parents and their children are explained by overlapping genetic influences. Moreover, they show that children's comorbid symptoms also rely in part on genetic influences that, in their parents, also influence adult ADHD symptoms. These findings provide empirical support for the continuity of genetic influences on ADHD and common comorbid disorders, insofar as overlapping genetic effects

explained phenotypic associations between mothers' adult ADHD symptoms and their offspring's child ADHD and comorbid symptoms.

In regard to the debate around whether ADHD manifesting in adulthood could be aetiologically distinct from childhood ADHD (Asherson & Agnew-Blais, 2019), my findings show that in a large, representative sample of families, adult ADHD symptomatology in mothers shares an aetiology with symptoms of ADHD and comorbid disorders in children. This suggests that, as pertains to phenotypic variance in the majority of the population, ADHD symptomatology in adults is not aetiologically distinct from that in children, but is likely to represent the same aetiological entity. The results do not rule out the existence of a distinct form of adult-onset ADHD in a small subset of cases. It is possible that some individuals may experience newly occurring ADHD symptoms in adulthood that do not depend on a shared aetiology with their parents or children, perhaps in cases where relatively low genetic risk is later compounded by exposure to particularly high environmental risk. Conversely, early protective environments may delay the onset of ADHD in some cases, as shown by a recent study finding that later-onset ADHD in adolescence and young adulthood was associated with having higher levels of childhood resources (Riglin et al., 2022). There could also be rarer, genetically distinct forms of ADHD occurring within certain families, wherein both parents and children may show a pattern of newly occurring ADHD symptoms only as they reach adulthood. While the relatively rare occurrence of adult-onset ADHD may preclude the availability of adequately large samples for MCoTS analyses specifically focused on adult-onset ADHD, smaller family studies could be conducted by ascertaining cases of adult-onset ADHD and recruiting their family members. Such work could then assess whether or not the children or siblings of those presenting with adult-onset ADHD show a comparable pattern of symptoms arising only when they reach adulthood. If so, this would suggest that rarer presentations of adult-onset ADHD may indeed represent an aetiologically distinct but familial form of ADHD. More broadly, it would be of clinical interest to characterise whether there are distinct environmental risk factors or exposures that are associated with cases of adult-onset ADHD specifically, and

whether these cases display similar or distinct patterns of comorbidity and functional impairment compared to typical cases of childhood-onset ADHD.

Besides investigating overlap between adult and child ADHD, the MCoTS approach used in Chapter 2 could also be used to investigate aetiological overlap between childhood ADHD symptomatology and a range of long-term health outcomes later in adulthood. For example, genetic and environmental risk factors for ADHD in childhood may drive an increased risk for later disorders such as heart disease and Alzheimer's disease. The current lack of longitudinal cohorts following children into later adulthood means it is not yet possible to directly assess genetic and environmental overlap between childhood ADHD symptomatology and these longer-term health outcomes. However, it is possible to assess aetiological overlap between children's ADHD symptoms and various phenotypes in their parents. Such approaches could provide an indication of whether childhood ADHD is associated with risk for a range of outcomes later in life. These could include the aforementioned physical health outcomes, but also socioeconomic, functional and quality of life measures. There may be limitations to this approach for certain phenotypes, for instance that parental quality of life in parents may depend on the environmental effects of their children's ADHD-related behaviour as well as their own overlapping risk for ADHD. However, MCoTS models can also estimate the effects of exposure to children on the parent phenotype (McAdams et al., 2018), and indeed, the effects children's symptoms may have on parent outcomes is an interesting area in itself. Future studies making use of intergenerational datasets and genetically sensitive methods such as MCoTS could produce a range of informative findings about how ADHD and related phenotypes in both parents and children can interact to affect parents' own functioning and ADHD-related outcomes.

5.1.2. Environmental influence of parenting

The findings of Chapters 3 and 4 provide distinct forms of evidence that ADHD and certain comorbid symptoms may rely in part on the environmental influence of parents. The trio GCTA

findings in Chapter 3 quantify the overall effect of heritable parent behaviours and characteristics on children's ADHD symptoms up to ages 5 and 8. Only maternal indirect genetic effects were found at age 5, while equal maternal and paternal indirect genetic effects were found at age 8. After controlling for population structure, estimates of indirect genetic effects primarily capture genetic nurture, wherein heritable parent behaviours exert environmental effects on children's ADHD symptoms (Young et al., 2018). In distinction from both PGS-based approaches and associational studies on specific environmental risk factors, extended GCTA methods do not implicate any specific parental phenotype or behaviour, instead capturing the (environmentally mediated) effects of all common SNPs in parents on the child phenotype (Eilertsen et al., 2022). These could include not only the effects of adverse or protective parenting behaviours, but, for instance, genetically driven influences on the family's socioeconomic status, or biological effects on early intrauterine conditions. Furthermore, despite controlling for population structure, indirect effects may also have captured residual subtle population stratification effects not captured by principal components (Morris et al., 2020). Estimates therefore capture the overall contribution of any environmental effects tagged by common parental SNPs, providing a robust quantification of the importance of the parent-related environment for children's ADHD symptoms. As discussed in Chapter 3, estimates of indirect genetic effects in early childhood may have captured rater biases, resulting in findings of only maternal indirect genetic effects and a marked absence of direct genetic effects when modelled together. In mid-childhood, however, the indirect genetic effects of parents were found to be roughly half as large as the direct effects of children's own genotype. This effect accounted for around 7% of total variance in children's ADHD symptoms, a substantial portion considering that it does not encompass all environmental effects of parents but only those tagged by common SNPs. Indeed, given that twin estimates of environmental effects on ADHD symptoms in childhood typically fall below 25% (Faraone & Larsson, 2019), parental indirect genetic effects stand to form a relatively large component of

the total environmental effect. This underlines the ongoing need for research aimed at identifying family-level risk factors for ADHD that are amenable to early intervention.

As in Chapter 2, the use of a large, representative population-based sample means that these findings are applicable to phenotypic variation in ADHD symptoms in children who do not meet criteria for ADHD, and whose parents are not necessarily at high genetic risk for ADHD themselves. However, the importance of genetic nurture effects may differ in families where children (and thereby, typically one or both parents) have clinically significant symptoms of ADHD. As discussed previously, children with ADHD may be more prone to the environmental impacts of parent behaviour due to neurobiological predispositions, while parents with ADHD are likely to display more harsh or other negative parenting behaviours (Park et al., 2017; Steinberg & Drabick, 2015). This may increase both their exposure and their sensitivity to parental genetic nurture effects. Equally, however, it may be that for children at higher genetic risk for ADHD, direct genetic effects on symptoms are more pronounced, such that parent behaviour has less of an impact on their symptoms. These possibilities bear investigating in future research, particularly as larger samples of genotyped families become available. Such samples could provide adequate power for approaches comparing effects in higher versus lower risk families, or analyses conditioned on covariates such as child or parental ADHD diagnosis. Researchers could also assess indirect genetic effects on comorbid disorders, again comparing high and low risk families or conditioning analyses depending on ADHD severity in children and/or parents. For example, genetic nurture effects on symptoms of comorbid disorders could be moderated by children's ADHD severity, either positively or negatively. That is, children with more severe ADHD symptoms could be more prone to the environmental effects of genetic nurture on comorbid symptomatology. Conversely, it could be that genetic nurture effects are relatively less important for children with more severe ADHD symptoms, which would suggest that children's own genetic risk for ADHD symptoms was the primary driver of variance in comorbid symptomatology. In addition, future studies could investigate whether indirect genetic effects are accounted by specific risk environmental

exposures by including these as covariates. For example, if significant indirect genetic effects on children's ADHD symptoms were attenuated after accounting for socioeconomic status, this would implicate socioeconomic factors as mediators of SNP-associated indirect genetic effects.

