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ADHD, EPILEPSY, AND RELATED CHILDHOOD PSYCHOPATHOLOGY:

UNDERSTANDING SHARED GENETIC RISK, DEVELOPMENTAL TRAJECTORIES, AND PHARMACOLOGICAL TREATMENT SAFETY

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ADHD, EPILEPSY, AND RELATED CHILDHOOD PSYCHOPATHOLOGY: Understanding shared genetic risk, developmental trajectories, and pharmacological treatment safety

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“Most problems have either many answers or no answer.
Only a few problems have a single answer.”
- Edmund C. Berkeley

ABSTRACT

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder, affecting 5-7% of children and 2.5-5% of adults worldwide. The disorder is characterized by excessive and age-inappropriate symptoms of inattention, hyperactivity, and impulsivity, which impair everyday functioning across several settings (home, school, work). Although great advances have been made in ADHD research during the past decades, many questions remain regarding the causes and consequences of ADHD.

ADHD is conceptualized as an early onset disorder, underpinned by varying degrees of neurological delay or dysfunction that may be exacerbated by environmental factors. The disorder is developmentally complex, and extensive comorbidity with other psychiatric and non-psychiatric disorders is the rule rather than the exception. In this thesis, quantitative and molecular genetic research designs were used to explore important and poorly understood questions regarding development, treatment safety, and comorbidity in ADHD, epilepsy and related childhood psychopathology.

In Study 1, we addressed the question of whether perceived immaturity is related to the developmental course of ADHD from childhood to early adulthood. Using data from a longitudinal twin study, we estimated the overlap between ADHD and immaturity from ages 8-9 to 19-20 years. Results showed that immaturity plays a small but significant role in ADHD in childhood and adolescence, largely due to shared genetic factors that diminish in importance with age. We also showed evidence for ADHD-related genetic stability across ages, and genetic innovation during adolescence and early adulthood. These findings may partly explain why some children show a decrease in ADHD symptoms from childhood to early adulthood, whereas others show a more persistent, chronic, disorder expression.

In Study 2, we explore whether common genetic risk variants associated with ADHD also influences a broad range of related childhood psychopathology. Results suggested that genetic risk for ADHD, summed to a polygenic risk score (PRS), is associated with higher levels of neurodevelopmental, externalizing, and to a lesser extent, internalizing problems. Importantly, these associations could largely be attributed to a general psychopathology factor, capturing covariance across symptoms dimensions. These findings provide evidence for wide-spread genetic pleiotropy across psychiatric conditions, and support the notion that many identified genetic risk variants associated with ADHD are likely to non-specifically increase liability towards broad childhood psychiatric problems.

In Study 3, we broaden our focus beyond psychiatric conditions to address the overlap between ADHD and epilepsy using a family co-aggregation design. Results from this large, population based cohort suggest that ADHD and epilepsy commonly co-occur and that this risk increase extends to family members of epilepsy patients. Quantitative genetic analyses revealed only a moderate genetic overlap across the disorder. These findings suggest that, although highly comorbid, epilepsy may be less genetically related to ADHD as compared to traditional neurodevelopmental disorders.

In Study 4, we address the safety of ADHD pharmacological treatment in patients with a history of epileptic seizures. Using a within-individual comparison design to adjust for time-constant confounders that vary between individuals (e.g. baseline disorder severity, shared genetic liability), we found that ADHD medications were not associated with an increased risk of acute epileptic seizures. Despite long-standing concerns regarding the safety of stimulant ADHD medications in epilepsy patients, these findings suggest that ADHD medication treatment may be a safe and viable option even in patients with a seizure history.

The main findings from this thesis suggest that ADHD is related to both later maturation and a wide range of comorbid psychiatric conditions, partly due to shared genetic risk factors. Importantly, the shared genetic liability between ADHD and related psychiatric conditions appears to be in part attributable to a general liability towards broad childhood psychopathology. In contrast, epilepsy and ADHD comorbidity seems to be less influenced by shared genetic factors and more strongly influenced by environmental factors not shared by family members. ADHD medication does however not appear to be a risk factor for acute epileptic seizures among individuals with a seizure history.

Taken together, results from this thesis highlight important aspects of development and comorbidity in ADHD, and lends support to the hypothesis ADHD may be considered part of broader continuum of psychopathology that is underpinned by partly shared genetic factors. Based on evidence thus far, this genetic shared liability appears less strongly related to epilepsy.

LIST OF SCIENTIFIC PAPERS

I. Brikell I, Kuja-Halkola R, Larsson J-O, Lahey BB, Kuntsi J, Lichtenstein P, Rydelius PA, Larsson H. Relative Immaturity in Childhood and Attention-Deficit/Hyperactivity Disorder Symptoms From Childhood to Early Adulthood: Exploring Genetic and Environmental Overlap Across Development. *J Am Acad Child Adolesc Psychiatry*. 2016;55(10):886-95

II. Brikell I, Larsson H, Lu Y, Pettersson E, Chen Q, Kuja-Halkola R, Karlsson R, Lahey BB, Lichtenstein P, Martin J. The contribution of common genetic risk variants for ADHD to a general factor of childhood psychopathology. *Manuscript.*

III. Brikell I, Ghirardi L, D'Onofrio BM, Dunn DW, Almqvist C, Dalsgaard S, Kuja-Halkola R, Larsson H. Familial Liability to Epilepsy and Attention-Deficit/Hyperactivity Disorder: A Nationwide Cohort Study. *Biological Psychiatry*. 2018;83(2):173-80

IV. Brikell I, Chen Q, Kuja-Halkola R, D'Onofrio BM, Wigg KK, Quinn PD, Chang Z, Larsson H. ADHD medication treatment and the risk of seizures in individuals with a seizure history: A nationwide cohort study. *Manuscript.*

RELATED PUBLICATIONS

(not included in thesis)

I. Brikell I, Kuja-Halkola R, Larsson H. Heritability of attention-deficit hyperactivity disorder in adults. *Am J Med Genet B Neuropsychiatr Genet*. 2015;168(6):406-13

II. Chen Q, Brikell I, Lichtenstein P, Serlachius E, Kuja-Halkola R, Sandin S, et al. Familial aggregation of attention-deficit/hyperactivity disorder. *J Child Psychol Psychiatry*. 2017;58(3):231-9.

III. Ghirardi L, Brikell I, Kuja-Halkola R, Freitag CM, Franke B, Asherson P, et al. The familial co-aggregation of ASD and ADHD: a register-based cohort study. *Mol Psychiatry*. 2017

IV. Du Rietz E, Kuja-Halkola R, Brikell I, Jangmo A, Sariaslan A, Lichtenstein P, et al. *Predictive validity of parent- and self-rated ADHD symptoms in adolescence on adverse socioeconomic and health outcomes.* Eur Child Adolesc Psychiatry. 2017;26(7):857-67

V. Martin J, Walters RK, Demontis D, Mattheisen M, Lee SH, Robinson E, et al. A Genetic Investigation of Sex Bias in the Prevalence of Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry*.2017

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention-deficit/hyperactivity disorder
AEDs	Antiepileptic drugs
ANX	Anxiety symptoms
ASD	Autism spectrum disorder
ATC	Anatomical Therapeutic Chemical
CATSS	Child and Adolescent Twin Study in Sweden
CD	Conduct disorder
CDR	Cause of Death Register
CI	Confidence interval
CNV	Copy number variant
DAG	Directed acyclical graph
DEP	Depression symptoms
DSM	Diagnostic and Statistical Manual of Mental Disorders
GWAS	Genome-wide association study
HKD	Hyperkinetic disorder
HR	Hazard ratio
ICD	International Classification of Diseases and related health problems
ID	Intellectual disabilites
LD	Learning disorder
MBR	Medical Birth Register
MGR	Multi-Generation Register
NDD	Neurodevelopmental disorder
NPR	National Patient Register
ODD	Oppositional defiant disorder
OR	Odds ratio
PDR	Prescribed Drug Register
PGC	Psychiatric Genomics Consortium
PIN	Personal Identification Number
PRS	Polygenic risk score

RI	Relative immaturity
SNP	Single nucleotide polymorphism
STR	Swedish Twin Register
TCHAD	Twin Study of Child and Adolescent Development

1 INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most commonly diagnosed neuropsychiatric disorder among children today. On average, every classroom of 30 students will have 1 to 3 children with ADHD. Like all complex psychiatric conditions, ADHD is a multifactorial disorder, and no single risk factor is either necessary or sufficient to explain ADHD.[1] Epidemiological and genetic research is beginning to unravel the complex nature of ADHD, with considerable evidence highlighting the importance of genetics in the etiology, development and comorbidity of ADHD.

Despite showing strong heritability across the lifespan, ADHD is not a developmentally stable disorder, with some patients showing a steady decline of symptoms from childhood to adulthood and others showing a more persistent, chronic disorder progression.[2-4] The causes underlying these different trajectories remain unclear, but both maturational processes and genetic influences have been proposed to contribute to the developmental course of ADHD.[5-7] Studying the contribution of genetic and environmental factors to the association between maturity and ADHD thus has the potential to improve understanding of remission and persistence of ADHD from childhood into adulthood.

Beyond developmental complexity, comorbidity is a hallmark feature of ADHD.[8] Growing evidence from genetic research suggest that widespread sharing of genetic risk across psychiatric conditions may partly explain this high level of comorbidity.[9,10] Due to the central role of ADHD in childhood psychiatry, studying the influence of ADHD genetic risk on related psychiatric traits may provide important insights of the genetic architecture of childhood psychopathology.

ADHD does not only co-occur with psychiatric conditions, but is also associated with neurological disorders. Among children with ADHD, 2-4% are affected by epilepsy,[11,12] whereas 10-30% of children with epilepsy have an ADHD diagnosis.[13-15] Despite this, research on comorbid ADHD and epilepsy is limited. To complicate matters further, there are concerns regarding the safety of pharmacological treatment of ADHD in this patient group. Well-powered epidemiological studies investigating the underlying causes of comorbidity, and treatment safety of ADHD in comorbid ADHD and epilepsy are therefore urgently needed.

This thesis includes four studies investigating the role of shared genetic factors for maturity and childhood psychiatric comorbidity in ADHD, as well as etiology and treatment safety in comorbid ADHD and epilepsy. In order to study the role of genetic and environmental factors in disease associations, and to evaluate treatment safety, these studies relied on data from Swedish national registers and population-based cohorts, and employed various quantitative and molecular genetic research methods.

2 BACKGROUND

2.1 ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

ADHD is a childhood onset neurodevelopmental disorder (NDD), characterized by excessive and age-inappropriate symptoms of inattention, hyperactivity, and impulsivity.[16] ADHD was first made reference to in medical literature in 1775 and further described in 1902 in the Lancet in a case series of children presenting with characteristic ADHD.[1] The disorder shows marked heterogeneity at clinical, etiological, and pathophysiological levels and although given the same diagnosis, symptoms presentation and degree of impartment varies greatly between individuals with ADHD.[1] To date, there are no tests or biomarkers for ADHD and diagnosis is made based on symptom assessment.[17]

Table 2.1. Key diagnostic symptoms of ADHD

Inattentive symptoms	Hyperactivity or impulsivity symptoms
❖ Does not give close attention to details or makes careless mistakes	❖ Fidgets with or taps hands or feet, or squirms in seat
❖ Has difficulty sustaining attention on tasks or play activities	❖ Leaves seat in situations when staying seated is expected
❖ Does not seem to listen when directly spoken to	❖ Runs about or climbs when not appropriate (may present as feelings of restlessness in adolescents or adults)
❖ Does not follow through on instructions and does not finish schoolwork, chores, or duties in the workplace	❖ Unable to play or undertake leisure activities quietly
❖ Has trouble organizing tasks or activities	❖ "On the go", acting as if "driven by a motor"
❖ Avoids, dislikes, or is reluctant to do tasks that need sustained mental effort	❖ Talks excessively
❖ Loses things needed for tasks or activities	❖ Blurts out answers before a question has been finished
❖ Easily distracted	❖ Has difficulty waiting his or her turn
❖ Forgetful in daily activities	❖ Interrupts or intrudes on others

2.1.1 Diagnostic assessment

ADHD is classified according to two parallel diagnostic systems: The International Classification of Diseases and Related Health Problems (ICD),[18] which is predominantly used in Europe, and the Diagnostic and Statistical Manual of Mental Disorders (DSM),[16] which is predominantly used North America. In the ICD, ADHD is referred to as Hyperkinetic disorder (HKD). HKD requires the presence of both inattentive and hyperactive/impulsive symptoms across two or more settings (e.g. school and home) and tends to capture more severe cases. In the DSM-5 which was introduced in 2013, ADHD diagnosis can be based on the presence of either inattentive or hyperactive/impulsive symptoms that are inconsistent with developmental level and cause impairment in social and academic/occupational functioning. Unlike the ICD,

the DSM-5 recognizes three subtypes of ADHD; primarily inattentive, primarily hyperactive-impulsive, and a combined type.[16] Core diagnostic symptoms of ADHD are outlined in Table 2.1. Several changes were made in the diagnostic criteria of ADHD in the DSM-5: ADHD was moved from the disruptive behavior disorders category, which includes conduct disorder (CD) and oppositional defiant disorder (ODD), and reclassified under the NDD umbrella, together with intellectual disabilities (ID), communication disorders, autism spectrum disorder (ASD), and specific learning and motor disorders. Further, the age of onset changed from prior to age 7 to age 12, and age-appropriate criteria for assessment in adults were included. These changes were the result of more than a decade of research demonstrating the high degree of persistence in ADHD across the lifespan, variability in the age of onset, and considerable phenotypic and genotypic overlap with other NDDs.

2.1.1 Prevalence

ADHD affects 5-7% of children[19,20] and 2.5-5% of adults worldwide.[21,22] Variability is primarily explained by methodological differences between studies, including diagnostic criteria used, source of information, and requirement of functional impairment for a diagnosis.[21,23] Although there is concern regarding the rising rates of clinical ADHD diagnoses, there is no strong evidence to suggest that the prevalence of the underlying symptoms have increased over the past three decades according to meta-analyses.[21] In a recent Swedish study, clinical diagnosis of ADHD were found to have increased fivefold from 2004 to 2014. However, the prevalence of diagnostic-level ADHD based on parent-ratings among 19,271 9-year old twins were found to not changed significantly over time.[24] Research suggest that increased rates of clinically diagnosed ADHD may be largely explained by changes in clinical practices, greater public awareness of ADHD, and better access to healthcare. Nonetheless, over-diagnosis in certain age groups and geographical areas cannot be ruled out, whereas under-diagnosis is likely still an issue in females and adult populations, although this seem to be changing.[25-29] In childhood, boys are significantly more likely have an ADHD diagnosis than girls, with a male-to-female sex ratio of 4:1 in clinical samples and 2.4:1 in population-based samples.[30] These differences decrease with age.[31] The reason for such sex difference remain largely unknown.[32]

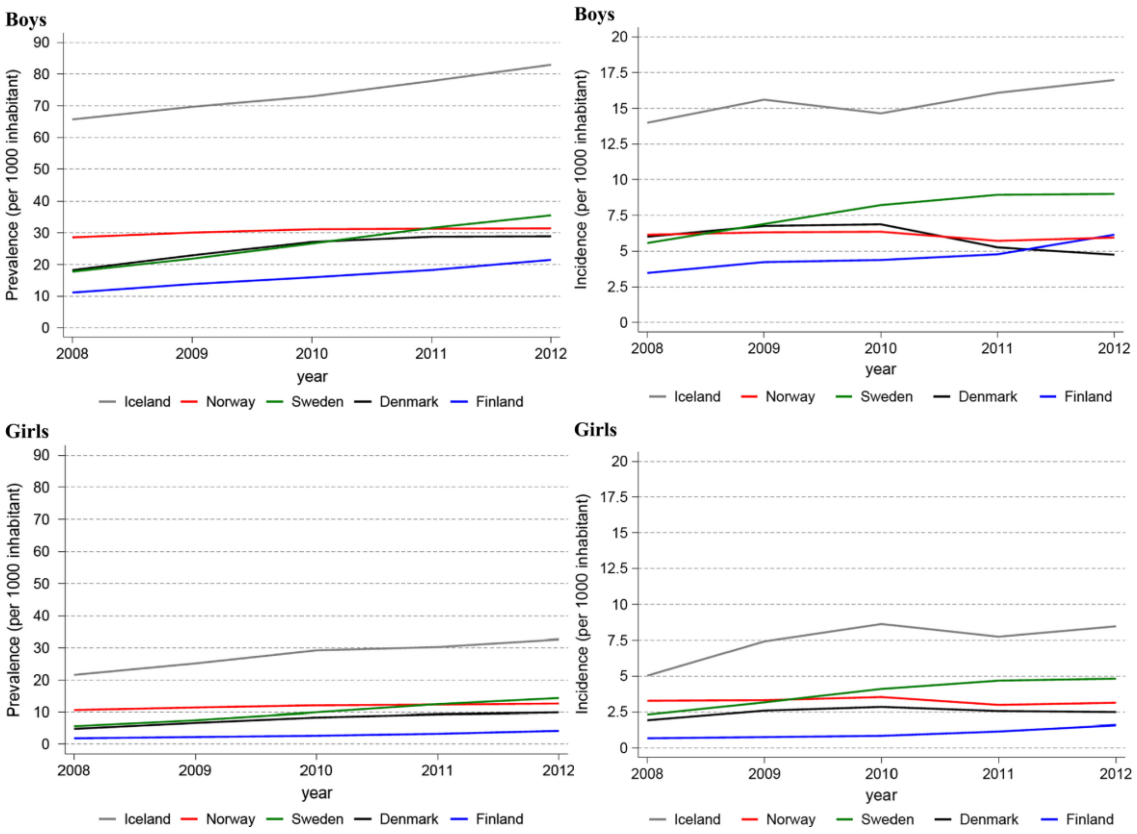
2.1.2 Pharmacological treatment

Stimulant mediations are first-line pharmacological treatment for ADHD. Currently approved medications in Sweden are methylphenidate, amphetamine, dexamphetamine, and lisdexamfetamine. ADHD can also be treated with non-stimulant medications when patients do not respond to stimulant treatment, in the presence of comorbidities where there are concerns regarding the pharmaceutical action of stimulants, or when wishing to avoid their addictive potential. Non-stimulant medications approved in Sweden are atomoxtine, and since 2015, guanfacin. Treatment guidelines from the Swedish Medical Products Agency recommend pharmacotherapy with methylphenidate from age six onward, when considered necessary and in conjunction with non-pharmacological interventions.[33]

There is considerable support for the short-term efficacy of stimulant medication treatment, and to a lesser extent non-stimulant medications, in the reduction of ADHD core symptoms in children and adults.[34,35] Evidence from pharmacoepidemiological studies further suggest that pharmacological treatment of ADHD is associated with a decreased risk of crime,[36] accidents and injuries,[37,38] suicide,[39,40] academic failure[41], and development of later substance use and mood disorders.[42,43] Common adverse effects of stimulants include small increases in blood pressure, headache, sleep disturbances, decreased appetite, abdominal pain, and small, although often not persistent, delays in growth amongst children.[44] Whilst treatment is considered relatively safe in patients with ADHD alone, less is known about the safety in patients with comorbid conditions, including epilepsy (see section 2.3.2.6).[35,44,45]

In the past two decades, prescription rates of ADHD medications have progressively increased, with the highest rates observed in western countries.[46,47] In the Nordic countries, the highest increase of prevalent and incident users are reported in Sweden, Iceland and Finland (Figure 2.1),[48] with variations reported by geographic region within countries.[33,49] In general, increasing prescription rates tend to follow the increased prevalence of ADHD diganoses.[33,49]

Figure 2.1. Annual prevalence (per 1000 boys/girls) and annual incidence (new users per 1000 boys/girls) of ADHD drug use among boys and girls aged 6–17 years by country, 2008–2012.



Note: New users were defined as not filling a prescription for ADHD drugs during the previous 24 months. *©2016 Nordic Association for the Publication of BCPT (former Nordic Pharmacological Society). From Furu K, et al. Basic & Clinical Pharmacology & Toxicology. Volume 120, Issue 4, pages 373-379, 30 JAN 2017 DOI: 10.1111/bcpt.12724. Reproduced with permission from Wiley Press.*

2.1.3 Etiology

It is well established that genetic factors strongly contribute to the disease liability in ADHD.[50-52] Whilst there are non-genetic and environmental factors that have been robustly associated with ADHD, the causal nature of such factors, and their interplay with genetic risk, remain unclear.[1] Much of our current understanding of the etiology of ADHD comes from quantitative genetic research. Interestingly, evidence from more recent and fast-paced advances in molecular genetic ADHD research generally supports many of the robust, replicated findings from twin- and family studies. An overview of these findings is provided Table 2.2 and discussed throughout this thesis.