Another interesting finding was that indirect genetic effects of parents had negative covariances with the direct genetic effects of children's own genotype. As discussed in Chapter 3, this may indicate that parental genetic nurture effects act in an opposing direction to the direct effects of children's own genotypes (Cheesman et al., 2020; Eilertsen et al., 2022). This presents an interesting possibility, namely that some of the genetic influences driving ADHD symptomatology in children may manifest in the form of regulating or otherwise ameliorating behaviours in parents, exerting a protective genetic nurture effect on children's symptoms. Whereas such effects have been described in animal research and there is some evidence that they may regulate factors such as gestational weight gain in humans (Lee, 2002; Warrington et al., 2018), the possibility of family-level regulatory mechanisms on behavioural phenotypes such as ADHD is a novel but potentially informative one. Interestingly, Eilertsen et al. (2022) found that while indirect genetic effects on inattention and conduct symptoms had negative covariances with direct effects, indirect effects on hyperactivity symptoms had positive covariances with direct effects. This suggests that whether there is a compounding effect of parent genotype, or a protective or regulating one, can depend on the specific behavioural phenotypes in question. In this case, direct genetic effects on hyperactivity were compounded or additionally contributed to by the indirect effect of the parental genotype. Future studies could investigate a wider range of behavioural phenotypes to explore these effects further. In particular, covariates could be included in analyses to determine if specific parenting behaviours, or other environmental factors, such as socioeconomic status or household conditions, could account for the additive or regulating indirect genetic effects of parents on specific child phenotypes.

In contrast to the total effects of all heritable parent characteristics tagged by common SNPs quantified in Chapter 3, the adoption findings in Chapter 4 implicate a specific environmental effect of early paternal hostility on children's ADHD symptoms at age 8, which in turn predicted later ADHD and ODD symptoms at age 11. Very few studies have investigated the role of specific parenting behaviours while combining the use of longitudinal data on genetically unrelated parents and children, different raters of parent and child phenotypes, and consistent repeated measures of all parent behaviours and child symptoms at earlier waves. This means that the prospective associations between paternal hostility and children's later symptoms accounts for prior covariances between all measures, and cannot be accounted for by passive rGE or shared rater bias. While this study used a smaller sample than those in other chapters, which may have hindered power to detect smaller effects, this does provide a degree of confidence that where prospective predictions were significant this was not simply due to Type 1 error.

Overall, the findings of Chapter 4 constitute a particularly robust piece of evidence in support of the notion that negative parenting may exert an environmental effect on children's ADHD symptoms as measured several years later. This has indirect implications for research showing that parents with ADHD display more negative parenting behaviours including child-directed hostility (Chronis-Tuscano et al., 2008; Johnston et al., 2012). An unanswered question within that literature is whether these negative parenting behaviours affect children's ADHD-related outcomes. As there is no reason to assume that children with clinically significant ADHD symptoms would be less prone to the effects of negative parenting behaviours such as child-directed hostility, my findings would suggest that an environmental effect of those behaviours on children's symptoms is likely. A key remaining question would be whether the effects would differ in magnitude in children with clinically significant ADHD symptoms. It seems plausible that the overall effects could be greater in these children due to more frequent exposure to hostility and similar behaviours in parents who themselves typically have elevated ADHD symptoms. Indeed, with increasing recognition and diagnosis of ADHD

in the population, future studies could investigate whether parental hostility and other parenting behaviours are predictive of children's later symptoms in samples where parents or children have clinically severe ADHD symptomatology. While this may not be plausible with adoption cohorts, large longitudinal cohorts of related parents and children could assess similar questions while using sibling controls to account for genetic confounding.

5.2. Implications for theory and future research

5.2.1. Families with ADHD and the role of parents in shaping childhood environments

Broadly, the findings of the studies within this thesis support a shift away from conceptualisations of ADHD that overemphasise the unidirectional effects of children's ADHD symptoms on children and their families. Research investigating the 'impacts' of having a child with ADHD on parents and other family members continues to neglect the potential presence of ADHD symptomatology and a range of associated parenting deficits in parents (Peasgood et al., 2021; Zhao et al., 2019). My findings of genetically driven associations between maternal ADHD symptoms and children's ADHD and comorbid symptoms suggest that when children do display ADHD and/or a range of comorbid symptoms, this is unlikely to occur in isolation from similar symptoms also displayed by at least one of their parents. Furthermore, the findings of indirect genetic effects of mothers' and fathers' genotypes on children's ADHD symptoms, and the findings that child ADHD symptoms were predicted by earlier paternal hostility, suggest that children's ADHD symptomatology itself relies in part on the environmental effects of parental behaviour. In sum, this suggests that the characteristics seen in families of children with ADHD are not likely to be purely due to the added burden of the 'ADHD child'. Future research aiming to characterise or quantify the impacts of ADHD on families should therefore assess ADHD symptomatology in parents as well as children. Doing so is important not only for understanding the effects of ADHD on families, but for their effects

on behavioural interventions in the family, as there is evidence that parental ADHD can reduce the efficacy of parent training interventions (Harvey et al., 2003).

There remains a need for a more comprehensive body of genetically sensitive research establishing the extent to which parent behaviour accounts for the environmental component of ADHD, and which behaviours are the best targets for interventions. As discussed previously, a key obstacle to clear inferences about the environmental effects of parent behaviour on children's outcomes has been a lack of genetically sensitive methods that can control for passive rGE. As more large, genotyped family datasets become available, there is increasing potential for developing a wider body of robust findings on the effects of parental and other family characteristics on the development of ADHD and comorbid disorders in children. Such findings could further guide research on parent training interventions which, so far, has established that targeting negative parenting behaviours can produce improvements in children's ADHD symptomatology as rated by both parents and independent raters (Rimestad et al., 2019). More broadly, a more comprehensive literature on the environmental role of parents could aid clinicians and teachers in educating parents of children presenting with ADHD about the role their own ADHD-related behaviours could play in children's outcomes. As it stands, such information may not be seen as sufficiently evidenced to be applied in professional contexts outside of specific intervention trials.

Another potential area of interest is whether there are substantial indirect genetic effects on parental phenotypes. Methods such as trio GCTA, as well as PGS approaches, could be used to assess the indirect effects of children's and co-parents' genotypes on a range of parental measures, including adult ADHD symptoms, other psychopathologies, and specific parenting behaviours. These may depend in part on children's and co-parents' genetically driven behaviours over and above the direct effects of their own genotype. Assuming adequate sample sizes, it could also be possible to condition analyses on covariates such as parents' own ADHD symptoms. For example, if the indirect genetic effects of children's and/or co-parents' genotypes on parent psychopathology or specific parenting behaviours were

moderated by a parent's own ADHD symptoms, this would indicate that ADHD in the parent made them more susceptible to the indirect effects of their children's and co-parent's genotypes. Such findings would suggest that interventions aimed at helping parents with ADHD cope with family stressors could be useful for both improving their own wellbeing and/or for reducing their risk of exhibiting adverse parenting behaviours that could further affect family functioning and children's development.

5.2.2. ADHD as a lifelong disorder

Despite the recognition that ADHD and associated comorbidities and functional impairments typically persist into adulthood (Gjervan et al., 2012; Kooij et al., 2019), little is known about risk factors for both the persistence and severity of core ADHD symptomatology and wider functioning and mental health in adults who were diagnosed with ADHD in childhood. With regard to the studies contained in this thesis, further genetically sensitive research is needed to determine whether parental factors continue to influence children's longer-term ADHD symptomatology, comorbid disorders, and functional outcomes after they enter adulthood. Extended GCTA analyses investigating indirect genetic effects of parental genotypes on ADHD-related outcomes in adulthood are of particular interest, as these could provide a way of capturing any long-term impacts that heritable parent-related environments may have on children later in life, even as most go on to leave their family households. Such effects could include those on later psychiatric as well as functional and physical health outcomes. Indirect genetic effects on offspring could also influence their own later parenting behaviours, forming transgenerational mechanisms that could contribute to the persistence of ADHD and related disorders within families. Multigenerational GCTA approaches incorporating grandparent genotype data could be used to investigate such mechanisms, and would also provide better control for population stratification effects. This is because, extending the principle described by Young et al. (2018), the effects of population stratification would be captured in estimates of grandparent-driven indirect genetic effects. The indirect genetic effects of parents' genotypes on children's phenotypes could then be more confidently interpreted as primarily

representing genetic nurture effects. While genotyped multigenerational cohorts are not yet available, a recent study (currently available as a pre-print) inferred grandparent genotype effects on educational outcomes using parental sibling pairs (Nivard et al., 2022). Such approaches and future work using genotyped multigenerational cohorts could provide informative insights into transgenerational effects occurring across several generations, as well as providing more robust indications of the importance of genetic nurture effects after controlling for population stratification.

5.3. Conclusions

The genetically sensitive findings in this thesis support a conceptualisation of ADHD as a family-wide condition, with genetic risk manifesting simultaneously in children and parents who jointly shape the family environment. Parents were found to contribute to children's ADHD and/or comorbid symptomatology via genetic transmission as well as environmental effects, situating parental factors as important contributors to children's ADHD-related development. While the full extent and specific mechanisms of parental effects remain to be established, future research will benefit from the increased availability of large datasets that allow researchers to distinguish genetic and environmental effects. Such findings could aid early interventions that target modifiable family-level factors while acknowledging the joint role of ADHD and related symptomatology in parents and their children.

5.4. References

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Appendix 1

Supplementary materials for Chapter 2

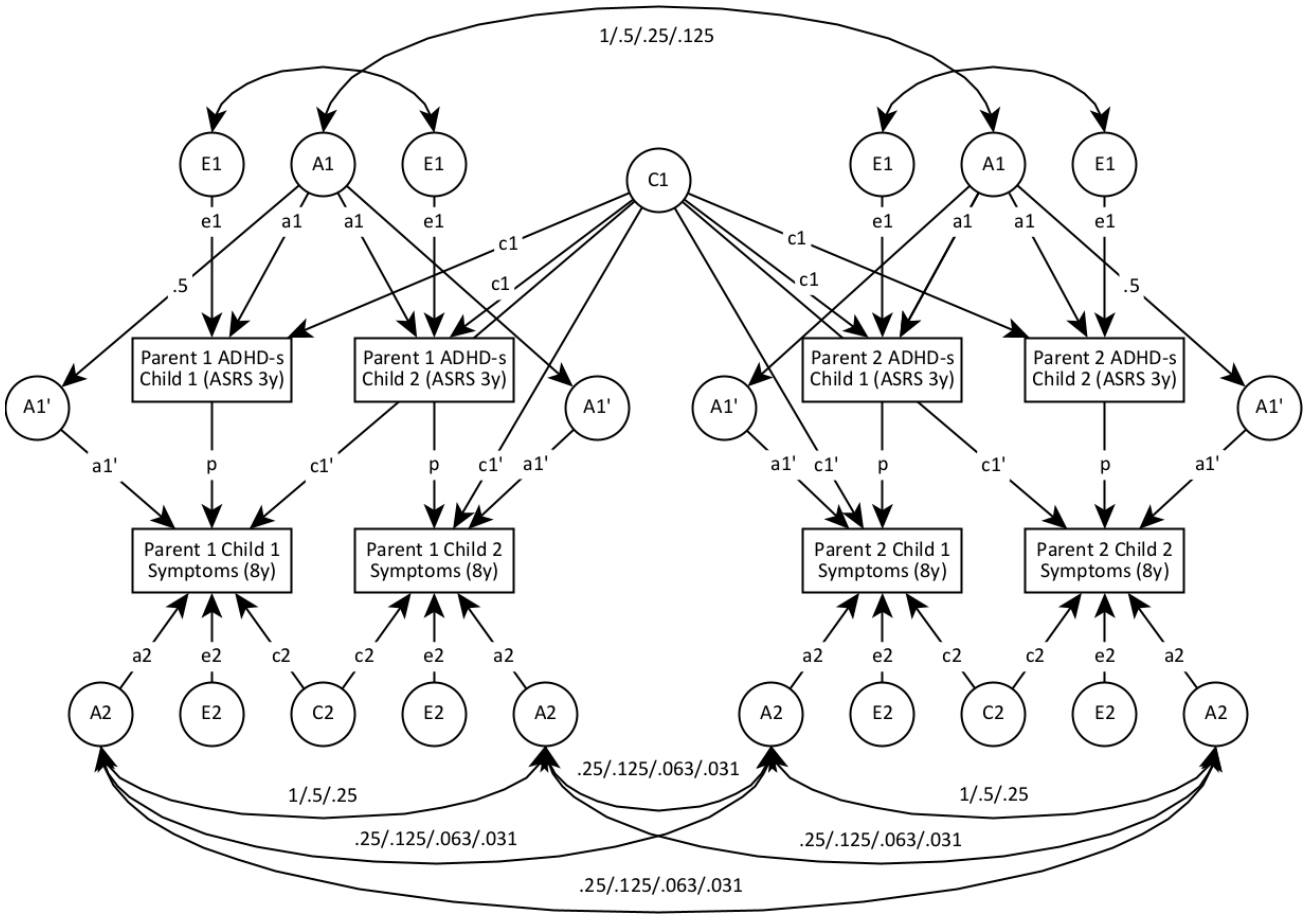
Table S1. Sample frequencies for extended families in MCoTS and bivariate twin design analyses.