2.1.3.1 Genetic factors in the etiology of ADHD

Meta-analyses of twin studies have estimated the heritability (i.e. the proportion of variation in a trait that can be attributed to genetic factors) of ADHD to be 70-80% in childhood, making it one of the most heritable psychiatric conditions.[50] Heritability estimates are similar across sex and symptom dimensions of inattention and hyperactivity/impulsivity.[50,53-55] Although heritability estimates of ADHD in adults tend be lower, this appears to be largely explained by rater effects, with self-ratings which are commonly used in adult samples leading to lower heritability estimates. When estimated from multiple raters or clinical diagnoses, heritability estimates for ADHD do not differ substantially with age.[51] Twin studies have reported strong genetic links between clinically relevant ADHD and subthreshold variation in ADHD,[56,57] and a genetic correlation (r_g) of 0.56 between ICD-based ADHD and ADHD symptoms.[58] This suggest that the clinical diagnosis of ADHD represents the extreme end of ADHD traits that are continuously distributed in the population, and that the genetic factors which influence the clinical disorder also account for the symptoms distribution in the population.

More recent molecular genetic studies have provided convincing direct evidence that ADHD is a highly polygenic trait (i.e. many genes of small effect contributing to disorder liability). The largest genome-wide association study (GWAS) of ADHD to date, including 20,183 cases and 35,191 controls, has identified 12 genome-wide significant independent loci associated with ADHD case status.[59] The study also showed that when estimating heritability from all common genetic variants (i.e. single nucleotide polymorphisms [SNPs]) measured in the GWAS, the SNP-based heritability of clinical ADHD was estimated at 22%.[59] Similarly, previous estimates from GWAS data collected in population-based samples have reported SNP-based heritability of 5% to 34% for ADHD symptoms.[60] Further, several recent studies suggest that rare mutations (e.g. copy number variants [CNVs] and non-inherited *de novo* mutations) are also implicated in the disease etiology of ADHD.[1,61-63] Molecular genetic findings also support the dimensional nature of ADHD; when considered *en masse*, genetic risk variants associated with clinical ADHD have been found to predict variation in ADHD symptoms,[58,64-67] and vice versa.[68] Further, the genetic correlation between GWAS summary statics based on clinical ADHD and ADHD symptoms has been estimated at r_g=0.94,[59,60] suggesting a near complete genetic overlap across clinically defined ADHD and population variation in ADHD symptoms.

Table 2.2. Understanding the etiology of ADHD: A summary of the top replicated findings from quantitative and molecular genetic research

Finding	Quantitative genetic	Molecular genetic
ADHD shows substantial genetic influence by many genes of small effect	❖ Twin-based h^2 =70-80%[50,69]	❖ 12 independent genome-wide significant loci associated with ADHD case status[59] ❖ SNP-based h^2 = 22%[59] ❖ Rare variants associated with ADHD[52,61-63]
Clinical ADHD and ADHD symptoms in the population are underpinned by the same genetic factors	❖ Strong genetic link between extreme and subthreshold variation in ADHD[56] ❖ Twin r_g = 0.56 between ICD-based ADHD and ADHD symptoms in the population[58]	❖ r_g=0.94 between clinical ADHD and ADHD symptoms[59,60] ❖ PRS for clinical ADHD predicts ADHD symptoms[58,64-67], and vice versa[68]
Phenotypic correlations between ADHD and comorbid traits show substantial genetic mediation	Twin r_g with ADHD (range) ❖ ASD (0.54-0.87) [9] ❖ LD (0.31-0.41) [70-72] ❖ ODD/CD (0.46-0.74) [73-76] ❖ Anxiety (0.45-0.58) [9] ❖ Depression (0.34-0.77) [9]	Significant r_g or PRS association with ADHD ❖ ASD[64,77,78] ❖ IQ, educational attinment, and LD[59,79-82] ❖ CD[83] ❖ Depression[59,81]
Stability in ADHD across ages is mainly due to genetics	❖ h^2 in ADHD is stable across lifespan[51] ❖ Genetic factor contribute to stability across ages	❖ ADHD PRS more strongly associated with persistent ADHD[65]
Many 'environmental' risk factors for ADHD are genetically mediated	❖ Association between smoking during pregnancy and offspring ADHD is genetically mediated[84-86]	❖ ADHD is genetically associated with smoking (r_g =0.48)[59,81]
Most environmental effects influencing ADHD are not shared by within families	❖ Limited evidence for role of twin and sibling shared environment in ADHD[69,87]	na

Note: h^2, twin or SNP-based heritability. na, not available. PRS, polygenic risk score (see section 5.2 3). r_g, twin or SNP-based genetic correlation. Table adapted from Plomin., et al (2016).[88]

2.1.3.2 Non-genetic factors in ADHD

Observational studies have linked ADHD to several non-genetic risk factors, including pre- and perinatal conditions, toxins, dietary factors, and psychosocial adversities.[89] Yet, it remains unclear whether they represent causal risk factors. For example, smoking during pregnancy was long postulated to be a causal risk factor for offspring ADHD, but evidence from genetically informative studies strongly suggests that the association is better explained by unmeasured familial confounding.[84,85,90] In contrast, risk factors such as low birth weight, advanced paternal age at childbearing, low family income, and severe psychosocial deprivation, continue to show associations with ADHD after accounting for important familial confounding, suggesting these may represent causal risk factors for ADHD.[91-94] Emerging evidence suggests a potential role of pre- and perinatal exposure to environmental toxins[95] and medication use[96-99] in the risk of ADHD but more research is needed to make firm conclusions.

2.2 DEVELOPMENT IN ADHD

Although ADHD was long considered a childhood limited disorder, it is now generally recognized that ADHD can be a chronic disorder associated with impairment in psychosocial, educational, occupational, and health related outcomes across the lifespan.[100-102] Meta-analyses of longitudinal studies suggest that whilst only about 15% of childhood cases retain a full diagnoses in early adulthood, an additional 65% continue to experience symptoms at an impairing level.[4] It remains largely unknown why symptoms remit for some and persist in others, however genetic factors and maturation have been associated with differential developmental trajectories in ADHD.[5,103]

2.2.1.1 Genetic factors and development in ADHD

Quantitative genetic studies suggest that persistence and remittance in ADHD are to some extent underpinned by different genetic factors. Family studies have found evidence for higher familial risk in relatives of adult ADHD cases, suggesting that persistent ADHD may be associated with a higher genetic burden.[69,104,105] Longitudinal twin studies have shown that stability in ADHD symptoms across ages is largely due to the stable genetic factors, whereas developmental changes in symptoms levels appear to be largely due to environmental factors and the emergence of new genetic factors influencing ADHD at later ages.[7,53,54,57,106,107] At least one longitudinal molecular genetic study has found individuals with persistent ADHD trajectories to have a higher burden of common ADHD associated variants, as compared to individuals with childhood-limited ADHD.[65] Together, evidence of stable genetic risk suggest that childhood ADHD and the adult form of the disorder are genetically linked, whereas evidence of dynamic genetic risk factors suggests that the set of genetic variants accounting for the onset of ADHD partly differs from those accounting for the persistence and remission of the disorder.

2.2.1.2 Maturation and ADHD

Neuro-imaging data have shown that children with ADHD attain peak cortical thickness and surface area 2-3 years later than controls, suggesting that ADHD may be related to delayed brain maturation.[108] Similar results have been found in normally developing children, where higher levels of attention and hyperactivity/impulsivity have been associated with slower cortical maturation.[109,110] Interestingly, there is some evidence to suggest that remittance of ADHD symptoms may be associated with a maturational catch-up in cortical development, whereas persistence of symptoms seem to be associated with atypical developmental trajectories of fixed or accelerated cortical thinning.[5]Although such findings suggests that ADHD in childhood may be linked to late neurodevelopmental maturation, the role of maturation in ADHD requires further research.

Several epidemiological studies have reported that birth-month is associated with the receiving a clinical ADHD diagnosis and medications, with a higher risk among children who are born late in the school-year and therefore the youngest in their grade. This effect has been found in countries with different school and health-care systems (i.e., Sweden, Norway, the US, Canada, Netherlands, Germany, Iceland, Spain, Israel, Australia and Taiwan).[111-122] Although these findings may in part reflect later neurodevelopmental maturation among the youngest children in a school-year, it likely also reflects an increased risk of misdiagnosis of ADHD due to parents and teachers subjective comparisons of immaturity across children within a school-year.[111]

Considering the age-dependent decline of ADHD symptoms, it is possible that perceived immaturity is more important for ADHD in childhood compared with adulthood, where maturational differences even out. Further, some of the dynamic genetic effects reported in developmental trajectories of ADHD could in part reflect etiological factor related to maturation. Therefore, longitudinal, genetic research is needed to understand the role of perceived immaturity in the development of ADHD, and how genetic and environmental influences contribute to the association across development.

2.3 COMORBIDITY IN ADHD

Comorbidity is the rule, rather than the exception in ADHD, with 60-70% of ADHD cases reported to have at least one or more comorbid psychiatric disorder.[8,123] In childhood, which is the primary focus of this thesis, the most common co-occurring conditions are NDDs and externalizing problems, including CD and ODD. Prevalent comorbidities with a typically later onset extends to internalizing disorders, including depression and anxiety.[8,124,125] Beyond psychiatric comorbidity, there is a growing awareness that ADHD is also associated with neurological conditions, including epilepsy,[14,126] which is an additional focus of this thesis work. Despite the high level of comorbidity between ADHD and psychiatric disorders, and to a lesser extent neurological conditions, the genetic and environmental causes underpinning these associations are not fully understood.

2.3.1 ADHD and related childhood psychopathology

2.3.1.1 Shared genetic risk between ADHD and related childhood psychopathology

Quantitative genetic studies provide strong evidence that phenotypic correlations between ADHD and comorbid conditions are mediated by shared genetic factors (Table 2.2). Several twin studies have reported a substantial overlap between ADHD and ASD, measured as both as traits and categorical disorders.[9] Register-based family studies have also reported a significantly increased risk of ADHD in relatives of individuals with ASD.[127] Genetic associations between ADHD and learning problems have also been reported, with difficulties in reading and mathematics showing a stronger genetic association with inattentive, rather than hyperactive/impulsive, symptoms.[70-72] One recent large-scale family study found significant familial co-aggregation for ADHD and ID, and evidence suggesting that 91% of the cross-disorder correlation could be attributed genetic factors.[128] A large number of twin and family studies have demonstrated genetic overlaps of ADHD with ODD and CD, and comorbidity across all three conditions seems largely influenced by one shared genetic factor.[73-75,129] Although less researched, family studies suggest that the co-occurrence of ADHD, depression and anxiety is influenced by shared familial factors.[130-132], and twin studies have reported moderate to strong genetic correlations between the conditions.[9,133]

Recent evidence from molecular genetic studies have generally confirmed cross-disorder genetic associations previously found quantitative genetic studies. Genetic risk implicated in ADHD have been associated with lower cognitive abilities, IQ, and poorer educational attainment.[59,79-81] Several studies have reported significant genetic overlap between ADHD and ASD, at the level of both common and rare variants,[61,64,77,78] whereas other studies found no association.[134-137] Higher ADHD genetic burden has also been reported in children diagnosed with ADHD and comorbid CD, relative to children with ADHD-only and controls.[83] Three studies have reported no significant genetic overlap between ADHD, anxiety and depression,[136-138] whereas two more recent studies, relying on ADHD GWAS data with larger sample size, have identified a significant genetic association with depression.[59,81]

2.3.1.2 A shared genetic liability across all childhood psychopathology?

Based on the extensive phenotypic and genotypic overlap observed in psychiatry, is has been hypothesized that psychiatric comorbidity may be attributed to a general genetic liability that increases the risk for virtually all psychiatric conditions.[139,140] In twin studies, a latent genetic factor has been found to account for up to 45% of co-variance across childhood externalizing, internalizing and phobia symptoms,[139] and 31% of co-variance across childhood neurodevelopmental symptoms.[141] Similar results have been reported for register-based clinical diagnoses, with a general genetic factor explaining 10-36% of disorder liability across several psychiatric diagnoses.[142] The twin-based heritability of such a general psychopathology factor has been estimated at 43% in one twin-study,[143] and the SNP-based heritability at 18%[144] and 38%[145] in two pediatric population samples. Assessing the extent to which cross-disorder

associations in psychiatry can be attributed to a broadly shared genetic liability may provide insight into the genetic architecture of childhood psychopathology.

2.3.2 ADHD and epilepsy

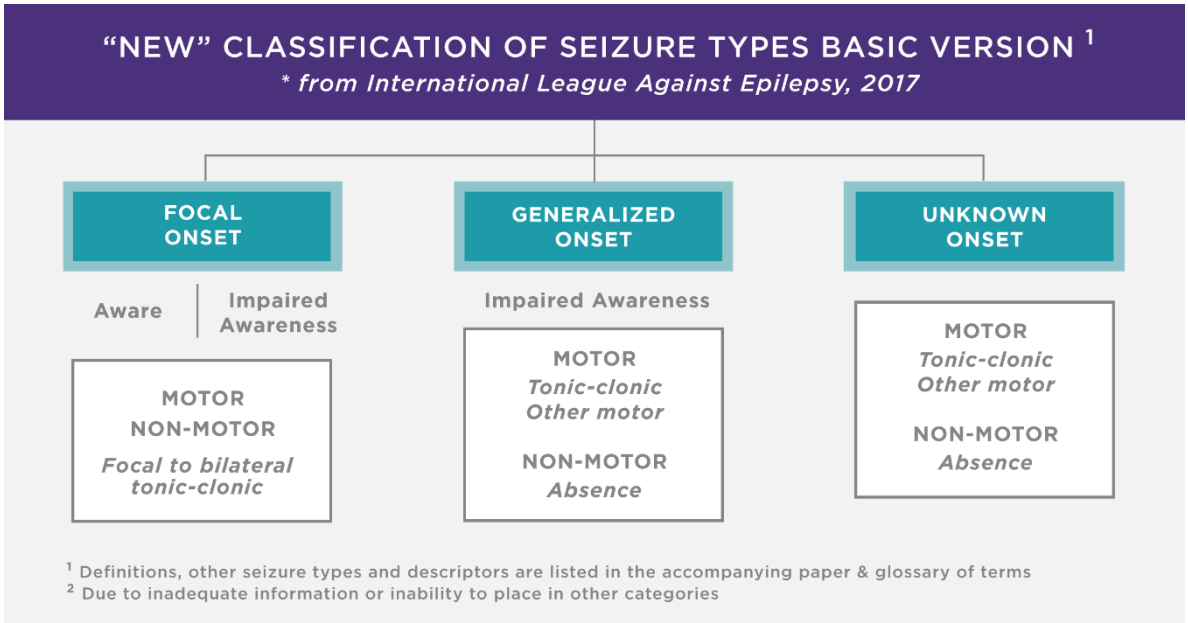
Compared to the available evidence on comorbidity in ADHD and related psychiatric conditions, the association between ADHD and epilepsy has received relatively little research attention. However, population-based studies have shown that children with epilepsy have a 3-to-5-fold increased risk of clinical ADHD,[14,126,146] with a similar to the risk increase for epilepsy reported in children with ADHD.[147] Despite the strong association, the underlying mechanisms influencing comorbid ADHD and epilepsy are not well understood. Further, epilepsy is also associated with an elevated risk for a range of other NDDs, leading to the hypothesis that epilepsy may share genetic risk factors with the broader neurodevelopment continuum.[148]

2.3.2.1 Epilepsy

Epilepsy is the most common neurological condition in children. Descriptions of epilepsy date back to antiquity, with written records found as early as 4000 BC.[149] The current operational definition of epilepsy by the International League Against Epilepsy (ILAE)[150] is

- At least 2 unprovoked (or reflex) seizures occurring greater than 24 hours apart.
- One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years.
- Diagnosis of an epilepsy syndrome
    - Epilepsy is considered to be resolved for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Figure 2.2 Classification of seizure types (basic version) from ILAE, 2017



Source: *https://www.epilepsy.com/learn/types-seizures*

Seizures are in turn defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain", and categorized as focal (originating in one brain half) or generalized (involving both brain halves)(Figure 2.2).[151,152] Epilepsy diagnoses are made based on clinical assessment of both seizure and epilepsy type, and commonly coded according to ICD-codes. As the classification of epilepsies are subject to continuous revision, correspondence between ILEA classification and the ICD is not complete, nor is mapping across ICD versions.[153] For these reasons, there is limited discriminative validity for studying epilepsy types using register data.[154]

2.3.2.2 Prevalence and incidence of epilepsy

Epilepsy affects approximately 1% of children at any given time-point[13], however prevalence and incidence rates vary considerably around the world and with age. Age-adjusted incidence range from 16 to 51 per 100,000 worldwide (with some exceptions),[155] whereas incident rates in children range from 35 to 128 per 100,000.[156] Variation across estimates is partly due methodological differences across studies, but factors such as access to health care, regional environmental exposures, ethnicity, and socioeconomic status are also likely to play a role. Unlike ADHD, the prevalence of epilepsy does not differ significantly across gender.[155,157]

2.3.2.3 Etiology of epilepsy

Epilepsy encompasses a collection of heterogeneous seizure disorders, with diverse clinical characteristics that preclude a singular etiological mechanism. Known risk factors for epilepsy include infections, certain metabolic and autoimmune disorders, head injuries, strokes, and tumours. Nevertheless, the cause of epilepsy is unknown for approximately half of all cases. A genetic etiology has been implicated in many types of epilepsies, yet, with the exception of certain monogenic epilepsy syndromes, there risk genes implicated are generally unknown.[152] Family studies suggest that first-degree relatives of epilepsy cases have a 2-6 fold increased risk of epilepsy themselves, depending on epilepsy type.[158] Similarly, twin studies suggest that genetic factors play a role in the etiology of epilepsy. [159] Molecular genetic research has identified several de novo mutations and CNVs contributing to both severe and mild epilepsies.[160] In the largest GWAS of epilepsy to date, including 8696 cases and 26,157 controls, one genome-wide hit was identified for generalized epilepsy and none for focal epilepsy.[161]

2.3.2.4 Underlying causes of comorbid ADHD and epilepsy

Several mechanisms have been proposed to influence comorbidity between ADHD and epilepsy, including adverse effects of antiepileptic medications (AEDs) and recurrent seizures leading to ADHD symptoms in epilepsy. Nevertheless, at least two studies have shown that ADHD symptoms are often present prior to first epileptic seizure and in medication naïve epilepsy patients. Together, this suggests that epilepsy and ADHD can be associated independently of the effect of seizures and AEDs.[162,163] Another postulated explanation is that epilepsy and ADHD share genetic risk factors.

2.3.2.5 Shared genetic risk in ADHD and epilepsy

Family studies provide some evidence for familial co-aggregation between the ADHD and epilipsy.[164,165] Results from a large Norwegian study reported a higher risk of ADHD in offspring of mothers with epilepsy, compared to the general population (relative risk 1.7, 95%CI 1.1–2.7).[165] However, studies involving only mother-offspring pairs cannot disentangle familial transmission from pregnancy related risk factors.[158] There are, to our knowledge, no twin studies investigating the association between ADHD and epilepsy. In terms of molecular genetic evidence, rare inherited CNVs have been implicated in many NDDs, including ASD, ID, ADHD and epilepsy, with some evidence for deletions and duplications in overlapping genomic regions.[148,166] At the level of common variants, molecular studies have not found any significant genetic correlation between ADHD and epilepsy. Nevertheless, this may be related to the relatively low sample sizes, particularly of the epilepsy GWAS sample.[135] Large-scale, well-powered family-based studies, including multiple types of relatives, can address several limitations of the research to date and improve current understanding of the causes underlying comorbidity between ADHD and epilepsy.

2.3.2.6 Pharmacological treatment safety of ADHD in epilepsy

There are longstanding concerns that ADHD pharmacological treatment, especially stimulant formulations, may lower the seizure threshold, interfere with seizure control and in rare cases, even induce new onset seizures in previously seizure free patients.[167] North American and European regulatory agencies caution against the use of ADHD medications in the presence of active seizures or a history of seizures.[33,168] However, the empirical evidence for an increased risk of seizures related to ADHD medication treatment is sparse. Many previous studies are limited by small sample sizes, exclusion of patients with active seizures, and insufficient consideration of important confounding factors, such as individual variation in baseline disorder severity. An overview of the current research is presented in Table 2.3.