Frequencies of mothers and children stratified by maternal relatedness and child relatedness, for paired extended families and for unpaired nuclear families (i.e. singleton mothers with more than one child in MoBa).		
Extended families (N = 19,201)		
N stratified by the parent pairs used to identify extended families	**rA**	**N**
Identical twin pair	1.00	60
Full-sibling or fraternal twin pair	.500	12,085
Maternal or paternal half-sibling pair	.250	690
Cousin pair	.125	6,366
N stratified by mothers' relatedness in each extended family	**rA**	**N**
Identical twin pair	1.00	43
Full-sibling or fraternal twin pair	.500	4,074
Maternal or paternal half-sibling pair	.250	261
First cousin pair	.125	2,716
Unrelated sisters/cousins-in-law pair	0	12,107
Number of offspring pairs linked to each mother	**rA**	**N**
Full-sibling pair	.500	5,089
Maternal half-sibling pair	.250	41
Unpaired (singleton) offspring	---	20,339
First cousin pair		
Unpaired nuclear families (N = 4,565)		
Number of offspring pairs linked to each mother	**rA**	**N**
Identical twin pair	1.00	172
Full-sibling or fraternal twin pair	.500	7,746
Maternal half-sibling pair	.250	32

Table S2. Internal consistency for measures used in MCoTS and extended bivariate twin analyses.

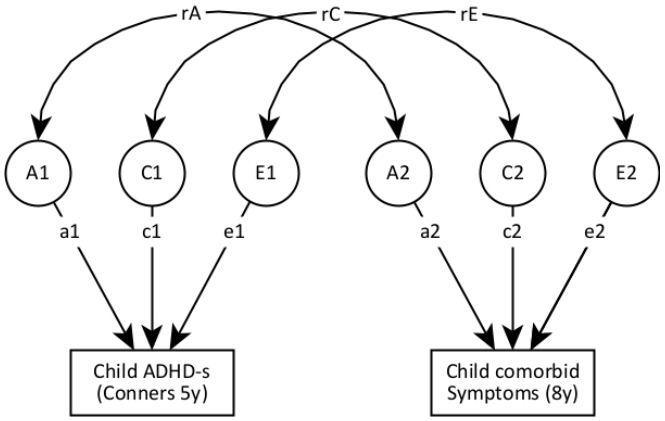
Number of items and Cronbach's alpha indicators of internal consistency for all raw measures (all mother-reported).		
Measure	Number of items	Cronbach's alpha (95% CI)
Adult ADHD (ASRS)	6	.73 (.72, .73)
Child ADHD Age 5 (CPRS-R)	12	.88 (.87, .88)
Child ADHD Age 8 (RS-DBD)	18	.91 (.91, .91)
Child ODD Age 8 (RS-DBD)	8	.84 (.84, .84)
Child CD Age 8 (RS-DBD)	8	.70 (.70, .71)
Child Anxiety Age 8 (SCARED)	5	.47 (.47, .48)
Child Depression Age 8 (sMFQ)	13	.79 (.79, .79)
ASRS = Adult Self-Report Scale; CPRS-R = Conners Parent Rating Scale-Revised Short Form; RS-DBD = Parent/Teacher Rating Scale for Disruptive Behavior; SCARED = Screen for Child Anxiety Related Disorders (SCARED); sMFQ = Short Moods and Feelings Questionnaire.		

Figure S3. MCoTS model specification



Model specification for the MCoTS model. A1, C1 and E1 latent factors represent parental additive genetic, shared environmental and non-shared environmental variance components. A2, C2 and E2 factors represent the equivalent variance components for children. A1' latent factors represent genetic variance components that are shared between the parent and child phenotype. Paths a1', c1', and p represent the proportion of the parent-child association explained by genetic transmission, extended family environmental influence, and residual association indicating an influence of exposure to the parental phenotype. *ADHD-s = ADHD symptoms.*

Figure S4. Extended bivariate twin model specification



Model specification for the Extended Bivariate Twin Model. A1, C1 and E1 latent factors represent additive genetic, shared environmental and non-shared environmental variance components for child ADHD symptoms at age 5. A2, C2 and E2 factors represent the equivalent variance components for child comorbid symptoms at age 8. Paths rA, rC, and rE represent genetic, shared environmental, and nonshared environmental associations underpinning the total phenotypic association between the two measures. *ADHD-s = ADHD symptoms.*

Table S5. Descriptive statistics of all measures used in MCoTS and extended bivariate twin analyses.

Descriptive statistics of all raw measures (all mother-reported).								
Measure	N	Mean	SD	Min.	Max.	Skew	Kurtosis	SE
Parity (no. previous births)	30,833	0.73	0.83	0	4	1.07	0.99	0.00
Maternal age at childbirth	30,833	30.12	4.18	17	45	0.03	-0.05	0.02
Year of childbirth	30,833	2005.68	1.78	2002	2009	-0.12	-0.84	0.01
Child sex	30,833	1.49	0.50	1	2	0.05	-2.00	0.00
Adult ADHD (ASRS)[a]	30,503	2.08	0.57	1	5	0.37	0.49	0.00
Child ADHD Age 5 (CPRS-R)	23,392	1.36	0.38	1	4	1.95	5.95	0.00
Child ADHD Age 8 (RS-DBD)	24,063	1.47	0.39	1	4	1.78	4.66	0.00
Child ODD Age 8 (RS-DBD)	24,021	1.43	0.39	1	4	1.38	3.11	0.00
Child CD Age 8 (RS-DBD)	24,010	1.10	0.19	1	3	2.92	11.42	0.00
Child Anxiety Age 8 (SCARED)	24,027	1.20	0.24	1	3	1.66	4.11	0.00
Child Depression Age 8 (sMFQ)	23,995	1.14	0.18	1	3	2.30	8.15	0.00

[a] *Includes 6,435 mothers who provided self-ratings of ADHD symptoms, but did not provide ratings of child symptom ratings at the waves studied (these extra maternal ADHD data were included to improve heritability estimates of adult ADHD symptoms). All other descriptives include only those mothers who provided at least one child symptom rating; ASRS = Adult Self-Report Scale; CPRS-R = Conners Parent Rating Scale-Revised Short Form; RS-DBD = Parent/Teacher Rating Scale for Disruptive Behavior; SCARED = Screen for Child Anxiety Related Disorders (SCARED); sMFQ = Short Moods and Feelings Questionnaire.*

Tables S6a and S6b. Preliminary univariate twin analyses for adult ADHD symptoms

Fit comparison tables and standardized parameter estimates from preliminary univariate models for adult (maternal) ADHD symptoms. Constraining shared environmental effects (C) to zero did not result in significantly worse model fit, whereas further constraining genetic effects (A) to zero did result in worse model fit. This indicated that variance on adult ADHD symptoms was explained by genetic and non-shared environmental effects, with no significant effect of shared environment. In the accepted AE models, the heritability of adult ADHD symptoms was estimated at 26%. Given the lack of shared environmental influences on adult ADHD symptoms, we opted not to estimate shared environmental influences (C1) nor extended family environmental influences (C1') on adult ADHD symptoms in MCoTS models.

Fit comparison tables of nested models testing the significance of genetic and shared environmental effects for adult ADHD symptoms.

Model	*-2LL*	*df*	*AIC*	∆*LL*	∆*df*	*p*
Full ACE	66488.79	23951	18586.79			
AE vs. ACE	66488.79	23952	18584.79	-1.29e-08	1	1
E vs. AE	66488.79	23953	18606.58	23.79	1	**< .001**

Standardized parameter estimates (95% CI) of genetic, shared, and non-shared environmental effects on adult ADHD symptoms.

Model	A	C	E
Full ACE	0.26 (0.17, 0.36)	<0.01 (0.00, 0.17)	0.74 (0.64, 0.91)
AE	0.26 (0.17, 0.36)	--	0.74 (0.64, 0.83)
E	--	--	1 (1, 1)

Table S7. MCoTS model fit comparisons

Fit comparison tables of nested models testing the significance of genetic transmission from adult (maternal) ADHD symptoms to each of the five child symptom measures at age 8.

Adult ADHD → Child ADHD 8y	*-2LL*	*df*	*AIC*	*ΔLL*	*Δdf*	*p*
Full model vs.	150441.1	54444	41553.10			
No genetic transmission (A1' = 0)	150583.4	54445	41693.38	142.28	1	**<.001**
Adult ADHD → Child ODD 8y						
Full model vs.:	150903.8	54433	42037.77			
No genetic transmission (A1' = 0)	151013.3	54434	42145.27	109.50	1	**<.001**
Adult ADHD → Child CD 8y						
Full model vs.:	151563.2	54486	42591.23			
No genetic transmission (A1' = 0)	151609.4	54487	42635.45	46.22	1	**<.001**
Adult ADHD → Child Anxiety 8y						
Full model vs.:	151737.7	54450	42837.69			
No genetic transmission (A1' = 0)	151799.0	54451	42897.03	61.34	1	**<.001**
Adult ADHD → Child Depression 8y						
Full model vs.:	150736.0	54418	41900.05			
No genetic transmission (A1' = 0)	150871.2	54419	42033.18	135.13	1	**<.001**

Table S8. Extended bivariate twin model fit comparisons

Fit comparison tables of nested models testing the significance of genetic and shared environmental overlap between child ADHD symptoms at age 5 and each of the five child symptom measures at age 8.

Child ADHD 5y → Child ADHD 8y	*-2LL*	*df*	*AIC*	*ΔLL*	*Δdf*	*p*
Full ACE	126790.2	47370	32050.22			
AE vs. ACE	126790.2	47373	32044.22	-1.37e-08	3	1
E vs. AE	127500.9	47376	32748.93	710.71	3	**<.001**
Child ADHD 5y → Child ODD 8y						
Full ACE	131527.0	47359	36809.04			
AE vs. ACE	131527.5	47362	36803.50	0.46	3	.93
E vs. AE	132322.6	47365	37592.65	795.15	3	**<.001**
Child ADHD 5y → Child CD 8y						
Full ACE	132705.1	47412	37881.09			
AE vs. ACE	132705.1	47415	37875.09	-1.40e-08	3	1
E vs. AE	133408.0	47418	38572.05	702.95	3	**<.001**
Child ADHD 5y → Child Anxiety 8y						
Full ACE	133814.8	47376	39062.79			
AE vs. ACE	133814.8	47379	39056.79	-7.74e-09	3	1
E vs. AE	134295.1	47382	39531.06	480.27	3	**<.001**
Child ADHD 5y → Child Depression 8y						
Full ACE	131637.3	47344	36949.30			
AE vs. ACE	131640.9	47347	36946.86	3.56	3	.31
E vs. AE	132349.4	47350	37649.45	708.59	3	**<.001**

Table S9. MCoTS and extended bivariate twin model parameter estimates

Standardized parameter estimates (95% CI) of phenotypic and genetic correlation coefficients between child ADHD symptoms at age 5, adult (maternal) ADHD symptoms, and each of the five child symptom measures at age 8.

Child measure at 8y	Child ADHD 5y		Adult ADHD	
	rPh	rA	rPh	rA
Child ADHD 8y	.60 (.59, .61)	.84 (.80, .89)	.25 (.23, .26)	.55 (.43, .93)
Child ODD 8y	.36 (.34, .37)	.70 (.64, .76)	.19 (.18, .20)	.80 (.46, 1)
Child CD 8y	.27 (.25, .28)	.43 (.36, .50)	.12 (.11, .14)	.44 (.28, 1)
Child Anxiety 8y	.10 (.09, .12)	.41 (.31, .51)	.11 (.10, .13)	.72 (.48, 1)
Child Depression 8y	.35 (.34, .37)	.64 (.57, .70)	.22 (.21, .23)	1 (.66, 1)

Appendix 2

Supplementary materials for Chapter 3

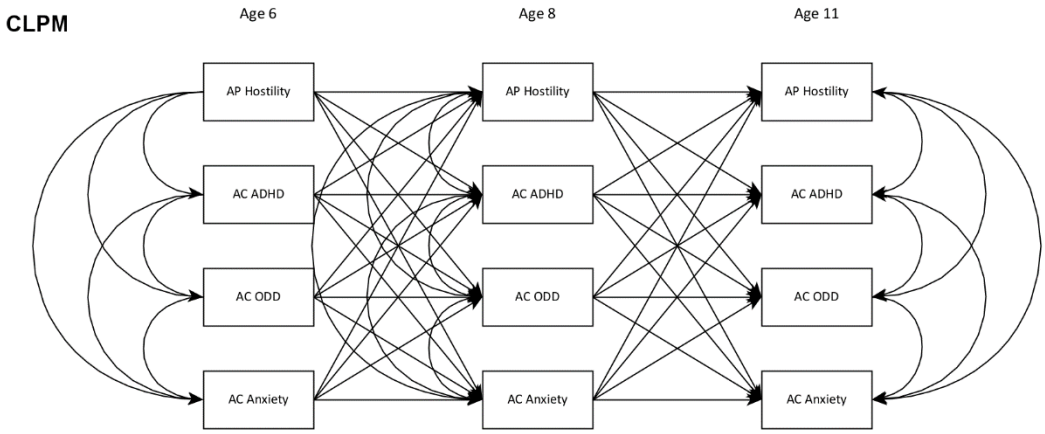
Table S1. Descriptive statistics for samples used in trio-GCTA analyses

Descriptive statistics for age 5 and age 8 subsamples.								
Measure	*N*	*Mean*	*SD*	*Min.*	*Max.*	*Skew*	*Kurtosis*	*SE*
Age 5								
Parity (no. previous births)	11,538	0.69	0.84	0	4	1.17	1.12	0.01
Maternal age at childbirth	11,538	30.45	4.32	18	45	0.10	-0.07	0.04
Year of childbirth	11,538	2006.08	1.52	2004	2009	0.13	-1.16	0.01
Child sex	11,538	1.49	0.50	1	2	0.05	-2.00	0.00
Child ADHD Age 5 (CPRS-R)	11,538	1.37	0.38	1	4	1.97	6.13	0.00
Age 8								
Parity (no. previous births)	11,526	0.72	0.85	0	4	1.12	0.97	0.01
Maternal age at childbirth	11,526	30.49	4.28	17	45	0.07	-0.05	0.04
Year of childbirth	11,526	2005.55	1.85	2002	2009	-0.04	-1.00	0.02
Child sex	11,526	1.48	0.50	1	2	0.06	-2.00	0.00
Child ADHD Age 8 (RS-DBD)	11,526	1.47	0.41	1	4	1.87	5	0.00
CPRS-R = Conners Parent Rating Scale-Revised Short Form; RS-DBD = Parent/Teacher Rating Scale for Disruptive Behavior.								