To summarize, stimulants do not appear to increase the frequency of seizures in well-controlled epilepsy.[169-173] Other studies have reported either inconclusive results due to limited sample size or potential evidence of seizure exacerbation in patients with active epilepsy.[174-176] Two studies found methylphenidates safe in difficult-to-treat epilepsies,[177] and in patients with brain injury and active seizures.[178] Although less researched, there is no strong support for an increased risk of seizures associated with atomoxetine. Finally, two studies have reported a decreased risk of seizures associated with ADHD medications. One of these is a recent large-scale, medical-claims study that relied on a within-individual design to adjust for confounding factors that may differ between individuals and influence the association between ADHD medication and seizures.[179] Although these findings do not support the hypothesis of an increased risk of seizures related to ADHD medication, findings need to be replicated in other populations, using complimentary analytic methods. Further, there is still a dearth of knowledge regarding the safety of ADHD treatment in patients with epilepsy and additional NDD comorbidities, where polypharmacy and severity of neurodevelopmental insults may be of greater concern.

Table 2.3. Overview of studies assessing ADHD medication and seizure risk

PUBLICATION	POPULATION	EFFECT	DRUG	N	STUDY TYPE
Feldman *et al.*, 1989	Well-controlled epilepsy and ADHD	No risk increase	Stimulant	10	Double-blind medication-placebo crossover study *
Wroblewski *et al.*, 1992	Seizures due to brain injury	Risk reduction	Stimulant	30	Retrospective observational study
Gross-Tsur *et al.*, 1997	Active or well-controlled epilepsy and ADHD	Increased risk in participants with active epilepsy	Stimulant	30	4 months open-trial
Hemmer *et al.*, 2001	ADHD only	Increased risk in participants with EEG abnormalities	Stimulant	234	Observational retrospective study*
Gucuyener *et al.*, 2003	Active epilepsy or EEG abnormalities and ADHD	No risk increase	Stimulant	119	1 year open-trial
Van der Feltz-Cornelis *et al.*, 2006	Active epilepsy and adult ADHD	No risk increase	Stimulant	6	6 weeks open-trial
Gonzalez-Heydrich *et al.*, 2010	Active epilepsy and ADHD	Increased risk	Stimulant	33	2-6 weeks double-blind placebo-controlled crossover trial
Santos *et al.*, 2013	Complex epilepsy	Reduced risk	Stimulant	22	3 month open label, non-controlled trial
Rheims *et al.*, 2016	Active or well-controlled epilepsy and ADHD	No risk increase	Stimulant	167	Prospective observational study with 12-16 weeks follow-up
Adams *et al.*, 2017	Adult EP	No risk increase	Stimulant	31	Double-blind, randomized, single-dose trial
Wiggs *et al.*, 2017	ADHD with and without epilepsy	Reduced risk	Stimulant & Atomoxetine	801,838	Medical-claims database study
Wernicke *et al.*, 2007	ADHD-EP	No risk increase	Atomoxetine	na	Review of clinical data in medical trial databases
McAfee *et al.*, 2008	ADHD only	No risk increase	Atomoxetine	34,727	Medical-claims database study
Torres *et al.*, 2011	Active epilepsy	No risk increase	Atomoxetine	27	Medical chart review

Note: Majority of reported effects were not significant, due to limited power. * indicates insufficient study information to report follow-up time or exact study designs.

3 AIMS

3.1 OVERARCHING AIM

The overarching aim of this thesis was two-fold: 1) to explore the role of shared genetic liability for maturity and comorbidity in ADHD, in order to increase the understanding of the genetic architecture of prevalent childhood psychopathology. 2) To investigate the underlying causes of comorbid ADHD and epilepsy, and to evaluate treatment safety in this patient group.

3.2 SPECIFIC AIMS

Study 1. To examine whether perceived immaturity in childhood is associated with ADHD symptoms across development from childhood to early adulthood, and to estimate the contribution of genetic and environmental factors to the association.

Study 2. To examine whether ADHD genetic risk is associated with a range of neurodevelopmental, externalizing, and internalizing childhood psychiatric traits, and to investigate the extent to which such associations can be attributed to a general liability towards broad childhood psychopathology.

Study 3. To investigate the familial co-aggregation of ADHD and epilepsy, and to estimate the contribution of genetic and environmental risk factors to their co-occurrence.

Study 4. To examine whether incident and repeated ADHD medication treatment is associated with an increased risk of seizures in individuals with a seizure history, with and without additional NDDs.

4 DATA SOURCES AND MEASURES

Study 1 and 2 of this thesis takes advantage of data from two prospective cohort studies nested within the Swedish Twin Register (STR). STR was established in the 1960s, and now includes almost 200,000 twins, of which zygosity information is available for nearly 85 000 twin pairs. STR is the largest twin register in the world, and contains rich health related and sociodemographic data across the life span. The STR is hosted at the Department of Medical Epidemiology and Biostatistics at Karolinska Institutet.

4.1 THE SWEDISH TWIN STUDY OF CHILD AND ADOLESCENT DEVELOPMENT (TCHAD)

TCHAD is a prospective, longitudinal twin study targeting all 1,480 twin pairs born in Sweden from May 1985 to December 1986, who were alive and living in Sweden in 1994.[180] Twins and their parents were contacted by mailed questionnaires when the twins were aged 8-9, 13-14, 16-17, and 19-20 years. Majority of parent reported information was provided by mothers rather than fathers (range: 75%–90%). Data was collected across broad socio-demographic and health related domains.[180] Zygosity was assessed via DNA when available or determined based on an algorithm derived for validated zygosity questionnaires. In case of contradictions between the assignments (n=100), zygosity was set to unknown[106] and twins were excluded from analyses. Parent-ratings were collected at all four ages, with a response rate of 75%, 73%, 74%, 78%, and twin self-ratings at ages 13-14, 16-17, and 19-20 years with a response rate of 78%, 82%, 59%. The sample has been shown to be representative in terms of neighborhood characteristics for educational level, unemployment, and crime-rates. However, families from more ethnically diverse areas were less likely to participate.[181] Attrition rate analyses have reported no significant differences in sex and parent-rated ADHD symptoms between responders and subjects lost to follow-up at wave 2. Between wave 2 and 3, attrition analyses showed no statistically significant difference for sex, family socioeconomic status and parent-rated inattention between responders and non-responders. However non-responders in wave 3 did have significantly higher rates of hyperactivity/impulsivity symptoms.[181]Similary, non-responders at wave 4 were more likely to be male and have higher levels of childhood ADHD symptoms.[106]

4.1.1 Measures in TCHAD

4.1.1.1 ADHD

Study 1 was conducted using data from TCHAD, relying parent and self-rating of ADHD symptoms assessed using The Achenbach System of Empirically Based Assessment (ASEBA). ASEBA scales are empirically derived, standardized questionnaires consisting of similar, but developmentally appropriate items for parent and self-ratings of problems experienced in the last six months. All items were rated on a 3-point Likert scale (1=not true, 2=sometimes true, 3=often true) and summed, with higher scores reflecting greater problems. Parent-ratings were collected using the Child Behavior Checklist (CBCL)[182] at ages 8 to 17 years, and the Adult Behavior Checklist (ABCL)[183] at ages 19 to 20 years. Self-ratings were collected using the

Youth Self-Report form (YSR)[184] at ages 13 to 17 years and the Adult Self-Report form (ASR)[183] at ages 19 to 20 years. ADHD was assessed using the Attention Problem (AP) scale, which including both inattention and hyperactivity symptoms. The psychometric properties of the AP scales have been evaluated in population-based and clinical samples, with results showing good reliability and convergent and discriminant validity [185,186]

4.1.1.2 Relative Immaturity

Perceived level of maturation, from now referred to as relative immaturity (RI), was assessed in TCHAD using parent-ratings on two items assessed when the twins were aged 8-9 years. For item one, parents were asked to estimate their child's level of maturity in relation to same age peers on a 5-point scale (1=very mature, 2=somewhat mature, 3=average, 4=somewhat immature, 5=very immature). For item two, parents were asked to estimate their child's perceived age independent of their chronologic age. The correlation between the two items was r=0.75 and the items were standardized and summed to create a continuous measure, with higher scores indicating higher level of immaturity. The RI measure has been evaluated in two prior studies. Within the TCHAD sample, RI was showed weak correlations to measures of early physical maturation (birth weight, r=0.19; age at walking, r=0.10; age at teething, r=0.06) and weak to moderate correlations with indicators of early mental maturation (ability to handle scissors, r=0.38; ability to tell the time from a watch, r=0.24).[187] In a separate case-control study, higher RI was related to a more childish body appearance, fine motor function problems, peer problems, lower general knowledge and slightly lower mean IQ scores.[188] in Study 1, RI was also significantly associated with birth-month, with younger children within each school-year showing higher RI.

4.2 THE CHILD AND ADOLESCENT TWIN STUDY IN SWEDEN (CATSS)

CATSS is an ongoing nationwide study targeting all twins born in Sweden since the 1st of July 1992 [189]. The study was initiated in 2004, and since then parents of twins identified via the STR are systematically invited to participate in a telephone interview regarding their children's health and social environment on the twins 9th birthday. In the first three years of the study, 12 year old twins were also included. By January 2017, parental interviews have been completed for more than 30,000 twins, with an overall response rate of ~70%. DNA has been collected for more than 12,500 of the participants, and further genotyping is underway.[190] Analyses of the differences between non-responders and responders, based on a merge of data with national registers, suggest that non-responders on average have lower socio-economic and more neuropsychiatric diagnoses, including ADHD and ASD.[189]

4.2.1 Measures in CATSS

4.2.1.1 The Autism-Tics AD/HD and other Comorbidities inventory (A-TAC)

Study 2 was conducted using data from the CATSS-9/12 cohort, were primary assessment is conducted using A-TAC.[189] A-TAC is a comprehensive parental telephone interview, administered by laypersons, and designed for use in large-scale epidemiological settings.[191]

Items in A-TAC are formulated to reflect symptom criteria for child psychiatric disorder according to the DSM-IV. Questions are asked in a lifetime perspective, in relation to same-age peers and coded according to three response categories (no=0, yes to some extent=1, yes=2). A-TAC consists of 96 symptom items that have been assessed in all waves of CATSS. Several validation studies have been conducted for A-TAC, showing excellent inter-rater agreements (<0.90) and good to excellent test re-test reliability (<0.70). Diagnostic cut-offs for ADHD and ASD have been found to show excellent sensitivity and specificity, with cut-offs for other diagnosis's, including learning disorders (LD), ODD and CD, showing moderate to good classifications.[191-194] In the first five waves of CATSS-9/12, eight anxiety and five depression items were also included in the A-TAC interview. The internal and external validity of these items scales have not been formally assessed. In subsequent data collection, A-TAC internalizing items were replaced with two more in-depth, validated anxiety and depression questionnaires.

4.2.1.2 Screen for Child Anxiety Related Emotional Disorders (SCARED)

SCARED is a 41 item questionnaire measuring child and adolescent anxiety symptoms experienced in the last three months, coded according to three response categories (no=0, yes to some extent=1, yes=2).[195,196] The questionnaire measures symptoms of five anxiety subtypes; panic disorder (PD), generalized anxiety disorder (GAD), separation anxiety disorder (SAD), school anxiety (SA) and social phobia (SP). Validity and psychometric properties of SCARED have been validate in different cultures and ages, showing strong internal consistency, a five-factor structure corresponding to the diagnostic subscales, and moderate predictive validity for clinical diagnoses of anxiety.[195-199]

4.2.1.3 Short Mood and Feelings Questionnaire (SMFQ).

SMFQ is a 13 item questionnaire measuring child and adolescent depressive symptoms experienced in the last two weeks, coded according to three response categories (no=0, yes to some extent=1, yes=2). [200,201] SMFQ has been validated, with strong internal consistency and moderate predictive validity for clinical diagnoses of depression.[200-202].

In study 2 of this thesis, parent-ratings of childhood psychopathology symptoms were used. The sample was split by available assessment for internalizing items. A-TAC assessment of anxiety and depression was used for twins born 1992-1997 (from now on referred to as the A-TAC subsample), and SCARED and SMFQ for twins born from 1998 and onward (from now on referred to as the SMFQ/SCARED subsample). In addition to internalizing items, 49 symptom items assessing ADHD, ASD, LD, ODD and CD were included. ADHD was further divided into the A-TAC subscales for attention and hyperactivity/impulsivity symptoms.

4.2.1.4 Genotype data

Collection of saliva samples for DNA extraction started in CATSS in 2008, in connection with being contacted for the telephone interview. Twins born earlier were re-contacted and asked to submit saliva samples. To date, a total of 11,551 individuals in CATSS have been genotyped

using the Illumina Infinium PsychArray-24 BeadChip. All genotype data were subjected to stringent quality control (QC) procedures applied to genotyped markers and individuals,[67] using standardized procedures (see Table S1 in manuscript for Study 2). Ancestry outliers were identified using principal components analysis and removed. After QQ, 561,187 genotyped SNPs and 11,081 samples were retained and genotypes for another 2,495 MZ twins were imputed from their genotyped co-twin. Genotype imputation was performed using Minimac3 for 13,576 samples on autosomes with 1000-Genomes data (Phase 3, Version.5) as the reference panel. Only SNPs with good imputation quality (imputation R2 ≥ 0.8, MAF≥0.01) were retained. Genotype data was used to derive ADHD polygenic risk scores in Study 2.

4.3 SWEDISH NATIONAL REGISTERS

Study 3 and 4 of this thesis take advantage of Swedish nationwide registers. Data in these register are not primarily collected for research, but can be requested for such purposes from the register holders. National registers containing primarily demographic information are kept by Statistic Sweden, and the population-based national health registers by the National Board of Health and Welfare (NBHW). Since 1947, every resident in Sweden is assigned a ten-digit personal identity number (PIN). The PIN serves as a unique identifier for public administration registers in Sweden, thus enabling unambiguous linkage across national registers. Children born in Sweden are assigned a PIN number at birth, whereas immigrants who become permanent residents, or live in Sweden longer than one year, are assigned a PIN upon registration. The National Tax Board is responsible for administration of PIN numbers.[203]

Total population register

The Total Population Register (TPR) was established by Statistics Sweden in 1968. Information on births, deaths, place of residence, civil status, migration, relations and citizenship are reported from the local tax offices to the National Tax Board.[204] Information from the TPR was used to obtain demographic data, including information on emigration, date of birth, and sex in Study 3 and 4.

Multi-Generation Register

The Multi-Generation Register (MGR) is part of the TPR and links all Swedish residents to their parents, allowing for identification of family pedigrees.[205] The register was established in the early 1990s' and includes all individuals, so-called index persons, born after 1932 and alive and registered in Sweden since January 1, 1961. Linkage between index persons and parents is feasible for parents who were alive and living in Sweden from 1947 onwards. Immigrated index persons are only linked to their parents if they immigrated together with parents before age 18. Information on family relatedness was used in study 3 to identify pairs of parent-offspring, full-siblings, half-siblings and full cousins (see Figure 4.1 for example).

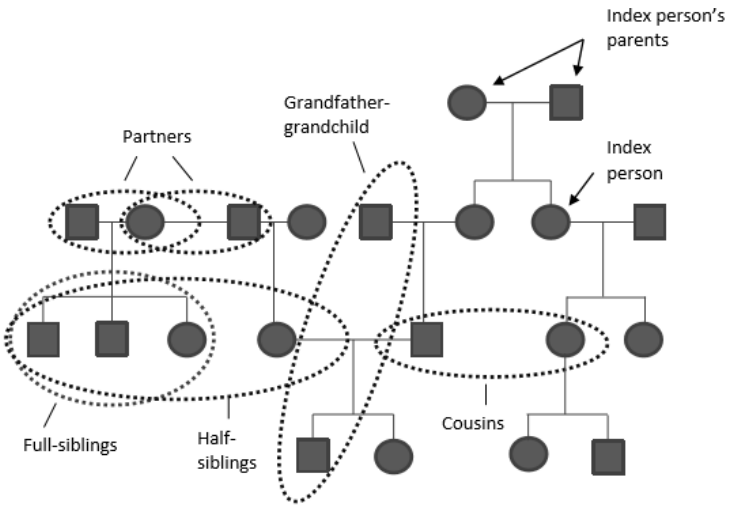


Figure 4.1. Graphic presentation of four generations in the Multi-Generation Register, where circles represents females and squares represents males. Different family constellations that can be identified from the register are suggested. *Reproduced with permission from Anne Örtqvist.*

The Medical Birth Register

The Medical Birth Register (MBR) is kept by the National Board of Health and Welfare (NBHW). The register contains information on prenatal and perinatal variables related to nearly all pregnancies and births in Sweden since 1973, with complete missing data for approximately 2% of all births.[206,207] Information in the register is obtained from medical records from the antenatal care of the mother, the delivery record and the record of the newborn infant examination. The MBR was used to identify the study population in Study 3.

National Patient Register

The National Patient Register (NPR) was established in 1964 by the NBHW and covers somatic inpatient care since 1964 and psychiatric inpatient care since 1973, with complete coverage achieved from 1987. Data on outpatient visits to specialist physicians in public care are available since 2001, with approximately 80% coverage.[208,209] The register includes information on dates of admission and discharge, whether the hospital visit was scheduled or not, the type of care unit, and the cause of hospitalization. Each discharge has one primary and up to seven secondary discharge diagnoses, coded according to the current version of the ICD.[18] Data from primary health care clinics are not included in the NPR. Information from the register was used to identify individuals with ADHD and epilepsy diagnoses in Study 3 and 4, as well as outcome seizure events and covariates in Study 4.

The Prescribed Drug Register

The Prescribed Drug Register (PDR) covers all dispensed prescriptions medications from outpatient and primary health care for all Swedish residents since July 1, 2005.[210] The register contains information on the dispensed medication, including dosage, expenditure and reimbursement, age, sex and place of residence of the patient, prescription and dispensing date, a prescriber code and the prescriber's profession. All drugs are classified according to the

international Anatomical Therapeutic Chemical (ATC) classification system. The PDR does not include information on medications sold over-the-counter, medications used in hospitals or prescribed medications that were not dispensed. The PDR was used to identify individuals who had received ADHD medications as a proxy for ADHD case status in Study 3, and to define ADHD medication periods as a time-varying exposure in Study 4.

The Cause of Death Register

The Cause of Death Register (CDR) was established in 1952, with complete coverage since 1961. The CDR is updated yearly, and provides information on all deaths among Swedish residents, including both Swedish citizens and non-citizens. The register includes information on contributing causes of death, coded according to the ICD, and the date of death.[204] The CDR was used to obtain date of death for censoring in Study 3 and 4.

4.3.1 Measures in Swedish National Registers

4.3.1.1 ADHD

ADHD cases were defined via in- or outpatient discharge diagnosis of HKD according to ICD-codes (ICD-9 314; ICD-10 F90) in the NPR. Further cases were identified via dispensations of ADHD medication in the PDR. Approved medications for treatment of ADHD in Sweden during the study period were methylphenidate [N06BA04], amphetamine [N06BA01], dexamfetamine [N06BA02], lisdexamfetamine [N06BA12], and atomoxetine [N06BA09]. We only considered diagnosis and medication dispensations after age three, as diagnosis prior to this age is unusual, and because medication treatment is not recommended for children under the age of six. In Study 4, ADHD cases were identified from the NPR only. ADHD case status was treated as categorical (0/1) life-time diagnosis in both Study 3 and 4.

4.3.1.2 Epilepsy

Epilepsy cases were defined via in- or outpatient discharge diagnosis for any type of epilepsy according to ICD-codes (ICD-8 345; ICD-9 345; ICD-10 G40, G41) in NPR. Epilepsy case status was treated as categorical (0/1) life-time diagnosis. In Study 3, earlier ICD revisions were used to identify epilepsy in the parent generation (ICD-7 353; ICD-8 345). In Study 4, ICD-8, 9 and 10 were used to identify a cohort with a history of seizures. Additionally, inclusion criteria required that the first observable diagnosis in the NPR had occurred prior to age 30. Date of first identifiable seizure was used to define the start of follow-up, if the seizure occurred after age five or after 1st January 2006.

4.3.1.3 Seizure events

In Study 4, seizure events were the outcome of interest. Seizure events were defined as an unplanned in- or outpatient visit to hospital or specialist care with a primary discharge diagnosis for seizure according to ICD-10. For sensitivity analyses, we used a stricter seizure event definition, including only unplanned emergency care visits, ambulance rides or inpatient care

visits requiring overnight stay with a primary seizure discharge diagnosis. Discharge diagnosis for status epilepticus (G41), which by definition is an acute seizures, were also included.