Appendix 3

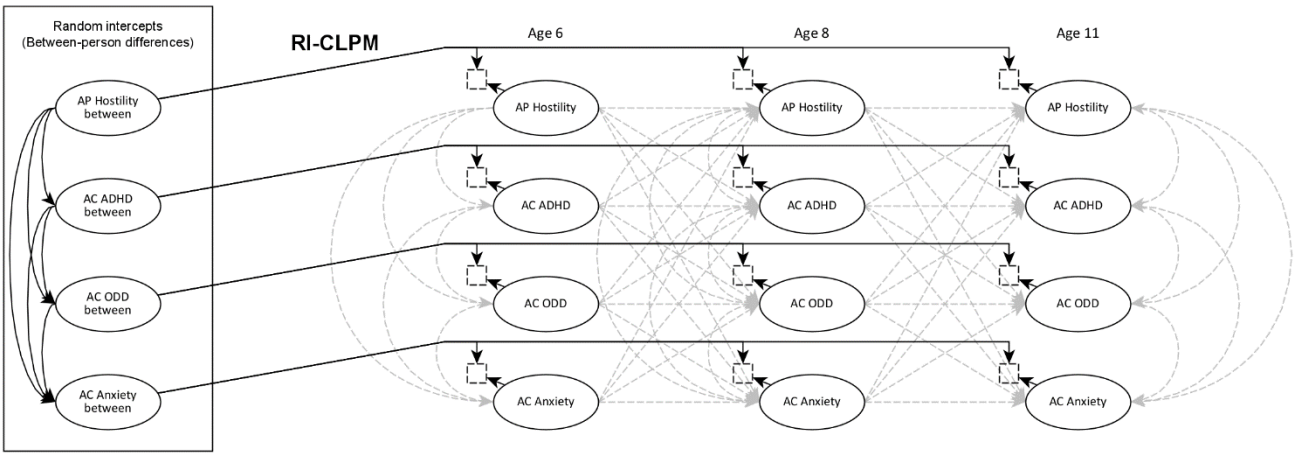
Supplementary materials for Chapter 4

Figure S1a. Model specification showing the standard CLPM model structure



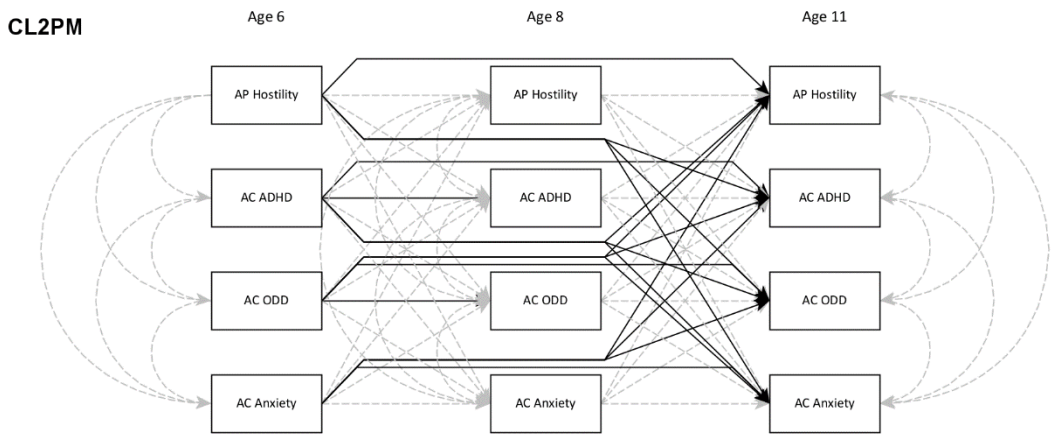
Model specification for the standard CLPM, including autoregressions, cross-lagged paths, first-wave correlations and second-wave (residual) correlations (control variables not shown). *AP = adoptive parent; AC = adopted child.*

Figure S1b. Model specification showing the RI-CLPM model structure



Model specification for the RI-CLPM, including all paths estimated in the CLPM, but observed variables decomposed into latent random intercepts (between-person factors) and latent mean-centred variables (within-person factors) All autoregressive, cross-lagged and correlation paths are then between mean-centred variables rather than observed variables. *AP = adoptive parent; AC = adopted child.*

Figure S1c. Model specification showing the CL2PM model structure



Model specification for the CL2PM, including all paths estimated in the CLPM, and additional lag-2 paths from measures at age 6 to measures at age 11. *AP = adoptive parent; AC = adopted child.*

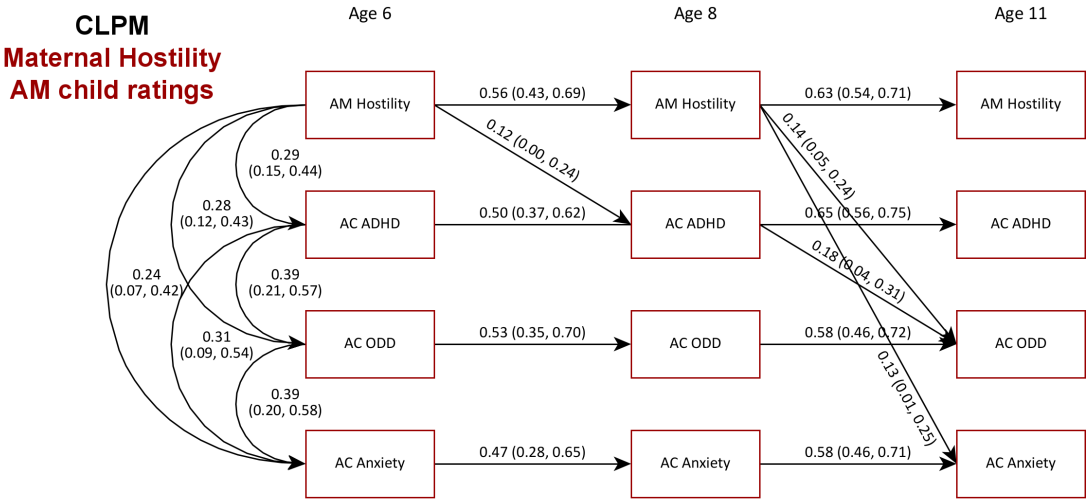
Table S2. Descriptive statistics for adoptive parent and adopted child measures

Descriptive statistics for all adoptive parent and adopted child measures at child ages 6, 8, and 11 years.					
	n	Mean	*SD*	Min	Max
Maternal Hostility (self-rated)					
6 years	237	10.87	2.94	5	21
8 years	215	10.71	2.88	5	21
11 years	242	11.39	3.36	5	24
Paternal Hostility (self-rated)					
6 years	217	10.94	3.23	5	22
8 years	170	10.5	3.07	5	19
11 years	212	10.82	3.39	5	21
Child ADHD symptoms (mother-rated)					
6 years	239	52.01	3.71	50	71
8 years	216	55.95	6.75	50	77
11 years	243	56.76	6.86	50	80
Child ODD symptoms (mother-rated)					
6 years	239	53.62	5.47	50	80
8 years	216	55.65	6.31	50	80
11 years	243	56.47	6.79	50	77
Child anxiety symptoms (mother-rated)					
6 years	239	52.23	4.97	50	82
8 years	216	53.86	6.31	50	82
11 years	243	55.62	7.61	50	91
Child ADHD symptoms (father-rated)					
6 years	222	52.29	3.89	50	76
8 years	172	55.55	6.38	50	78
11 years	211	56.1	7.05	50	80
Child ODD symptoms (father-rated)					
6 years	222	52.81	5.3	50	80
8 years	172	54.97	5.88	50	77
11 years	211	55.45	6.37	50	77
Child anxiety symptoms (father-rated)					
6 years	222	51.98	4.37	50	79
8 years	172	53.06	5.33	50	79
11 years	211	54.61	7.22	50	91

Table S3. Sensitivity model fit comparisons

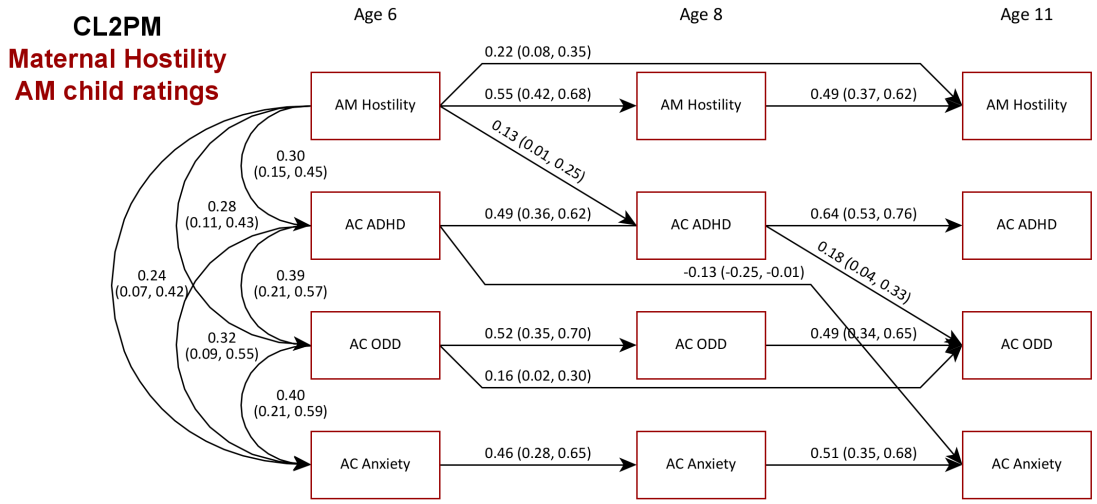
Fit statistics of Maternal and Paternal Hostility Sensitivity CLPMs, CL2PMs, and RI-CLPMs.						
	Sensitivity analyses (same parent ratings of child measures)					
	Maternal Hostility			Paternal Hostility		
	RMSEA (90% CI)	CFI	SRMR	RMSEA (90% CI)	CFI	SRMR
CLPM	0.058 (0.041, 0.076)	0.966	0.031	0.029 (0.000, 0.052)	0.990	0.027
CL2PM	0.058 (0.035, 0.079)	0.978	0.023	0.035 (0.000, 0.056)	0.987	0.021
RI-CLPM	0.051 (0.030, 0.071)	0.977	0.034	0.040 (0.001, 0.065)	0.986	0.030

Figure S4. Path diagram of the Maternal Hostility Sensitivity CLPM



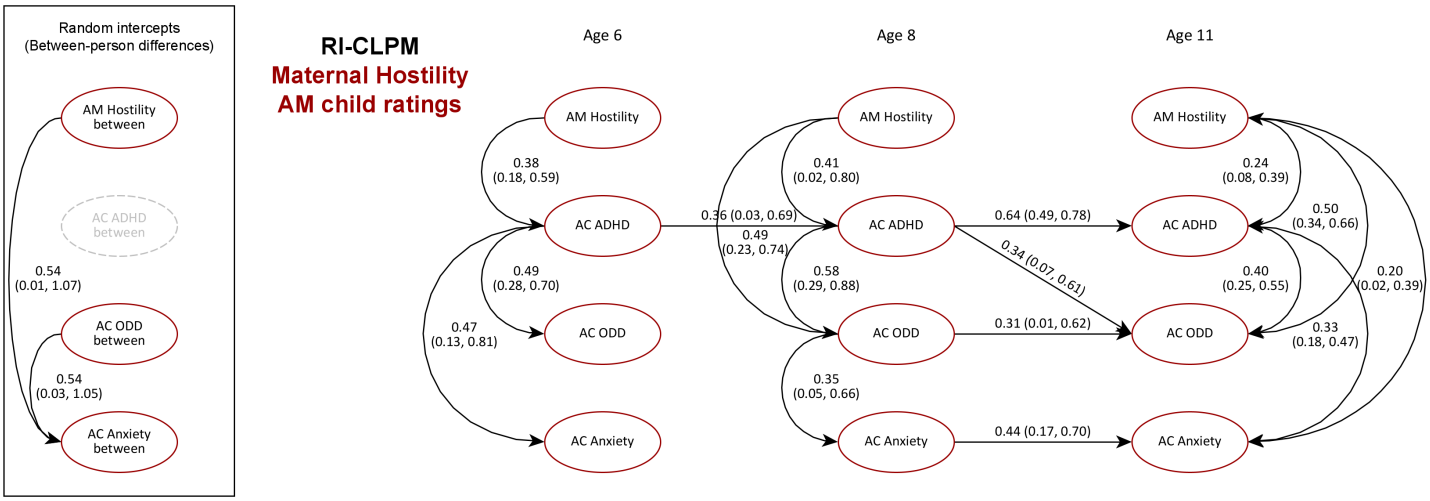
Path diagram of the Maternal Hostility Sensitivity CLPM with mother-rated child measures. Included are standardised parameter estimates of all significant cross-lagged, autoregressive and first-wave correlation paths. *AM = adoptive mother; AC = adopted child.*

Figure S5. Path diagram of the Maternal Hostility Sensitivity CL2PM



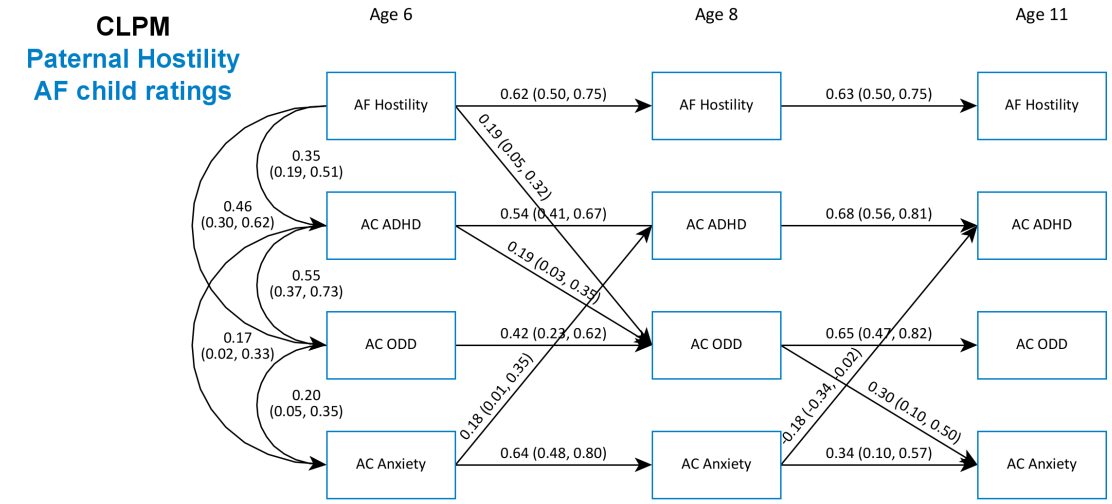
Path diagram of the Maternal Hostility Sensitivity CL2PM with mother-rated child measures. Included are standardised parameter estimates of all significant cross-lagged, autoregressive and first-wave correlation paths. *AM = adoptive mother; AC = adopted child.*