4.3.1.4 ADHD medication periods

In Study 4, ADHD medication periods were treated as a time-varying exposure. All dispensations of ADHD medications (see ATC codes in section 4.3.1.1) in the PDR from 1 January, 2006 until 31 December, 2013 were identified. For each individual with at least one record of prescribed ADHD medication, the follow-up time was divided into on- and off-treatment periods (Figure 4.2).

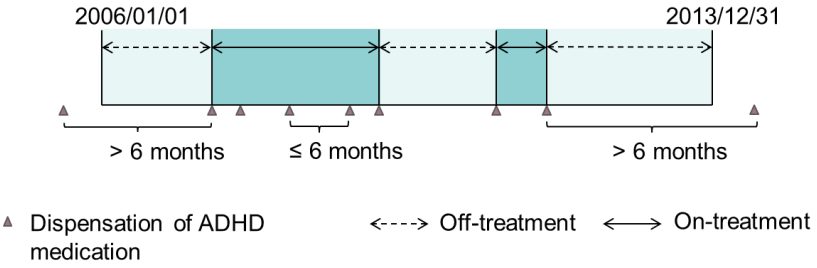


Figure 4.2. ADHD medication periods as a time-varying exposure, illustrated for 1 individual

On-treatment periods were defined as a time period of at least two ADHD medication dispensations occurring no longer than six months (183 days) apart. Time periods not occupied by the on-treatment periods were defined as off-treatment. Each treatment period started on the date of the first prescription and ended on the date of the last prescription. We took dispensations in 2005 and 2014 into account when defining the treatment status over the first and the last periods during the follow-up (Figure 4.2). For sensitivity analyses, we varied the exposure definition by I) adding 90 days to the date of last prescription in each medication period, and II) defining treatment periods as two subsequent prescriptions within 90 days, rather than 183 days. The 90 day cut-off was chosen as three months is the maximum quantity of drugs allowed at a single dispensation according to Swedish reimbursement regulations.[211]

4.3.1.5 Covariates

In Study 4, AED periods were defined based on dispensations for any drug belonging to ATC class N03A (antiepileptic drugs) in the PDR. AED periods were treated as a time-varying covariate, and defined the same as for ADHD medication (section 4.3.1.4). Life-time diagnosis for ASD (ICD-9 299; ICD-10 F84), ID (ICD-9 317-319; ICD-10 F70-F79), and other pervasive and specific developmental disorders (ICD-9 315; ICD-10 F80-F89) were obtained based on a discharge diagnosis in the NPR. These were used to stratify analyses based on the presence or absence of one or more additional NDDs, over and above epilepsy and ADHD.

5 METHODS

5.1 OVERVIEW OF STUDY METHODS AND MATERIALS

STUDY	PARTICIPANTS	MEASURES	STATISTICAL ANALYSES
1	1,302 twin pairs from TCHAD born 1985 to 1986	*Exposure:* Parent-rated immaturity relative to same age peers at ages 8-9 years. *Outcome:* Parent- and self-rated ADHD symptoms assessed via ASEBA scales at ages 8-9, 13-14, 16-17 and 19-20 years.	❖ Longitudinal, multivariate, multi-rater twin model, estimated using structural equation modeling.
2	13,457 twins aged 9 or 12 from CATSS	*Exposure:* ADHD polygenic risk scores *Outcome:* Parent-rated neurodevelopmental, externalizing and internalizing symptoms, assessed via A-TAC, SCARED and SMFQ *Covariates*: Sex, age and six ancestry principal components	❖ Confirmatory factor analysis and linear regressions, estimated using structural equation modeling. ❖ Cluster robust standard error to account for non-independance of data.
3	Relatives pairs identified from 1,899,654 individuals born in Sweden 1987-2006	*Exposure:* Epilepsy status in exposing relative *Outcome:* ADHD status in outcome relative* *Covariates:* Birth year and sex	❖ Logistic regression to estimate familial aggregation. ❖ Bivariate extended sibling model to estimate genetic and environmental effects, estimated using structural equation modeling. ❖ Cluster robust standard error to account for non-independance data.
4	44,827 individuals born 1968-2007, with a history of seizures	*Time-varying exposure:* ADHD medication treatment *Outcome:* Time to seizure event *Covariates:* Time-varying AED medication treatment, age, sex and additional NDDs	❖ Conditional Poission regression for incident ADHD medication analysis ❖ (Stratified) Cox proportional hazard regression for repetead ADHD medication analysis

Note: Study 1 and 3 are quantitative genetic studies, which do not aim to establish an exposure-outcome relationship, but rather to estimate the bi-directional association between the traits of interest and the relative importance of genetic and environmental factor for that associations. The terminology exposure and outcome is merely used for consistency.

5.2 STUDY DESIGNS

All four studies included in this thesis are, at their core, variants of the classical observational study design, with the distinct feature that they by design also incorporate genetic information. Study 1, 3 and 4 rely on known family relationship, whereas Study 2 relies on directly measured genetic variants. The common purpose of all study designs included in this thesis, which can be described as genetically informative designs, is to quantify the importance of genetic and environmental factors in disorder associations, or to control for the influence of genetic confounding in exposure-outcome associations.

5.2.1 Quantitative genetic designs

Quantitative genetic designs include a range of study designs that are primarily concerned with answering the questions;

I) To what extent does genetic factors contribute to the etiology of complex traits (i.e., traits that do now show a classical Mendelian inheritance)?
II) What is the relative contribution of genetic and environmental factors to variance in complex traits?

These question are addressed by studying the patterns of trait similarity across different types of relatives, who vary in their degree of genetic and environmental sharing. [212]

5.2.1.1 Family studies

Family studies are concerned with investigating the degree of familial aggregation, or clustering, of a disorder or co-aggregation across disorders.[212] Such clustering can be due genetic or environmental factors that are shared within the family. In family studies, the risk of a disorder in individuals of a relative with the same disorder is compared to the risk among individuals without a relative with the disorder. Similarly, familial co-aggregation estimates the risk of disorder A in individuals with a relative affected by disorder B, compared to the risk of disorder A among individuals who do not have a relative affected by disorder B. Having one (or several) relative(s) affected by a disorder can be considered a proxy of an individual's genetic liability for the disorder in question. As this liability is fixed at conception, the exact timing of diagnosis carries little information and the association may be estimated using life-time prevalence of disorder status for both the outcome person and relative. This is a reasonable estimation method of familial risk if the study population has passed through the period of risk,[212] but not if many individuals in the cohort may still go on to develop the disorder (i.e. the familial risk is not yet observed). The method may therefore be better suited for studying childhood onset disorder like as ADHD, as compared to late-onset disorders. The appropriateness of estimating familial aggregation without or without considering time will vary based on previous knowledge regarding the temporal ordering of the disorders, age of disorder onset, and the observed follow-up time for the cohort.[212]

Hudson et al.,[213] has proposed a framework using directed acyclic graphs (DAG) to illustrate how the familial co-aggregation between two disorders may be estimated and interpreted under

specific disorder association conditions. Figure 5.1 shows a DAG of the hypothesized familial co-aggregation between ADHD (AD) and epilepsy (EP) as an example (Study 3 of this thesis). In this DAG, the parameter of interest is the latent factor $F_{AD\text{-}EP,}$ which represents shared familial causes contributing to disorder liability for AD and EP. By estimating all open paths to $F_{AD\text{-}EP,}$ a measure of the familial association can be obtained. Under the assumptions that there are no direct of one disorder on the other within the same person (depicted by the dashed arrows), estimation of the open path $EP_2 \leftarrow F_{AD\text{-}EP} \rightarrow AD_1$ (which is assumed to be symmetric with $AD_2 \leftarrow F_{AD\text{-}EP} \rightarrow EP_1$) will give an estimate of the familial co-aggregation between AD and EP. Nonetheless, in the presence of a direct effects of EP on AD (or vice versa), the additional path $EP_2 \leftarrow F_{EP} \rightarrow EP_1 \rightarrow AD_1$ will also be open. In this scenario, the total estimated familial association will be due to both $F_{EP,}$ which represent familial factors contributing to disorder liability in EP only, and $F_{AD\text{-}EP}$. To isolate the effect of $F_{AD\text{-}EP}$ from F_{EP} requires making several assumptions that are often not known, e.g., about the direction of effect between the disorders, distribution of the latent variables (e.g. $F_{AD\text{-}EP}$), and whether the considered paths are likely to represent positive or negative association.[213] The extent to which such assumptions are valid will differ depending on the disorders under study and prior knowledge.

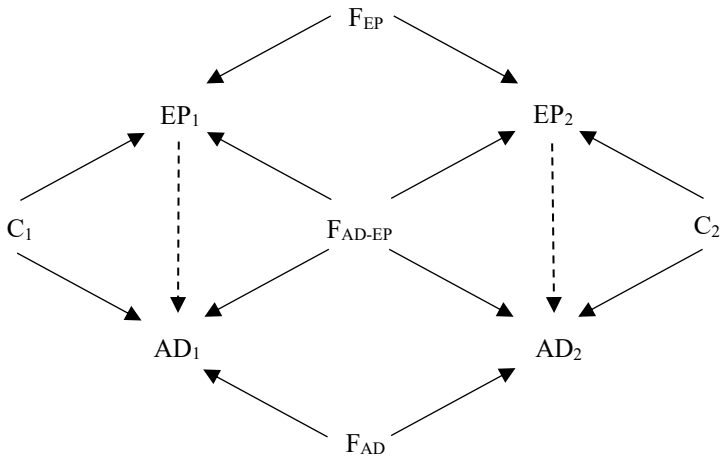


Figure 5.1. Directed acyclic graph depicting the hypothesized relations between ADHD (AD) and epilepsy (EP).

Note: $EP_{1\ \&2}$, Epilepsy in relative 1 and 2; $AD_{1\ \&\ 2}$, ADHD in relative 1 and 2; $F_{AD\text{-}EP:}$ Shared familial causes for ADHD and EP; $F_{EP,}$ familial causes unique for EP. $F_{AD,}$ familial causes unique for ADHD.$C_{1,}$ common causes for EP and ADHD specific to relative 1; $C_{2,}$ common causes for EP and ADHD specific to relative 2. Dashed arrows denote possible direct within-individual effects of EP on ADHD.

In addition to showing familial aggregation, family studies including multiple types of relatives can also be used to infer the relative importance of genetic and family environmental factors for the disorder aggregation (Table 5.2). For example, if the strength of disorder association across relatives increases along with the increasing degree of genetic sharing, the importance of genetic factor for the disorder association can be assumed. In Study 3, we assessed the familial co-aggregation between ADHD and epilepsy across multiple types of relatives, based on life-time prevalence for both disorders.

Table 5.2. Assumed degree of genetic and environmental sharing across relatives

RELATIVE	GENETIC SHARING	ASSUMED ENVIRONMENTAL SHARING
Mother-offspring	50% additive genetics 0% dominant genetics	❖ Mothers provide the in-utero and early rearing environment to their offspring. ❖ A higher risk in mother-offspring, compared to father-offspring, suggest a maternal-specific effect over and above shared familial factors.
Father-offspring	50% additive genetics 0% dominant genetics	❖ Fathers provide the early rearing environment to their offspring.
MZ twins	100% additive and dominant genetics	❖ Environmental sharing is assumed to be 100%. ❖ MZ twins also share in-utero environment.
DZ twins	50% additive genetics 25% dominant genetics	❖ Environmental sharing is assumed to be 100%. ❖ DZ twins also share in-utero environment.
Full siblings	50% additive genetics 25% dominant genetics	❖ Environmental sharing is assumed to be 100%. ❖ Share pregnancy related factors, constant in the mother across pregnancies. ❖ A higher risk in full siblings pairs, compared to maternal half siblings, indicate the importance of genetic factors.
Maternal half siblings	25% additive genetics 0% dominant genetics	❖ Environmental sharing is assumed to be 100%. ❖ Share pregnancy related factors, constant in the mother across pregnancies. ❖ A higher in risk maternal, compared to paternal, half siblings indicates the importance of shared environmental factors, as they share their environment to a greater extent.
Paternal half sibling	25% additive genetics 0% dominant genetics	❖ Environmental sharing is <100%, and is assumed to be 0%, as children tend to reside predominantly with mothers after parental separation, particularly early in life.
Full cousins	12.5% additive 0% dominant genetics	❖ Environmental sharing is assumed to be 0%. ❖ An observed risk across cousins provides strong support for the importance of genetic factors, since environmental sharing tends to be minimal across cousins.

Note: In parent-offspring pairs, 50% of segregating genes are shared, and in MZ pairs 100%. For other types of relatives, percentages refer to on average sharing for (autosomal) segregating genes.

5.2.1.2 Twin designs

Twin studies are concerned with investigating genetic and environmental contributions to individual differences in complex human traits. The twin method can be considered a natural experiment that utilizes the different degree of genetic sharing between monozygotic (MZ) and dizygotic (DZ) twins to quantify the contribution of genetic and environmental factors to variance in a trait.[214] MZ twins are genetically identical, whereas DZ twins share on average 50% of their segregating genes. Under the assumptions that MZ and DZ twins share their environments to a very similar extent (from the prenatal environment to later environmental factors), a higher similarity within MZ twin pairs for the trait of interest, as compared to DZ twin pairs, may be interpreted as evidence for the genetic contribution to variation in the trait.[214] Similarity for a given phenotype within a twin pair is commonly estimated via intraclass correlations (ICC), and similarity across phenotypes by the cross-twin-cross-trait correlation (CTCT).

Comparison of correlations across MZ and DZ pairs allows for the variance (V) of a given trait to be decomposed into three latent factors: Additive genetic effects (A, additive across alleles) shared environmental effects (C, all factors that contribute to similarity between family members beyond genetic resemblance), and non-shared environmental effects (E, factors that contribute to dissimilarity among family members), which also includes measurement error. Dominant genetic effects (D, interaction between alleles at the same gene locus) may also be estimated depending on the pattern of twin correlations. Under assumption of no interaction and no covariance between A, D, C, and E, the total variance of a phenotype (P) can be expressed as

$$Var(P) = A + D + C + E$$

Narrow sense heritability is defined as the proportion of variance in a trait due to additive genetic effects(A), and broad sense heritability as the proportion of variance due to additive and dominance genetic effects($A + D$)

$$h^2 = \frac{Var(A + D)}{Var(P)}$$

The classical twin method can be extended to test for etiological differences between males and females, using sex-limitation models as in Study 1 of this thesis. It can also be extended to study bivariate and multivariate traits association, as in Study 1 and 3.

5.2.1.3 Extended family designs

Similar to the twin method, extended family designs aim to estimate unknown variance components (A, D, C and E) from known or assumed information regarding the degree of genetic and environmental sharing across different types of relatives.

Extended family designs, have some advantages over the classic twin design. In the classical twin design, variance components A, C and D are mutually confounded and cannot be

estimated within the same model since three unknown parameters cannot be simultaneously estimated from only two pieces of information (the MZ and DZ covariance). Another common critique of the twin method is that twins are not representative of the general (singleton) population. Additionally, the study of relativity rare disorders measured categorically may not feasible in twin studies due to power limitation. By extending the classical twin design to include other types of relatives, simultaneous estimation of A, C, D and E is possible, and generalizability and statistical power is improved.[215,216] As in the twin method, certain assumptions must be made regarding the degree of genetic and environmental sharing across relatives types (Table 5.2). Whereas the calculation of on average sharing of segregating genes is straightforward across relative types, assumptions regarding the degree of shared environment are more challenging. These need to be made on prior knowledge, for example of how relatives usually co-habit. Such assumptions are likely subject to some misspecification, the effect of which will vary depending on the trait(s) under study.[142] In Study 3 of this thesis, we employed an extended sibling design, using data from full siblings and maternal and paternal half siblings, to estimate genetic and environmental contributions to the association between ADHD and epilispy.[142,217]

5.2.2 Within-individual designs

Within-individual designs are a type of genetically informative study designs that can be used to study exposure-outcome association, when the exposure varies over time and can be measured at across time-points. Although there are different flavors and estimation techniques of the within-individual design,[36,218,219] the basic premise is that each individual acts as their own control, and the risk of the outcome is compared between exposed time periods (e.g. treatment) and unexposed periods (e.g., no treatment) within the same person. By doing so, the within-individual estimate is adjusted for confounding by all covariates that are constant within an individual during the follow-up (e.g. genetic predisposition, baseline disease severity, and environmental exposures preceding start of follow-up). This makes the within-individual comparison a powerful design for pharmacoepidemiological studies, particularly when large-scale RCT's are not feasible or ethical. Within-individual comparisons also enables the researcher to address the issue of confounding by indication or severity, i.e. when the indication for treatment is also associated with the outcome. The DAG in figure 5.2 depicts the issue, using Study 4 in this thesis as an example. We are interested in estimating the association between ADHD medication and the risk for epileptic seizures. However, ADHD, which is the indication for receiving ADHD medication, is also associated with epilepsy. In turn, the association between the disorders may be attributed to unknown or unmeasured (U) confounding factors that vary between individuals, e.g. shared genetic or environmental factors that increase the risk for both disorders. In Study 4, we address this issue by estimating the effect of ADHD medication on the risk of epileptic seizures, adjusting for U by using a within-individual comparison design.

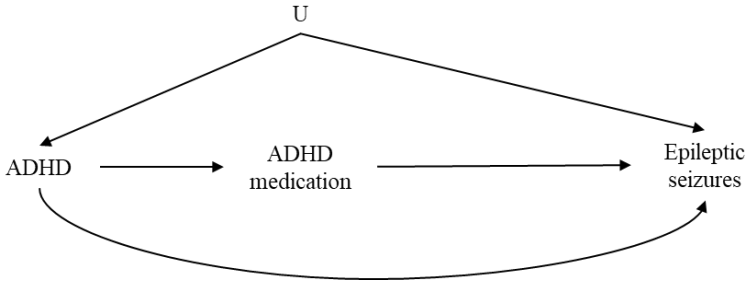


Figure 5.2. DAG depicting the hypohtesized association between ADHD medications and seizures

5.2.3 Molecular genetic designs

Molecular genetic designs differ from the above outlined genetically sensitive designs, in that actual measured genetic variation is used to study disease etiology, rather than inferred differences in genetic similarity across relatives. Molecular genetic designs include a wide range of study types, of which genome wide association studies (GWAS) and polygenic risk score (PRS) studies are of relevance to this thesis.

Thanks to fast-paced methodological advances, extensive collaborative networks such as the Psychiatric Genomics Consortia (PGC), and nationwide bio-banking efforts like the Danish Neonatal Screening Biobank, large-scale GWAS are now commonplace and available for a wide breadth of human complex traits. The primary aim of GWAS is to identify common genetic variants (SNPs), that are associated with a continuously measured trait or with an increased risk of a categorically defined disorder (0/1).[220] As association is tested across million SNPs, a stringent *p*-value threshold is required for significance (generally $p < 5 \times 10^{-8}$). Thus, large sample sizes are required to have sufficient statistical power to detect significant associations. [221] Nevertheless, the utility of GWAS extends beyond the investigation of genome wide significant hits, and one of the most commonly used applications of GWAS results is polygenic risk prediction.[220]

Polygenic risk score (PRS) provide a measure of individuals genetic liability for a given phenotype. To conduct a PRS study, two independent samples with genotype data are required; firstly, association results from a GWAS for the phenotype of interest is needed. This is commonly referred to as the discovery sample. Secondly, an independent sample with both genotype and phenotype data, into which the PRS prediction will be made, is needed. Risk alleles which show association with the phenotype of interest below a predefined *p*-value threshold in the discovery GWAS, and their corresponding effect sizes, are then used to derive a PRS for each individual in the independent target sample. PRS are calculated as the sum of the count of risk alleles weighted by their effect size (e.g. log odds ratio (OR) for case–control GWAS and z-scores or beta coefficients for continuous trait GWAS) in the discovery sample (Figure 5.3).

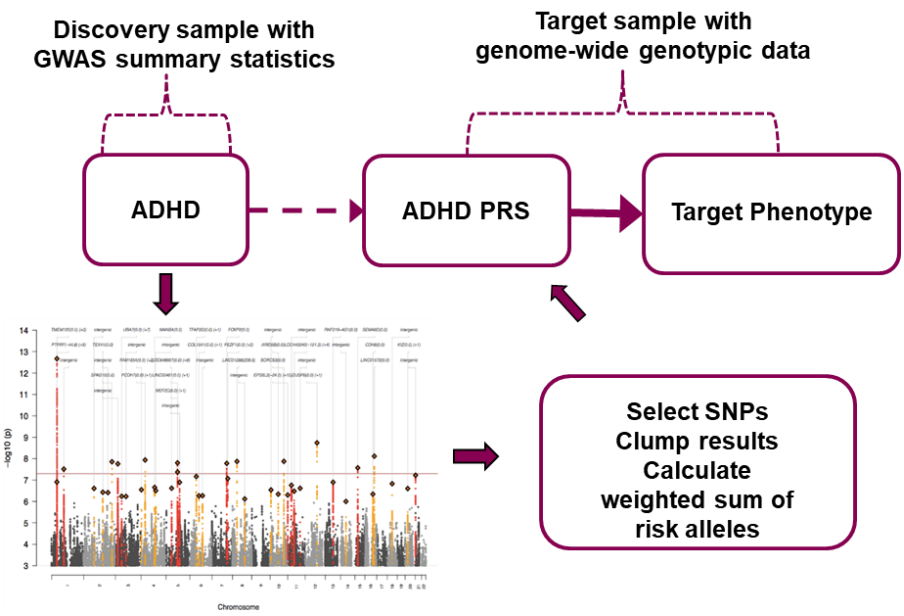


Figure 5.3. Overview of method for deriving polygenic risk scores (PRS)

As with all genetic analyses, population stratification must be considered; Ancestry outliers should be removed and PRS analyses need to be adjusted for ancestry by including principal components (PCs) derived from the genomic relationship matrix to account for genetic substructure of the data in the target sample.[221] Further, PRS estimates will be biased upwards in case of any sample overlap between the discovery and the target sample.[222] PRS prediction is usually assessed through regression analyses, estimating the association between the genetic liability for a given phenotype, as captured by the PRS, with the target phenotype, after accounting for covariates. In Study 2, we estimated the association between PRS for ADHD and a broad range of childhood psychiatric traits.

5.3 STATISTICAL METHODS

5.3.1 Structural equation modeling

"*When evaluating a model, at least two broad standards are relevant. One is whether the model is consistent with the data. The other is whether the model is consistent with the 'real world.*'" Kenneth A. Bollen, Structural Equations with Latent Variables (1989)

Structural equation modeling (SEM) is a statistical framework to model covariance matrices that can be applied in wide array of analyses. SEM may be viewed as a combination of factor and regression analyses, were the interest lies in describing the latent (unmeasured) constructs which are assumed to underpin the observed data. The relationship between these latent construct are represented by regression or path coefficients. All SEM models can be expressed as a set of equations with a corresponding path diagram, which represent the modelled or expected covariance matrix. Model fit is then evaluated on how well the modelled covariance structure represent the observed covariance structure of the sample data. SEM models are very flexible and allow for the simultaneous estimation of multiple standard statistical models.[223,224]

SEM is often conducted using continuously measured variables, but can also be applied to analyze categorical traits by using liability threshold models. The observed binary or ordinal trait is then assumed to be underpinned by a continuous liability distribution in the population, with a fixed mean and variance. Individuals who present with symptoms exceeding a given threshold on this liability distribution are cases, and those below are non-cases. The level of the threshold is given by the life-time prevalence of the disorder in the population.[212] It should be noted that analyses of categorical data using liability threshold models requires substantially larger sample sizes as compared to analyses of continuous traits. For twin analyses, approximately three times as many twin pairs are needed to reach equivalent power between categorical and continuous analyses if the threshold is 50%, and the ratio increases to roughly 10:1 if the threshold is 10%.[225] Liability thresholds models were used in Study 2 and 3 of this thesis to model ordinal symptom data and categorical diagnosis data, respectively.

5.3.1.1 Quantitative genetic analysis using SEM

Quantitative genetic models are commonly implemented in OpenMx, an open-source SEM package in the software R.[226] In this thesis, OpenMx was used in Study 1 and 3 to estimate the latent genetic and environmental factors assumed to underpin variance in the measured traits of interest, and the covariance between them. The path diagram in Figure 5.4 depicts the bivariate Cholesky decomposition[227] used in Study 3. The bivariate twin model simultaneously estimates the effects of the latent factors A, C and E to variation in both traits individually, and the extent to which genetic and environmental contributions are shared between the two traits. Latent factors A, C and E are represented as circles and the measured traits as rectangular boxes, presented for the two siblings in a pair. The double-headed arrows represent the assumed correlations across siblings in pair, based on sibling type. As E is by definition not shared between siblings, these latent factors are not correlated. Following path tracing rules,[228] the expected variance and covariance for the two phenotypes can be estimated. Path coefficients a_{11}, c_{11}, e_{11} reflect variance unique to trait 1, and a_{22}, c_{22}, e_{22} reflect variance unique to trait two. Taking full-siblings as an example, the genetic effect contributing to the covariance between sibling 1 and sibling 2 on trait 1 are given by

$$(a_{11} * 0.5 * a_{11}) = 0.5a_{11}^2$$

and the genetic effects on trait 2 are given by

$$(a_{21} * 0.5 \ * a_{21}) + \ (a_{22} * 0.5 * a_{22}) = 0.5a_{21}^2 + 0.5a_{22}^2$$

The same principle is applied to estimate the paths for the latent factors C and E. The paths a_{21}, c_{21}, and e_{21}, represent the covariance between ADHD and EP. To obtain the cross-trait correlation for A, C and E, the covariance between the traits is divided by the square root of the variance for each trait. For the genetic correlation (r_g), this is given by

$$r_g(\ ADHD_1, EP_1) = \frac{a_{11} * a_{21}}{\sqrt{a_{11}^2 \ * \ (a_{21}^2 \ + \ a_{22}^2)}} = \frac{a_{21}}{\sqrt{a_{21}^2 \ + \ a_{22}^2}}$$

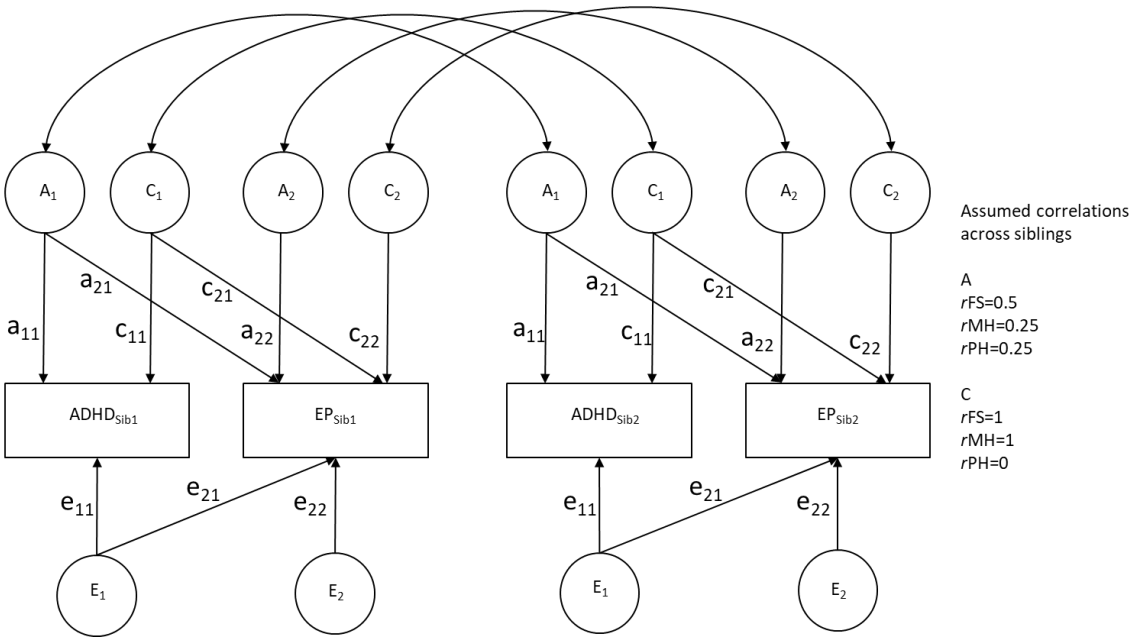


Figure 5.4. Bivariate Cholesky decomposition for sibling data used in Study 3

Note: Latent factors A, C and E are represented in circles, and are specific to ADHD (trait 1: A_1, C_1, E_1) and epilepsy (trait 2: A_2, C_2, E_2). Path coefficients (single headed arrows) are either unique to the ADHD (a_{11}, c_{11}, e_{11}) and epilepsy (a_{22}, c_{22}, e_{22}) or indicate the effect of latent factors related to ADHD, which also contribute to epilepsy (a_{21}, c_{21}, e_{21}). The correlations between A and C are determined by the type of siblings pair (FS, full-siblings. MH, maternal half-sibling. PH, paternal half-siblings).

Although the Cholesky decomposition[227] implies a causal ordering between the variables, it can be transformed into a correlated factors solution which is a standardized version of the bivariate Cholesky, where the order of the two variables is irrelevant, and arrows between latent factors are bi-directional.[227] This was done in Study 3, where results were interpreted and presented as a bivariate correlated factor model.

5.3.1.2 Factor analysis using SEM

Factor analysis (FA) is a statistical technique which aims to uncover the underlying latent factors that gave rise to the covariance structure among a set of observed variables. Within FA, there is exploratory and confirmatory FA. Whilst the first is an exploratory analysis to understand the clustering of variables based on the observed covariance matrix, the latter is a confirmatory technique where a hypothesized model is used to estimate a covariance matrix that is then compared to the observed covariance matrix in the sample data. Model fit is evaluated based on the difference between the estimated and observed matrices. Each latent variable in a CFA is measured by a set of observed indicator variables, which are the measured variables. A simplified path diagram of the CFA in Study 2 is given in section 6.2.2. FA is commonly estimated by SEM, using a similar method as described above. However, because quantitative genetics and FA come from different research traditions, FA is often implemented using other SEM software, such as Mplus.[229] It should be noted, that FA techniques rely on many decision that are largely pragmatic, and not necessarily driven by theory or firm prior knowledge. The number of extracted latent factors, rotations used, specification of correlations

across latent factors, and the interpretation of factors will have implications for the validity of the modelled factor structures. Cross-validation of is therefore a key issue in FA, and more generally for SEM models.

In Study 2 of this thesis, we used SEM to combine CFA and multiple regression. The measurement part of the model constituted the CFA, where the latent factor assumed to give rise to the observed correlations across measures of childhood psychopathology were defined. In the structural part of the model, the regressions between ADHD PRS and the latent variables were estimated.

5.3.1.3 Model fit in SEM

Several goodness-of-fit statistics may be used to estimate the fit of a SEM model (i.e., how well the model explains the underlying data structure), and to compare the goodness-of-fit across multiple models. The choice of fit statistic should be guided by the complexity of the model, and the distribution and sample size of the data to which the model is applied.

Maximum Likelihood estimation (MLM), which uses all available information are commonly used in SEM to test the probability of observing the sample data, given the specified parameters of the SEM model. Model comparison between nested models may be done using the likelihood ratio test, where the change in minus twice the log-likelihood (-2LL) follows a χ^2-distribution, with difference in number of parameters being the number of degrees of freedom. In general, more parsimonious models are preferred, as indicted by a non-significant change in the -2LL for the more restricted (nested) model. With large sample size, the likelihood ratio test is sensitive, and even small changes in model fit may results in a significant change for the -2LL (although this is an area of debate). Thus, other fit-statistics such the Bayesian Information Criterion (BIC),[230] which was used in Study 1 of this thesis, can be used to aid model selection. BIC has been shown to be more robust to distributional misspecification and to outperforms other fit statistics in larger samples and when comparing more complex models.[231] A lower BIC indicates better fit, taking into account the complexity of the proposed models (i.e. the number of parameters in the model) as well as the sample size.[230]

Whilst the likelihood ratio test and BIC are commonly used in quantitative genetic SEM, other goodness-of-fit statistics are often reported for CFA. In this thesis, we relied on the root mean square error of approximation (RMSEA) and the comparative fit index (CFI) to assess model fit in Study 2. RMSEA is an absolute fit index that assess how well the model fits the sample data in comparison to no model at all, taking parsimony into account. Better model fit is indicated by lower RMSEA. It has been suggested that a RMSEA statistic of ≤ 0.06 is needed to indicate good model fit.[232] The CFI also is commonly used as it is not greatly affected by sample size. The CFI statistic evaluates the model by comparing the χ^2 value of the model to the χ^2 of a null model, where all latent variables are specified as uncorrelated. A cut-off criterion of CFI ≥ 0.95 is suggested to indicate good fit.[232]

5.3.2 Regression models

Regression models included in this thesis include the Cox Proportional Hazard Model (discussed below) and different types of generalized linear models (GLM). GLM are widely used for estimation of exposure-outcome associations, with the possibility to conduct statistical adjustment for other covariates. GLM provides a flexible framework where an outcome is associated with covariates (including the exposure) through a link function. The choice of link function (and the assumed underlying distribution) determines on which scale inferences are made. A GLM may be expressed as

$$g\big(E(Y_i|x_i)\big) = \boldsymbol{x_i^T\beta} = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \cdots,$$

where $g(\cdot)$ is the link function, $E(Y_i|x_i)$ is the expected value of the outcome Y_i, for observation i, given the vector of covariates x_i and $\boldsymbol{\beta}$ is a vector of regression coefficients. In this thesis, the following link functions were used; identity (linear regression for continuous outcomes in Study 2, with the associations expressed as regression coefficients), logit (logistic regression for binary outcome in Study 3, with the associations expressed as odds ratios [OR]) and log (Poisson regression for count outcomes in Study 4, with the associations expressed as incidence rate ratios [IRR]). In general terms, the estimated coefficient in GLM are interpreted as the change in the outcome (interpreted on the scale for which is was estimated; e.g. log-odds for the OR) for every unit change in the exposure, holding all other covariates constant.

A few things should be noted for the specific regression models used:

- In logistic regression models in cohort studies were the outcome is rare, the OR will approximate the risk ratio, and can be interpreted as such. Logistic regression was used in Study 3 to estimate OR of ADHD case status among relative of individuals with epilepsy and we interpreted the OR as a relative risk.

- In Poisson regression, one can explicitly model differing time of follow-up, to estimate rates per time unit. This is achieved by including an offset term in the regression model, thus estimating rates as the number of events per time unit specified. Poisson regression was used in Study 4 to estimate the IRR of seizures in different time-bands prior and post ADHD medication initiation, accounting for time by including an offset for the number of weeks in each time-band.

5.3.2.1 Cox proportional hazards regression

Cox proportional hazards regression are used for analyzing time to event, or survival, data. The interest lies in the hazard, $h(t)$ of an event at time t, as a function of the baseline hazard and a set of the covariates (including the exposure)

$$h(t) = h_0(t)exp(\beta_1 x_{i1} + \beta_2 x_{i2} + \cdots,$$

where $h_0(t)$ is the baseline hazard at $time = t$, for a person with 0 on all covariates. In this model, no assumptions are made about the shape of baseline hazard, and it is never explicitly

estimated. However, it is assumed that the hazards are proportional throughout follow-up across the different level of covariates (e.g. exposed and unexposed), which may be a very strong assumption.[233] Proportionality of hazards across time should therefore be assessed, e.g. via visual inspection of the Schoenfeld residuals. The Cox model is appealing due to the very efficient adjustment for underlying time-scale, especially when the selected time-scale may potentially confound the association of interest, and because time-varying covariates may be modeled. The choice of underlying time-scale will depend on the research question (e.g. if the outcome is strongly correlated with attained age, this should use this as the underlying timescale). In Study 4, we used Cox proportional hazards regression to estimate the hazard ratio of epileptic seizures during ADHD medicated compared to non-medicated periods, with time since last seizure at the underlying time-scale.

5.3.2.2 Clustered data in regression models

An assumptions of most statistical tests is the independence of observations for the outcome, given the included covariates. In this thesis, we rely on correlated data where this assumption is likely to be violated (i.e. twin and family data, repeated observations from the same individual). As a results, standard errors of the estimated regression coefficients may be biased. This can be addressed using different statistical or methodological techniques. For between-cluster analyses (population-level) the issue may be addressed using methods that produce cluster robust standard errors, such as the sandwich formula or bootstrap sampling [234,235]. The sandwich estimator accounts for model misspecifications due to data clustering and was used in Study 2-4 of this thesis to generate so-called robust standard errors. Nonparametric bootstrap sampling was used in the quantitative genetic analyses in Study 3, by repeatedly drawing (with replacement) families, re-computing the model estimates in 1000 bootstrap samples, and estimating standard errors from the distribution of the bootstrap replicates. In within-cluster analyses, the clustering of the data is not a threat to the validity of the study, but can instead be used to condition the analyses on the cluster (i.e. repeated measures from the same individual) as a means to control for unmeasured cluster-constant confounding. In Study 4, we used Conditional Poisson and Stratified Cox regression in order to control for time-constant factors within the same individual, by entering each individual into the model as a separate stratum.[236]

6 STUDY SUMMARIES AND RESULTS

6.1 ADHD AND RELATIVE IMMATURITY (STUDY 1)

6.1.1 Rationale

Study 1 is a classical twin study investigating the etiological overlap between parent's perceptions of their child's immaturity relative to peers (RI) in childhood, with the development of ADHD symptoms from childhood to early adulthood. Specifically, this study aimed to address two questions;

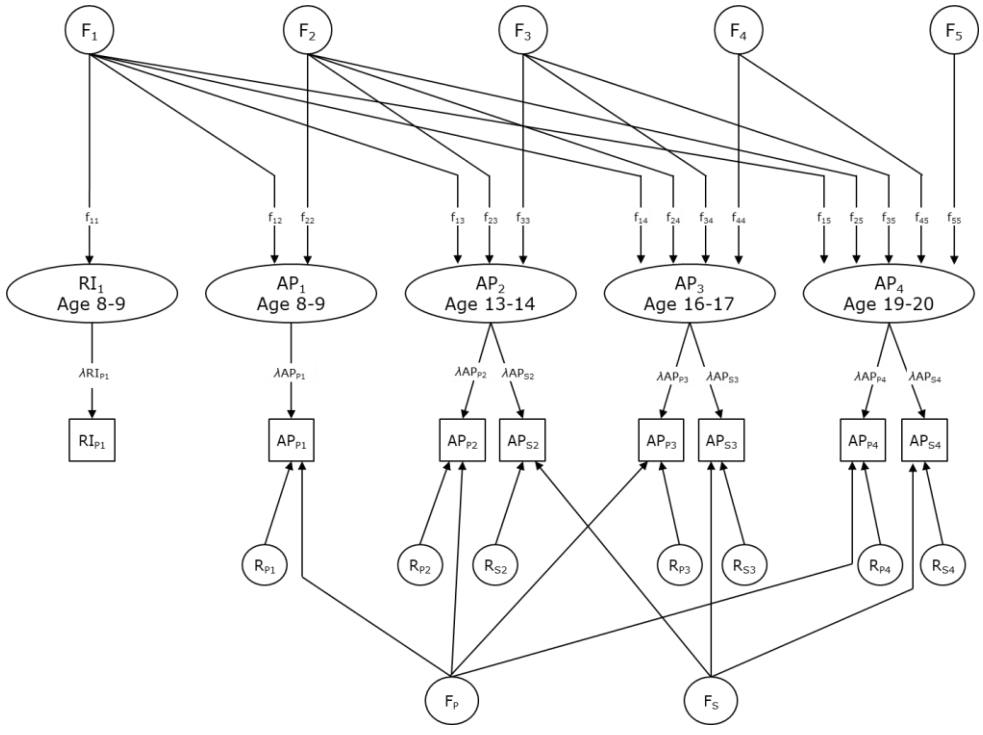
I) Is RI in childhood associated with ADHD symptoms across development and does this assocation decrease with increasing age?

II) To what extent can an observed assocation between RI and ADHD across development be explained by shared genetic factors?

6.1.2 Method

Parent-ratings of RI at ages 8-9 years and parent- and self-ratings of ADHD symptoms (AP; measured via the attention problems ASEBA scales) at ages 8-9, 13-14, 16-17 and 19-20 years for 1,302 twin pairs from TCHAD were used. A longitudinal twin model with multiple raters (parent- and self-ratings)[237] was used to estimate the relative contribution of genetic and environmental factors to covariance between RI and AP across ages (Figure 6.1.1).