Figure S6. Path diagram of the Maternal Hostility Sensitivity RI-CLPM



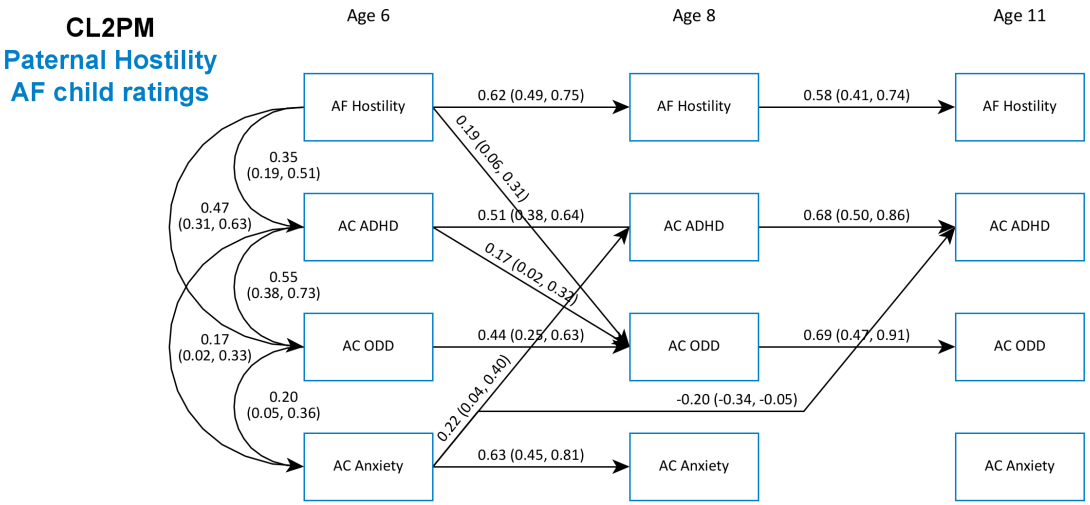
Path diagram of the Maternal Hostility Sensitivity RI-CLPM with mother-rated child measures. Included are standardised parameter estimates of all significant cross-lagged, autoregressive and first-wave correlation paths. Random intercepts and any significant correlations between them are displayed on the left, with non-significant random intercepts greyed out. *AM = adoptive mother; AC = adopted child.*

Figure S7. Path diagram of the Paternal Hostility Sensitivity CLPM



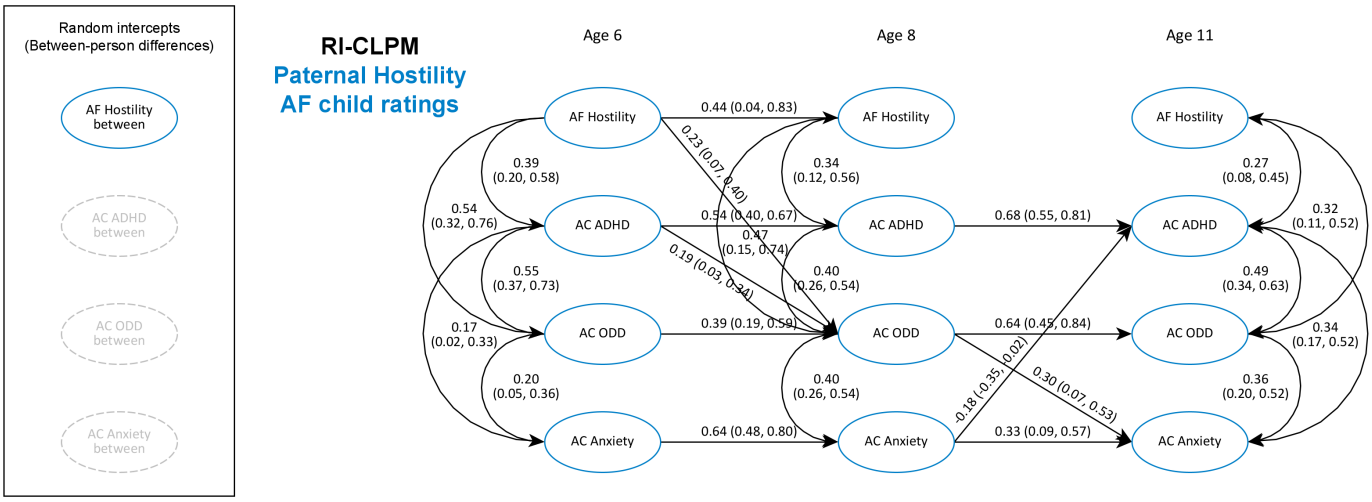
Path diagram of the Paternal Hostility Sensitivity CLPM with father-rated child measures. Included are standardised parameter estimates of all significant cross-lagged, autoregressive and first-wave correlation paths. *AF = adoptive father; AC = adopted child.*

Figure S8. Path diagram of the Paternal Hostility Sensitivity CL2PM



Path diagram of the Paternal Hostility Sensitivity CL2PM with father-rated child measures. Included are standardised parameter estimates of all significant cross-lagged, autoregressive and first-wave correlation paths. *AF = adoptive father; AC = adopted child.*

Figure S9. Path diagram of the Paternal Hostility Sensitivity RI-CLPM



Path diagram of the Paternal Hostility Sensitivity RI-CLPM with father-rated child measures. Included are standardised parameter estimates of all significant cross-lagged, autoregressive and first-wave correlation paths. Random intercepts and any significant correlations between them are displayed on the left, with non-significant random intercepts greyed out. *AF = adoptive father; AC = adopted child.*

Table S10. Standardised parameter estimates of tested indirect paths from Paternal Hostility models

Standardised parameter estimates, 95% confidence intervals and p-values of tested indirect paths from the Paternal Hostility CLPM and CL2PM.

Paternal Hostility CLPM (mother-rated child measures)		
	Estimate (95% CI) 3d.p.	p-value
ADHD 11y ← ADHD 8y ← Paternal Hostility 6y	0.118 (0.027, 0.209)*	0.011
ODD 11y ← ADHD 8y ← Paternal Hostility 6y	0.035 (0.001, 0.070)*	0.047
** < .05; ** < .01; *** < .001.*		
Paternal Hostility CL2PM (mother-rated child measures)		
	Estimate (95% CI) 3d.p.	p-value
ADHD 11y ← ADHD 8y ← Paternal Hostility 6y	0.124 (0.027, 0.220)*	0.012
ODD 11y ← ADHD 8y ← Paternal Hostility 6y	0.040 (0.001, 0.080)*	0.042
** < .05; ** < .01; *** < .001.*		