Figure 6.1.1 Path diagram of the longitudinal, multi-rater model, presented for one twin and one source of variance, such as additive genetic effects



Note: The model contained 5 latent trait factors; 1 for relative immaturity at ages 8 to 9 years (RI_1) and 4 for attention problems (AP_1–AP_4), reflecting the "shared" view of AP at each age. Latent variables were indexed by parent-ratings (*P*) and twin self-ratings (*S*) when available. The degree to which parent-

and self-ratings index the latent factors is reflected by the paths λ_p and λ_s. F_P and F_S reflect rater-specific latent common factors for parent- and self-ratings of AP. R_P and R_S refer to rater- and time-specific residuals for parent- and self-ratings of AP. The genetic and environmental influences on RI_1 and AP_1 to AP_4 were modeled using Cholesky decomposition,[227] with RI_1 preceding AP_1 to AP_4. Taking genetic contributions as an example, F_1 reflect RI-related genetic effects that contribute to variance in RI_1 (8–9 years) via path f_{11}. In addition, F_1 explains variance in AP at all ages through paths f_{12}, f_{13}, f_{14}, and f_{15}. The second factor (F_2) reflects AP-related stable genetic effects that contribute to variance in AP at aged 8 to 9 years, over and above any variance explained by RI_1, and contributes to genetic stability in AP through paths f_{22}, f_{23}, f_{24}, and f_{25}. F_3-F_5 are interpreted in a similar way, reflecting new genetic factors that come online at each age, influencing variance in AP. The factor structure depicted by F_1 to F_5 was implemented for the 3 sources of variance: A, C or D, and E. The figure is adapted from Kendler K, et al., 2008.[237]

6.1.3 Results

Phenotypic associations

Findings from Study 1 revealed significant phenotypic associations between RI in childhood and elevated AP throughout childhood and adolescence (Table 6.1.1). Associations across all ages were small to moderate, generally declined with age, and were stronger across RI and parent-rated AP (r=0.11-0.33), compared to RI and self-rated AP (r=-0.01-0.14) which were no longer significantly associated at age 19-20 years.

Table 6.1.1 Pearson's correlations between RI and AP across rater and time

Age (y)			8-9		13-14		16-17		19-20	
	Rater		Parent		Parent	Self	Parent	Self	Parent	Self
			RI	AP	AP	AP	AP	AP	AP	AP
8-9	Parent	RI	1.00	0.33	0.29	0.14	0.21	0.11	0.11	-0.01*
	Parent	AP		1.00	0.54	0.25	0.45	0.17	0.39	0.09
13-14	Parent	AP			1.00	0.38	0.61	0.29	0.49	0.20
	Self	AP				1.00	0.32	0.54	0.28	0.38
16-17	Parent	AP					1.00	0.39	0.55	0.18
	Self	AP						1.00	0.28	0.45
19-20	Parent	AP							1.00	0.32
	Self	AP								1.00

*Non-significant correlations; All other correlations significant at $p < 0.001$.

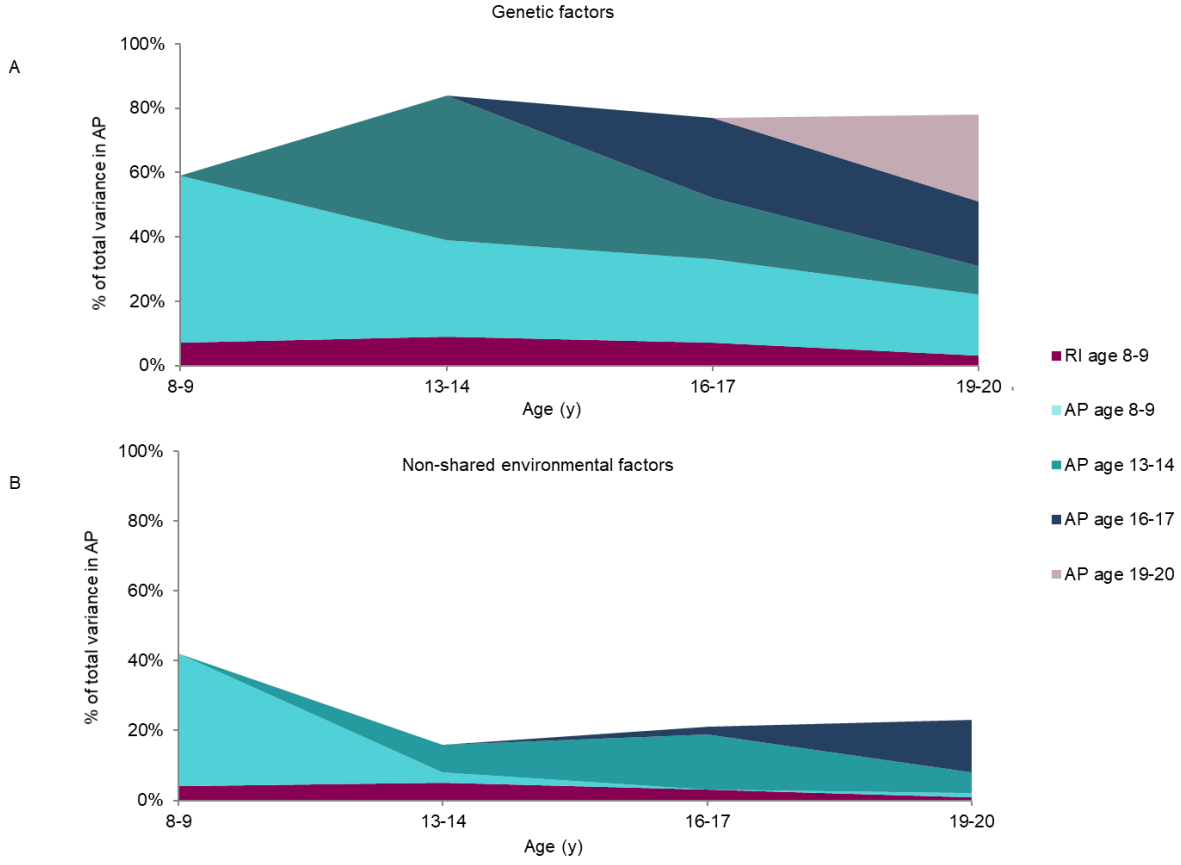
Twin analyses results

Twin correlations (not shown) within trait, and across trait and time, where higher in MZ twin pairs than DZ in twin pairs, suggesting that genetic factors contributed to variance and covariance between RI and AP, as well as to the associations in AP across ages. An AE model with no sex differences provided the best fit to the data. RI-related genetic effects (A_1) explained 86% of the variance in RI at ages 8-9. Further, 10% to 14% of the variance in AP during childhood and adolescence could be explained by etiologic (genetic and environmental) factors related to RI, with a stronger contribution of genetic factors. The association between RI and AP decreased substantially from late adolescence (ages 16-17) to early adulthood (ages 19-20), where RI-related etiological factors explained only about 4% of the variance in AP.

Non-shared environmental effects (E_1) related to RI showed a similar pattern of association with AP, but were of smaller magnitude. In contrast, AP-related stable genetic effects (A2) explained 52% of the variance in AP at aged 8-9 years and continued to explain 30%, 26%, and 19% of the variance in AP at ages 13-14, 16-17, and 19-20 years. In addition to showing considerable genetic stability, new AP-related genetic effects came online throughout development. Standardized parameter estimates from the AE model are presented in Table 6.1.2 and the % total variance explained in AP across ages in Figure 6.1.2.

In line with previous findings in the TCHAD,[106] the cross-rater latent factors (AP_1–AP_4) contributed more to parent-rated than to self-rated AP at assessment waves where both types of ratings were available. Rater-specific common factors contributed more toward self-rated AP than toward parent-rated AP, and a larger proportion of self-rated AP was modeled as rater- and time-specific residuals, as compared with parent-rated AP.

Figure 6.1.2. Proportion of total variance in attention problems (AP) explained by genetic and non-shared environmental factors across development.



Note: The y-axis represents the total phenotypic variance in AP accounted for by (A) genetic factors and (B) non-shared environmental factors. Relative immaturity (RI) corresponds to RI-related etiologic factors (F_1 in Figure 6.1.1) at age 8-9 years, and AP corresponds to AP-related etiologic factors across ages (F_2–F_5 in Figure 6.1.1).

Table 6.1.2. Standardized parameter estimates for the genetic and environmental factors (F1-F5 in Figure 6.1), together with percentage of the total variance in each factor explained by A (h^2) and E (e^2).

		Genetic Parameter Estimates				
Factor age (y)	Total h^2	A_1	A_2	A_3	A_4	A_5
RI 8-9	86%	0.93 (0.91-0.94) 86%				
AP 8-9	58%	0.26 (0.20-0.33) 7%	0.72 (0.68-0.77) 52%			
AP 13-14	84%	0.30 (0.23-0.36) 9%	0.55 (0.48-0.61) 30%	0.67 (0.62-0.72) 45%		
AP 16-17	78%	0.27 (0.20-0.34) 7%	0.51 (0.42-0.59) 26%	0.44 (0.35-0.53) 20%	0.50 (0.41-0.58) 25%	
AP 19-20	77%	0.17 (0.09-0.25) 3%	0.44 (0.34-0.54) 19%	0.30 (0.19-0.40) 9%	0.45 (0.30-0.60) 20%	0.51 (0.33-0.64) 26%

		Non-shared Environmental Parameter Estimates				
Factor age (y)	Total e^2	E_1	E_2	E_3	E_4	E_5
RI 8-9	14%	0.38 (0.35-0.42) 14%				
AP 8-9	42%	0.20 (0.14-0.27) 4%	0.61 (0.56-0.66) 37%			
AP 13-14	16%	0.22 (0.15-0.28) 5%	0.18 (0.12-0.30) 3%	0.29 (0.20-0.37) 8%		
AP 16-17	22%	0.17 (0.10-0.24) 3%	0.04 (-0.05-0.15) 0%	0.40 (0.30-0.50) 16%	0.16 (-0.01-0.31) 3%	
AP 19-20	23%	0.08 (-0.01-0.17) 1%	0.09 (0.01-0.20) 1%	0.25 (0.10-0.40) 6%	-0.39 (-0.54-0.14) 15%	0.00 (-0.49-0.49) 0%

Note: A1 to A5 and E1 to E5, latent factors presented separately for genetic and non-shared environmental effects. 95% profile likelihood CIs are presented in parentheses. AP, attention problems; e^2 total proportion of variance explained by non-shared environmental factors; h^2 total proportion of variance explained by genetic factors; RI, relative immaturity

6.2 GENETIC RISK FOR ADHD AND ASSOCATIONS WITH RELATED CHILDHOOD PSYCHOPHATOLOGY (STUDY 2)

6.2.1 Rationale

Study 2 is a PRS study conducted in a large population based twin cohort, investigating the associations between ADHD PRS and a broad range of childhood psychiatric traits. Specifically, this study aimed to;

I) Examine whether ADHD PRS is associated with a range of neurodevelopmental, externalizing, and internalizing psychiatric traits in childhood.

II) Quantify the extent to which any observed associations between ADHD PRS and the aforementioned trait dimensions can be attributed to a general psychopathology factor.

6.2.2 Method

Study 2 used parent-ratings in CATSS of neurodevelopmental (IA, H/I, ASD, LD), externalizing (ODD, CD), and internalizing symptoms (DEP, ANX). Analyses were run separately across two subsamples, based on the available assessment of internalizing items. A total of 6603 twins (3483 unrelated individuals) were available for analysis in the A-TAC subsample, and 6854 twins (3634 unrelated individuals) in the SMFQ/SCARED subsample.

ADHD PRS estimation

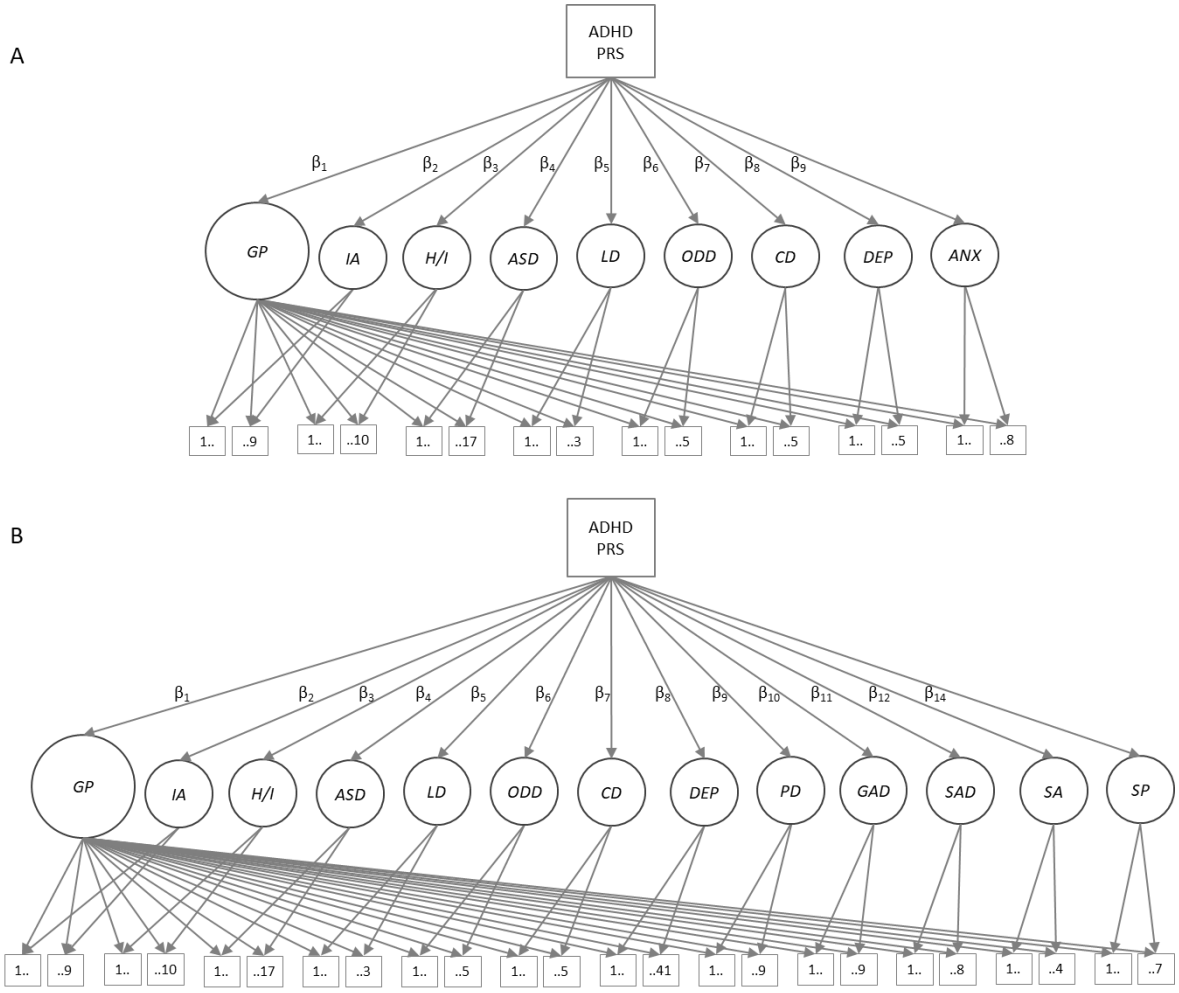
ADHD PRS were generated in CATSS, using summary statistics from a meta-analysis (MA) of the two largest available GWAS of clinical ADHD and ADHD symptoms.[59,60] Standardized betas were calculated for each SNP, based on available information of z-scores, effective sample size and allele frequency in the ADHD GWAS-MA.[238] ADHD PRS were derived in CATSS from best-guess imputed genotypes across seven p-value thresholds ($0.00001 \leq P_T \leq 1$). Indels, multi-allelic and symmetric/ambiguous SNPs were excluded. Autosomal SNPs with a minor allele frequency (MAF)≥0.05 and good imputation quality (INFO score)≥0.8 were clumped (linkage disequilibrium threshold $R^2 > 0.1, \pm 1000$ kb) to obtain an independent set of variants, using PLINK.v.1.9.[239] Retained reference alleles were scored across the set of SNPs in PLINK using standard procedures.[137] PRS including SNPs at a threshold of $P_T \leq 0.50$ were used for the main analysis, in line with previous publications.[65,80]

Statistical analysis

Associations between ADHD PRS and neurodevelopmental, externalizing, and internalizing traits were estimated using SEM. A CFA was fit to all measured symptom items, using two different models (Figure 6.2.1). We first fitted a correlated factors model where symptoms from each scale were set to load onto a corresponding single latent trait factor, and all latent factors were allowed to correlate. Second, a general psychopathology factor model was fitted, which in addition to the aforementioned latent trait factors, included a general psychopathology factor on which all symptom items loaded. A general factor model quantifies

the extent to which covariance among symptom dimensions reflects both a general factor (on which all assessed symptoms load) and a number of more specific factors (on which only a subset of the symptoms load). Correlations between the specific latent factors and the general factor are fixed at zero, whereas correlations between the specific latent factors are free to vary. In both models, the latent factors were regressed on ADHD PRS, with sex, age and the first six PCs (to account for possible population stratification) included as covariates. Analyses were conducted using Mplus.[229]

Figure 6.2.1. Path diagram of the general factor model, presented by study subsample



Note: General factor model in the A-TAC subsample (A) and SMFQ/SCARED subsample (B). Latent factors are depicted as circles. The models consisted of a latent general psychopathology factor (GP) and specific latent trait factors reflecting symptoms of inattention (IA) hyperactivity/impulsivity (H/I), autism spectrum disorder (ASD), learning difficulties (LD), oppositional defiant disorder (ODD), conduct disorder (CD), depression (DEP) and anxiety (ANX) *or* panic disorder (PD), generalized anxiety (GAD), separation anxiety (SAD), school anxiety (SA), and social phobia (SP). Variances for all latent factors were fixed at 1. Measured variables are depicted as squares, and include the ADHD PRS and all symptoms items from A-TAC, SCARED and SMFQ, with 1…X indicating the number of symptom items loading onto each specific latent trait factor. β_1-β_x represent the regression coefficients, regressing each latent variable onto ADHD PRS. For clarity, covariates (age, sex and six PC's) and correlations across latent trait factors are omitted in the above graphical representation

6.2.3 Results

Model fit and loadings

The correlated factor model fit the data well in both subsamples (CFI>0.94, RMSEA<0.02) (Table 6.2.1). All symptoms loaded positively and significantly onto their corresponding latent trait factor (Table 2, Manuscript 2). The general factor model also fit the data well in both subsamples (CFI>0.96, RMSEA<0.02). Furthermore, omitting the general psychopathology factor resulted in a statistically significant decrease in model fit based on the likelihood ratio test (Table 6.2.1). In the general factor model, all symptoms loaded positively and significantly onto the general psychopathology factor (Table 2, Manuscript 2). Mean loadings on the general psychopathology factor were strongest for neurodevelopmental traits, somewhat lower for externalizing traits, and weakest for internalizing traits. The general factor explained 56% of the covariance across traits (explained common variance [ECV]) in the A-TAC subsample and 40% in the SMFQ/SCARED subsample.

Table 6.2.1. Model fit for the correlated factor model and the general factor model

Model	CFI	RMSEA (95%CI)	$\chi 2$ (df)	$\Delta\chi 2$	Δdf	*p*
A-TAC subsample						
GF	0.97	0.02 (0.02-0.02)	6674.06 (2216)	-	-	-
CF	0.95	0.02 (0.02-0.02)	8636.54 (2287)	1962.48	71	< .0001
SMFQ/SCARED subsample						
GF	0.96	0.01(0.01-0.01)	12544.05 (5275)	-	-	-
CF	0.94	0.02 (0.02-0.02)	16123.77 (5382)	3579.72	107	< .0001

Note: GF, general factor model. CF, correlated factor model. CFI, comparative fit index. RMSEA, root mean square error of approximation. $\chi 2$, Chi-square. df, degrees of freedom. The likelihood ratio test was run using the DIFFTEST option in MPlus, comparing the fit of the nested correlated factor model to the general factor model.

ADHD PRS regression results

In the correlated factor models, higher ADHD PRS were statistically significantly associated with higher symptom levels for all the latent neurodevelopmental, externalizing and depression trait factors, after adjusting for covariates (Table 6.2.2) ADHD PRS was not statistically significantly associated with the latent anxiety factors, with the exception of panic disorder (β=0.06, p=0.014). In the general factor models, higher ADHD PRS were significantly associated with higher scores on the general psychopathology factor (β=0.09-0.10, p<0.0001), explaining ~1% of the variance in the general psychopathology factor. After accounting for covariance across all symptoms via the general factor, only the association between ADHD PRS and the specific hyperactivity/impulsivity factor remained significant in both subsamples (β=0.06-0.08, p<0.0001), explaining 0.37-0.69% of the variance. Somewhat surprisingly, ADHD PRS also showed a significant negative correlation with specific social phobia (β=-0.05, p=0.004) in the SMFQ/SCARED subsample. This may be explained by the latent SP factor showing a significant negative correlation with IA and H/I in the general factor model,

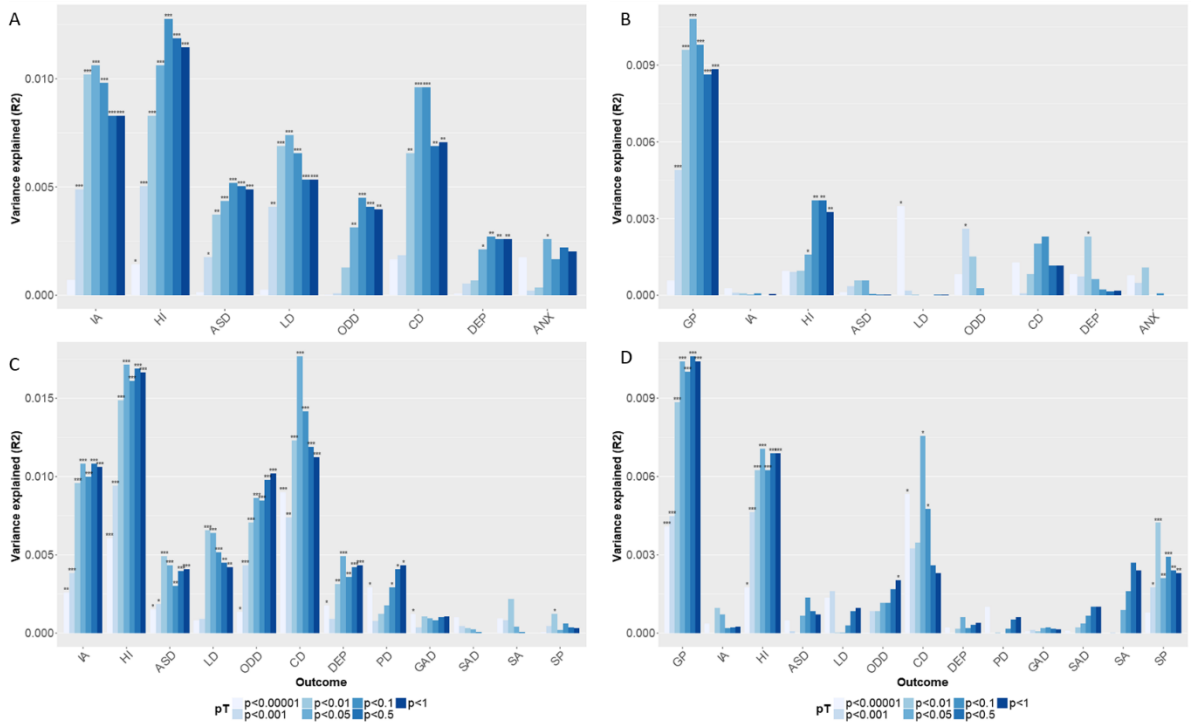
even prior to regression of the latent variables on ADHD PRS (results shown in supplementary materials of Manuscript 2). Results were consistent across *p*-value thresholds (Figure 6.2.3).

Table 6.2.2. Association between ADHD PRS and latent trait factors in the correlated factor model and the general factor model (PRS *p*-value threshold≤0.5)

	Correlated Factors Model				General Factor Model			
	Beta	S.E	p	R^2	Beta	S.E	p	R^2
A-TAC subsample (N= 6603)								
GP	na	na	na	na	0.09	0.02	**<.0001**	0.86%
IA	0.09	0.02	**<.0001**	0.83%	-0.01	0.02	.929	0.00%
H/I	0.11	0.02	**<.0001**	1.19%	0.06	0.02	**.003**	0.37%
ASD	0.07	0.02	**<.0001**	0.50%	-0.01	0.03	.862	0.00%
LD	0.07	0.02	**<.0001**	0.53%	-0.01	0.03	.873	0.00%
ODD	0.06	0.02	**<.001**	0.41%	0.01	0.02	.895	0.00%
CD	0.08	0.03	**.007**	0.69%	0.03	0.04	.390	0.12%
DEP	0.05	0.02	**.009**	0.26%	-0.01	0.02	.564	0.01%
ANX	0.05	0.02	.053	0.22%	0.00	0.03	.998	0.00%
SCARED/SMFQ Subsample (N=6854)								
GP	na	na	na	na	0.10	0.02	**<.0001**	1.06%
IA	0.10	0.02	**<.0001**	1.08%	0.02	0.02	.482	0.02%
H/I	0.13	0.02	**<.0001**	1.69%	0.08	0.02	**<.0001**	0.69%
ASD	0.06	0.02	**.001**	0.40%	-0.03	0.02	.220	0.08%
LD	0.07	0.02	**.002**	0.45%	-0.03	0.03	.308	0.08%
ODD	0.10	0.02	**<.0001**	0.98%	0.04	0.02	.058	0.17%
CD	0.11	0.03	**<.0001**	1.19%	0.05	0.03	.117	0.26%
DEP	0.07	0.02	**<.001**	0.42%	0.02	0.02	.411	0.03%
PD	0.06	0.03	**.014**	0.41%	0.02	0.03	.405	0.05%
GAD	0.03	0.02	.066	0.10%	-0.01	0.02	.450	0.02%
SAD	0.01	0.02	.826	0.00%	-0.03	0.02	.071	0.10%
SA	0.00	0.03	.996	0.00%	-0.05	0.03	.052	0.27%
SP	-0.02	0.02	.272	0.04%	-0.05	0.02	**.004**	0.24%

Note: All models were adjusted for sex, age and six principal components. Beta, standardized regression coefficients. S.E, standard error. R^2, variance explained (beta^2). IA, inattention factor. H/I, hyperactivity/impulsivity factor. ASD, autism spectrum disorder factor. LD, learning difficulties factor. ODD, oppositional defiant disorder factor. CD, conduct disorder factor. DEP, depression factor. ANX, anxiety factor. PD, panic disorder factor. GAD, generalized anxiety disorder factor. SAD, separation anxiety disorder factor. SA, school anxiety factor. SP, social phobia factor.

Figure 6.2.3. Variance explained by ADHD PRS in latent factors from the correlated factor model (A) and the general factor model (B) across PRS p-value thresholds



Note: Panel A, correlated factor model A-TAC subsample. Panel B, general factor model A-TAC subsample. Panel C, correlated factor model SMFQ/SCARED subsample. Panel D, general factor model SMFQ/SCARED subsample. R^2= $beta^2$.

6.3 COMORBIDITY BETWEEN ADHD AND EPILEPSY (STUDY 3)

6.3.1 Rationale

Study 3 is a nationwide register-based family study investigating the underlying causes of comorbidity between ADHD and epilepsy. Specifically, this study aimed to;

I) Investigate the familial co-aggregation of ADHD and epilepsy across multiple types of relatives.

II) Estimate the contribution of genetic and environmental risk factors to comorbidity between ADHD and epilepsy.

6.3.2 Method

A study population of 1,899,654 individuals born in Sweden between 1987 and 2006 was identified via multiple national Swedish registers. Each individual in the cohort was in turn linked to their relatives using the MGR. Individuals who died or migrated prior to age seven, who were adopted, or whose biological parents were not identifiable were excluded. ADHD and epilepsy cases were identified based on discharge diagnosis in the NPR. Further ADHD cases were identified in PDR based on ADHD medication prescription. Information on case status was collected from age 3 until December 31, 2013.

Familial co-aggregation and quantitative genetic analyses

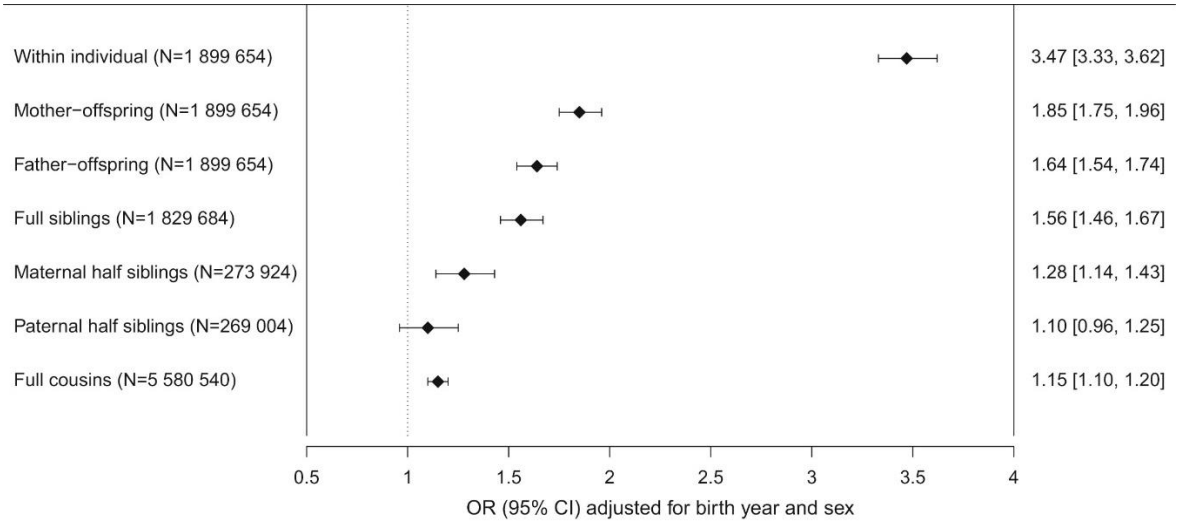
Familial co-aggregation was estimated in each relative cohort using logistic regression, comparing the risk of ADHD in individuals with a relative with epilepsy, to the risk in individuals without a relative with epilepsy, adjusting for birth year and sex. Genetic and environmental contributions to the association between ADHD and epilepsy were estimated by fitting a bivariate extended sibling model (see section 5.3.1.2) to data from all pairs of full siblings, maternal and paternal half siblings in the cohort. Parent-offspring pairs were not included due to changes in diagnostics practices and differential coverage of the registers across the two generations. The model was fit using the weighted least squares method and standard errors were obtained using nonparametric bootstrap sampling to account for the non-independence of sibling data. Analyses were implemented in OpenMx.[226]

6.3.3 Results

Familial co-aggregation results

Individuals with epilepsy had a statistically significant increased risk of ADHD, compared with individuals without epilepsy. Further, relatives of individuals with epilepsy also had statistically significant increased risk of ADHD, and the strength of association increased along with increasing relatedness (Figure 6.3.1). The association was significantly higher for mother-offspring pairs, compared to father-offspring (*p*=.004), and for maternal half siblings, compared to paternal half siblings, for whom the risk increase was not statistically significant.

Figure 6.3.1. Within-individual and familial co-aggregation of ADHD and epilepsy



Note: Odds ratios (ORs) represent the association between ADHD and epilepsy within-individual and across different types of relatives. ORs are adjusted for birth year and sex. The 95% confidence intervals (CI) are presented in parentheses.

Quantitative genetic results

The phenotypic correlation between ADHD and epilepsy was estimated at 0.24 (95% CI = 0.23–0.25) in the sibling cohort (N=1 186 306 sibling pairs). Sibling correlations were higher

in full siblings than in maternal half siblings, indicating the contribution of genetic factors to variance and covariance between liabilities for ADHD and epilepsy (Table 6.3.1). Furthermore, all correlations were somewhat higher in maternal half siblings, than in paternal half siblings, indicating a possible contribution of shared environmental factors. This is because both types of half siblings share 25% their segregating genes, but maternal half siblings tend to share more environmental factors, especially early in life.[240] There was no indication of dominance genetic effects which are indexed by maternal half-sibling correlations being less than half of the full sibling correlations.

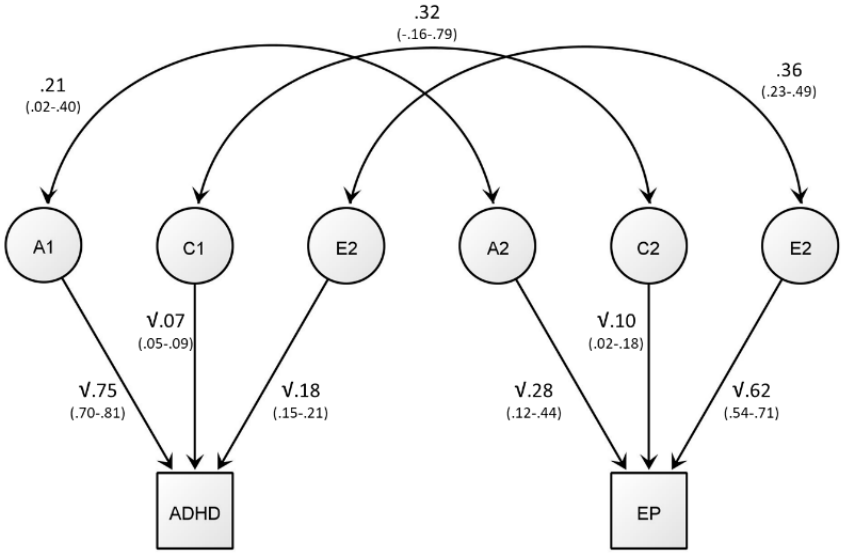
Table 6.3.1. Intra-class (ICC) and cross-trait-cross-sibling (CSCT) correlations between ADHD and epilepsy

	N Pairs	Concordant Pairs	ICC ADHD	ICC EP	CSCT
Full siblings	914 842	598	0.45 (0.44-0.45)	0.24 (0.22-0.26)	0.08 (0.06-0.09)
Maternal half siblings	136 962	198	0.26 (0.24-0.27)	0.17 (0.12-0.22)	0.04 (0.01-0.07)
Paternal half siblings	134 502	150	0.19 (0.17-0.20)	0.07 (0.02-0.13)	0.01 (-0.02-0.05)

Note: Concordant pairs refers to the number of sibling pairs where one sibling had a diagnosis of epilepsy and the other sibling had a diagnosis of ADHD. 95% CIs are presented in parentheses.

Based on the observed sibling correlations, an ACE model was fitted. Results showed that genetic and shared environmental factors together explained 51% of the phenotypic correlation between epilepsy and ADHD (additive genetic contribution = 40%, 95%CI=9-70; shared environmental contribution = 11%, 95%CI=-3-25). Remaining covariance (49%, 95%CI=32-67) was attributable to non-shared environmental factors (Figure 6.3.2).

Figure 6.3.2. Path diagram for the bivariate ACE model, estimating the genetic and environmental correlations between ADHD and epilepsy



Note: Values within the square root sign are the squared path coefficients and represent the % variance accounted for by A, C, and E for each trait. Curved double-headed arrows represent to the correlation between A, C, and E across liabilities for ADHD and epilepsy. 95% CI presented in parentheses.

6.4 SAFETY OF ADHD MEDICATIONS IN INDIVIDUALS WITH A SEIZURE HISTORY (STUDY 4)

6.4.1 Rationale

Study 3 is a nationwide register-based pharmacoepidemiological study, investigating the risk of seizures associated with ADHD medication use in individuals with a seizure history, with and without comorbid NDDs. Specifically, we aimed to investigate;

I) Whether the time around incident ADHD medication treatment is associated with an increased risk of seizures?
II) Whether repeated ADHD medication periods are associated with an increased risk of seizures?

6.4.2 Method

Individuals born in Sweden between 1968 and 2007, who had experienced a seizure before age 30 according to discharge diagnoses in the NPR, were included. All individuals were followed from January 1, 2006, their first seizure or age five, whichever came last, until December 31, 2013 or death, which ever came first. Individuals who migrated during follow-up were excluded, resulting in a study population of 44,827 individuals, representing 80% of the study base. ADHD medication periods identified via the PDR were treated as a time-varying exposure, and seizure events identified in NPR as the outcome. See section 4.3.1.3- 4.3.1.5 for details on definitions of exposure, outcome, and covariates.

Incident medication analyses

Incident ADHD medication dispensation was defined as a dispensation of ADHD medication preceded by at least 18 months without a dispensation. The rate of seizures during the 24 weeks before and after ADHD medication initiation were compared with the average rate during the same 48 weeks in the previous year. Follow-up time was split into 0-4, 5-12 and 13-24 weeks pre- and post-medication initiation. Incidence rate ratios (IRR) were estimated using conditional Poisson regression, entering each individual as a separate stratum to adjust for confounding by unmeasured covariates that are constant within-individual during follow-up.

Repeated medication analyses

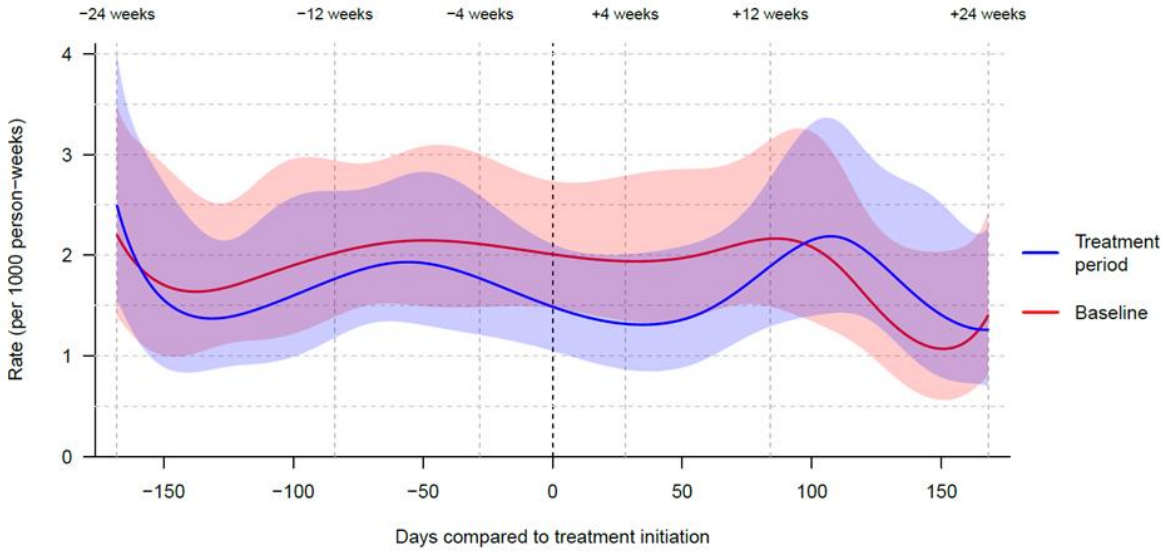
Cox proportional hazards models were used to estimate the population-level association between repeated ADHD medication periods (time-varying exposure) and the rate of seizure events, using robust standard errors to account for the non-independence of data. Population level analyses were adjusted for sex, age and concomitant AED medications. Stratified Cox proportional hazards models were used to estimate the within-individual association between ADHD medication periods and the rate of seizure events, entering each individual as a separate stratum in the model. These models were explicitly adjusted for categorical age and concomitant AED use. We further re-ran analyses among individuals with an ADHD diagnosis, and stratified the analysis on the presence or absence of additional NDDs.

6.4.3 Results

Incident medication analyses

Within the study population, 1539 individuals had an incident ADHD medication dispensation between 1 January, 2007 and 30 June, 2013. Among these, a total of 127 events occurred in 158 persons during 24 weeks pre- and post-medication initiation (Table 6.4.1). Overall, result showed no evidence for a statistically significant increased risk of seizures during 24 weeks prior and or post ADHD medication initiation, as compared to the rate during the same 48 weeks in the year prior (Figure 6.4.1).

Figure 6.4.1. Incidence rate (IR) of seizures pre and post ADHD medication initiation



Note: The blue line is the estimated IR per 1000 person-weeks throughout 24 weeks pre- and post ADHD medication initiation, presented with 95% CI. The red line indicates baseline IR with 95% CI. IRs are estimated with natural cubic splines with knots at -24, -12, -4, 4, 12, and 24 weeks

Table 6.4.1. Within-individual incidence rate ratio (IRR) for seizure events in the 24 weeks pre- and post ADHD medication initiation among 1539 individuals with a seizure history

Time-period (weeks)	No of events	Within-individual IRR (95% CI)
Baseline	141	-
Pre 24-13	30	0.85 (0.57-1.26)
Pre 12-5	23	0.98 (0.63-1.52)
Pre 4-0	13	1.11 (0.63-1.95)
Post 0-4	9	0.77 (0.39-1.50)
Post 5-12	16	0.68 (0.41-1.14)
Post 13-24	36	1.02 (0.71-1.47)

Repeated medication analyses

In the full cohort, a total of 24,337 seizure events occurred in 44,827 individuals during 293,876 person years of follow-up. Results from the Cox regression analyses are presented in Table 6.4.2. Overall, results from the population-level analyses showed no statistically significant difference in the rate of seizures during ADHD-medicated and non-medicated periods, after adjusting for age and sex. In the within-individual analyses, which adjust for all time-constant confounders within an individual, ADHD-medication periods were associated with a statistically significant decreased rate of seizures. These results did no differ markedly when adjusting for concurrent AED medication treatment, across sex, or when stratified based on clinical ADHD diagnosis, or by the absence or presence of additional NDDs.

Table 6.4.2. Hazard ratios for seizure events during ADHD-medication treatment periods, compared with non-treatment periods (2006-2013)

Analysis	N individuals	N seizure events	Population-level HR (95%CI)	Within-individual HR (95%CI)
Model 1				
ADHD meds	44827	24337	0.96 (0.77-1.19)	0.77 (0.62-0.95)
Model 2				
ADHD meds	44827	24337	0.92 (0.74-1.13)	0.77 (0.62-0.95)
AED meds	44827	24337	3.04 (2.87-3.22)	0.94 (0.87-1.00)
Model 3				
ADHD meds=1 | AED meds=0	1654	44	0.59 (0.42-0.83)	0.69 (0.41-1.18)
ADHD meds=0 | AED meds=1	26798	20151	3.02(2.85-3.19)	0.93 (0.87 -1.00)
ADHD meds=1 | AED meds=1	1444	432	0.97 (0.78-1.22)	0.78 (0.62-0.96)
Model 4				
Men only	23332	12225	0.85 (0.63-1.14)	0.80 (0.60-1.06)
Women only	21495	12112	1.04 (0.78-1.38)	0.73 (0.53-1.01)
Model 5				
ADHD	3554	2284	0.80 (0.63-1.00)	0.74 (0.59-0.93)
ADHD + no NDD	1633	761	0.78 (0.55-1.12)	0.61 (0.41-0.91)
ADHD + additional NDD	1921	1523	0.79 (0.60-1.05)	0.81 (0.61-1.08)

Note: Model 1 shows the association between ADHD medication and seizures, adjusted for sex and age at start of each observation periods in five age bins (5-10, 11-16, 17-22, 23-30 and 31-45 years). Model 2 is further adjusted for concurrent AED medications. Model 3 shows risk estimates in each strata of combinations for ADHD and AED medication periods, compared to reference periods (no medication). Individuals could contribute data to more than one strata. Model 4 shows the association stratified by sex, adjusted for age and concurrent AED medication. Model 5 shows the association stratified by ADHD diagnosis, ADHD and no additional NDD, ADHD and additional NDD, adjusted for categorical age, sex and concurrent AED medication. 95% CIs are presented parentheses.

7 DISCUSSION AND IMPLICATIONS

7.1 MAIN FINDINGS

The main findings from this thesis suggest that ADHD is related to both later maturation and a wide range of childhood psychiatric traits, and that these associations are partly due to shared genetic risk factors. Further, the shared genetic liability between ADHD and related childhood psychiatric traits can in part be attributed to a general liability towards broad childhood psychopathology. Comorbidity between ADHD and epilepsy also show moderate genetic influence, however individual specific environmental factors contributes more strongly to the cross-disorder overlap. ADHD medication does however not appear to be a risk factor for acute epileptic seizures among individuals with a seizure history.

7.1.1 Maturity – one developmentally important aspect of ADHD

Findings from Study 1 revealed that relative immaturity is significantly associated with higher levels of ADHD symptoms, primarily due to shared genetic factors. Nevertheless, the magnitude of the association was modest, and diminished with age, with little effect of relative immaturity on ADHD symptoms in early adulthood. Majority of the variance in ADHD symptoms at all ages was explained by immaturity-independent etiological factors. Results also showed evidence for ADHD-related genetic stability across ages, and genetic innovation during adolescence and early adulthood. This suggest that immaturity is merely one etiological factor contributing to ADHD, and that this effect is largely limited to ADHD symptoms in childhood and adolescence.

Results should be considered within the wider research context. First, it is possible that the attenuated genetic and phenotypic association between relative immaturity and ADHD with age may be related to the catch up in neurodevelopmental maturation previously reported in longitudinal neuroimaging studies of ADHD.[5] Together, such findings may partly explain why some children show a decrease in ADHD symptoms from childhood to early adulthood. Second, although there is clear evidence for a higher risk of clinical ADHD diagnoses among children who are born in the last months of the school-year,[111-122] our findings suggest that such effects may be more strongly related to ADHD in childhood, and less important for ADHD in adulthood.[112] Nevertheless, comparison across studies are challenging due to differences in measures and methodology. Whereas we relied on parent-rated relative immaturity and ADHD symptoms, other studies have used birth-month as a proxy for immaturity. There is evidence to suggest that the association between birth-month and clinical ADHD is more strongly driven by teacher-rated comparison of maturity between children in the classroom, than by parent-ratings.[111]

Increased awareness of the association between maturity and ADHD is important for clinical practice and policy. Studies from Denmark, where relatively young children can be held back from school start, have not reported an associations between birth-month and ADHD.[241,242] This suggest that flexible school-enrolment may reduce developmentally inappropriate demands on children and possibilities for misdiagnosis of ADHD in childhood. For clinicians,

the risk of misclassification of ADHD owing to subjective comparisons of immaturity must be carefully weighed against findings that immaturity and ADHD in childhood are partly explained by common etiologic factors.

7.1.2 ADHD genetic risk is associated with a liability towards general childhood psychopathology

Findings from Study 2 revealed that ADHD PRS are significantly and positively associated with childhood neurodevelopmental, externalizing, and to a lesser extent, internalizing traits. Importantly, these associations could largely be accounted for by a general childhood psychopathology factor. In addition, about 2/3 of the association between ADHD PRS and hyperactivity/impulsivity could attributed to general variance shared across childhood psychopathology traits, and about 1/3 to variance specific to hyperactivity/impulsivity. These results suggest that common genetic risk variants associated with ADHD, and captured by PRS, influence a more general liability towards broad dimensions of childhood psychopathology, in addition to specific associations with hyperactivity/impulsivity.

These findings add to a growing body of research supporting the hypothesis of a genetically influenced general psychopathology factor.[10,141-144,243] Exciting new work has reported significant SNP-h^2 for a general psychopathology factor (16%) and associations with reduced frontotemporal connectivity, suggesting that dysconnectivity may be a transdiagnostic brain-based phenotype associated with a genetic liability towards broad childhood psychopathology.[244] Together, these findings emphasize the utility of adopting a more dimensional, multivariate framework, and the need to account for the inter-related nature of psychiatric conditions when studying the genetic architecture of childhood psychopathology.[10] Our results add to accumulating quantitative and molecular genetic evidence, showing that genetic influences on psychiatric disorder and traits largely transcends current diagnostic boundaries, and categorical distinctions between clinical diagnosis and normal variation. Whilst taking a dimensional approach to both diagnostics and treatment in psychiatry may be premature, it is possible that future revisions of diagnostic systems like the DSM will rely on broader dimensions of psychopathology defined by shared etiology.[245]

Due to the low predictive power of PRS, identifying shared genetic etiology across psychiatric conditions does not yet have any direct clinical implications. Nevertheless, as the power and precision of PRS improves, our findings suggest that PRS may become meaningful for identifying individuals at risk for psychopathology more broadly, and potentially also for more disorder specific screening.[246]

7.1.1 Comorbidity between ADHD and epilepsy show moderate genetic influence and considerable non-shared environmental influence

In Study 3, clinically ascertained epilepsy was associated with a 3.5-fold increased risk of ADHD (OR=3.5 [95%CI 3.33-3.62]). The risk increase also extended to relatives of individuals with epilepsy, and the strength of association across relatives increased along with increased genetic relatedness. This suggest that familial co-aggregation between the ADHD and epilepsy

is at least in part due to shared genetic risk factors. Evidence from the quantitative genetic analyses in full and half-siblings suggested that about 40% (95%CI=9-70) of the phenotypic correlation between the liabilities of ADHD and epilepsy could be attributed to genetic factors. Nonetheless, the strength of familial aggregation and the estimated genetic correlation between ADHD and epilepsy (r_g=0.21 [95%CI=0.02-0.40]) was considerably weaker than that previously reported between ADHD, ASD and ID.[127,128] As these studies were conducted in Swedish register-based cohorts, using similar research designs, it is unlikely that this reflects methodological differences. Instead, these findings suggest that epilepsy is less genetically related to ADHD than traditionally defined DSM-based NDDs, supporting the demarcation between neurology and psychopathology. Evidence from a recent study relying on GWAS data from over 800,000 individuals support such a conclusion, with limited genetic associations observed across neurological and psychiatric disorders, including ADHD and epilepsy.[135]

However, an issue for most genetic studies on epilepsy, including the work in this thesis, is the necessary trade-off between sufficient sample sizes for statistical inference versus selection of a more homogenous phenotype. Considering the marked heterogeneity of epilepsy, current research can therefore not rule out a strong genetic link between certain types of epilepsy and psychiatric disorders.

7.1.1.1 If it is not in the genes, then where?

Nearly 50% of the phenotypic correlation between ADHD and epilepsy could be attributed to factors that are not shared by siblings. These findings may indicate direct effects of one disorder on the other (i.e. epilepsy causing ADHD, or vice versa) or the importance of non-genetic factors that increase the risk for both disorders. Interestingly, we also found slightly stronger associations between relative pairs delineated on the maternal side, suggesting that pregnancy related factors may be of importance for the cross-disorder association.[247,248] Such risk factors could contribute to shared familial effects if consistent across pregnancies, or manifest as non-shared risk if pregnancy specific. Antecedent central nervous system injury, including head trauma and neurological insults at birth, may provide a link between the ADHD and epilipsy.[165,249-251] Personal and maternal history of autoimmune disease have also been linked to both disorders respectively,[248,252] and a recent molecular study reported significant genetic correlations between ADHD and certain autoimmune disorders.[253] Finally, de novo mutations and CNVs likely contributes to multi-morbidity across epilepsy and neurodevelopmental disorder, at least in some cases.[148]

Further research is needed to improve understanding of non-genetic risk factors and their role in comorbidity across epilepsy, ADHD and other NDDs. For clinicians, evidence of familial co-aggregation suggests that ADHD should not merely be regarded as an epiphenomenon of epilepsy. Clinical vigilance for other plausible shared risk factors, such as head trauma or infections, may be warranted.

7.1.2 Pharmacological ADHD treatment is not associated with an increased risk of seizures

Findings from Study 4 showed no evidence for an increased risk of acute seizures associated with ADHD medication use among individuals with a history of seizures. Rather, when comparing the rate of seizures across ADHD-medicated and non-medicated periods within the same individual, estimates showed a statistically significant decreased rate of seizures associated with ADHD medication periods. Similar associations were found across sex and among individuals with additional NDDs. These finding provide converging evidence with several previous studies, using different research designs and measures[169,176,179,254,255], showing limited support for the hypothesis that ADHD medication in prescribed doses is associated with an increased risk of seizures. Unlike most previous studies,[179] we relied on a within-individual design to adjust for important time-constant confounders that varies between individuals (e.g. baseline disorder severity, shared genetic liability) and may influence the association between ADHD medication use and seizures.

Within-individual analyses of seizure rates in the 24 weeks pre- and post ADHD medication initiation indicated an overall (non-significant) lower rate of seizures around the time of ADHD medication initiation. Although interpretations should be cautious as all CIs included 1, this may suggest that starting ADHD medication treatment is more likely in stable seizure periods. If so, this could in part explain the reduced rates of seizures observed during ADHD medication periods. Alternatively, ADHD medications may improve adherence to AED medications, or reduce exposure to factors that can trigger seizures, such as stress and alcohol use. It should be noted that we were unable to study seizures which did not require specialist care. As patients with epilepsy are less likely to seek medical treatment for minor or typical seizures, we can therefore not exclude that ADHD medication may still exacerbate seizures which do not require medical attention.

In conclusion, findings from this study provide no evidence for an overall increased rate of seizure events severe enough to warrant medical attention, associated with ADHD medication treatment in individuals with a seizure history, without or without NDD multi-morbidity. This suggest that seizure history should not automatically preclude patients from receiving ADHD medication treatment.

7.2 METHODOLGICAL CONSIDERATIONS

7.2.1 Measurement error and misclassification

7.2.1.1 Parent- and self-rated measures

Measurements error is a contentious issue in psychopathology assessment for several reasons. First, the validity of measurement scales varies. For example, the RI measure used in this thesis relied on merely two questions, and has only been evaluated in two studies.[187,188] Similarly, the A-TAC internalizing scales have not been validated. Although this issues was partly addressed using a split a sample approach, showing similar results when using validated internalizing

scales (i.e. the SCARED and SMFQ), we cannot firmly assert what these measures capture. Secondly, agreement between raters (i.e. parent-, teacher and self-ratings) in psychopathology assessment is far from unity. Disagreement between raters may reflect lower measurement reliability of type of one rater. Previous research suggests that parent-report is preferential over self-report for ADHD[256] and ASD[257] symptoms, whereas the opposite has been shown for anxiety assessments in childhood and adolescence.[258] Differences between rater may also represent true rater specific variance, highlighting the fact that each rater may experience and report unique, yet valid, aspects of behavior.[259,260] Finally, rater effects can also indicate rater bias, referring to systematic measurement error that is introduced when a rater consistently over- or underestimates occurrences of behavior.[261] Regardless of the source, measurement error can lead to biased estimates of variance and covariance across measured variables. In Study 1 and 2, this was in part addressed using SEM to model the latent factors of interest separately from rater specific (Study 1) and item specific (Study 2) residuals variance.

7.2.1.2 Register based ADHD and epilepsy diagnosis

In Study 3 and 4, ADHD and epilepsy status was ascertained via register data, which may led to misclassification of disorder status for several reasons. First, ADHD cases were identified from ICD diagnosis given by psychiatric specialists and ADHD medication prescriptions. ICD criteria tends captures more severe, combined type ADHD, and until 2016, pharmacotherapy was reserved for patients with moderate to severe ADHD. As such, identified ADHD cases likely represent more severe cases meaning false negatives cannot be avoided, whereas bias due to false positives is less of a concern. Second, the NPR only includes outpatient care from 2001, possibly leading to misclassification due incomplete coverage. Sensitivity analyses using a younger a cohort, with more complete coverage, were run in Study 3 and 4 and suggested that results from the main analyses were not substantially biased by differences in the coverage of the NPR.

7.2.1.3 Treatment status by medication

In Study 4, the definition of ADHD treatment period was based on a sequence of dispensed prescriptions that might inaccurately reflect the actual consumption of medication, either due to non-adherence, or misspecification of the treatment periods. Although this issue was partly addressed via sensitivity analysis using different lengths of time between sequences of dispensed prescriptions, we were unable to assess the possibility that patients may discontinue treatment immediately after a seizure. This type of exposure time misclassification would lead to an underestimation of risk, if the seizure event occurred within 6 months after first prescription and no further prescription was filled, as the seizure would then be classified as occurring during a non-medicated period.

7.2.1.4 Seizure events

In Study 4, seizure events (the outcome) were defined as an unplanned in- or outpatient visit to hospital or specialist care for a seizure in the NPR. This relatively broad definition may have resulted in the inclusion of visits for ongoing medical management. To partly address this,

sensitivity analyses were conducted using a stricter outcome definition. Results from sensitivity analyses did not differ markedly from the main results.

7.2.2 Assumptions in quantitative genetic studies

The quantitative genetic models used in this thesis rests on several assumptions, some of which are outlined in Table 5.2, and some of which are considered below.

No assortative mating: Twin and extended family designs assumes no strong effects of assortative mating.[214] The extent to which that assumption holds will vary by trait,[262] and recent findings have reported evidence of non-random mating within and across psychiatric diagnoses, particularly within ADHD and across ADHD and ASD.[263] Non-random mating will over time lead an underestimation of heritability; given the high heritability found for ADHD it seem unlikely that such effects have greatly influenced findings in this thesis.

Equal environment assumption: The quantitative genetic designs in thesis relied on assumption regarding environmental sharing between relatives. The validity of assuming that MZ and DZ twins share their environment to a very similar extent has been evaluated and confirmed in numerous studies.[214] In Study 3, full- and maternal half siblings are assumed to share their environment to an equal extent, whilst paternal half siblings are assumed to share no environmental effects. Whilst this is clearly a simplification, one Swedish register-based sibling study found no significant effect of varying these assumptions, as shared environmental factors had a minimal influence on the psychiatric disorders considered in the study, including ADHD.[142] Considering that there is no strong evidence for the contribution of shared family environment to the etiology of ADHD,[50,87] this suggest that these assumption may not have greatly affected findings in Study 3.

No gene-gene or gene-environment interaction: Quantitative genetic models assume no interaction between A, D, C, and E, and these assumptions were not further evaluated in this thesis. Development of efficient methods for assessing gene-environment interplay will be important for future research to gain a more complete insight into the etiology of childhood psychopathology and neurology.

7.2.3 Generalizability

The studies included in this thesis rely on data from nationwide Swedish cohorts with prospectively collected information over the past few decades. As such, generalizability to countries with similar demographics and access to healthcare is likely to be high. Certain findings may also apply to other countries and populations. For example, Study 4 replicates findings from a recent large-scale US study,[179] despite substantially different health care systems and prescription practices for ADHD medication across Sweden and the US. Nevertheless, there are other limitations to the generalizability of findings in this thesis.

First, non-responders in TCHAD and CATSS were more likely to have higher levels of psychiatric problems, including ADHD. It is therefore possible that the variation of ADHD and

other psychiatric traits considered in Study 1 and 2 are truncated at the extreme, meaning results may not be generalize to more severe, clinical cases. Nevertheless, this is only likely to have attenuated estimated associations towards the null. Second, we were only able to study seizures that led to contact with specialist medical care in Study 4, meaning that findings may not generalize to less severe seizures. Third, findings may not generalize to more ethnically diverse populations. Families living in ethnically diverse areas were underrepresented in TCHAD (and likely also in CATSS). Further, individuals with non-European genetic ancestry were excluded from analyses in Study 2. Although methods development are ongoing to accommodate PRS analyses of ethnically diverse populations, findings can for now not be automatically generalized to non-European populations. Finally, we only included individuals born in Sweden to enable linking of family pedigrees in Study 3, meaning results may not generalize to residents born outside of Sweden.

7.2.4 Ethical considerations

All studies in this thesis were approved by the Regional Ethics Review Board in Stockholm, and fall under regulations of the Swedish Ethical Review Act (2003:460), which covers research including living and deceased persons, biological material and sensitive information. In medical research, researchers must weigh the benefits of the research against the welfare of the study participants. Observational studies, like those included this thesis, are generally less ethically challenging than experimental studies, as no intervention occurs during data collection. In study 1 and 2, all participants gave informed consent. Nonetheless, collection of sensitive data regarding children's health may still cause negative emotions. Study 3 and 4 rely on nationwide register-based data. As it stands today, no informed consent is needed in register-based research and although all register data is anonymized by Statistics Sweden, this may be considered a breach of privacy. However, it may also be argued that the use of national registers for medical research is of benefit to the Swedish people as it can lead to public health gains and provide guidelines for healthcare.[204] Beyond issues concerning data safety and consent, clear communication of research findings to the general public and affected patient groups is an important ethical issue. Findings showing familial risk and genetic liability to childhood disorder must be communicated in such a way that blame is not put on the affected families, and that it is clear that genetic influences are not deterministic.

8 CONCLUSION

This thesis set out to address two broad questions in relation to ADHD: 1) to investigate the role of shared genetic factors for maturation and childhood psychiatric comorbidity in ADHD, and 2) to improve understanding of the causes of comorbid ADHD and epilepsy, and treatment safety in this patient group. Findings from this thesis expand prior research in several ways.

First, we show that ADHD is related to parental perceptions of relative immaturity, primarily due to shared genetic factors. This association is modest, and limited to childhood and adolescence, highlighting that immaturity is merely one aspect contributing to the etiology of ADHD across development. Second, common genetic risk variants associated with ADHD, and captured by PRS, were found to also influence a wide range of related childhood psychiatric traits. Using a relatively novel approach to combine PRS analyses with factor analyses, we show that these cross-trait genetic associations may be attributed to a general liability towards broad childhood psychopathology. Finally, comorbidity between ADHD and epilepsy was found to be only moderately influenced by shared genetic risk factors, and more strongly influenced by non-familial risk factors. ADHD medication does however not appear to be a risk factor for acute epileptic seizures in individuals with a seizure history, suggesting that ADHD medications may be a viable treatment option even in patients with seizures.

Taken together, results from this thesis highlight important aspects of development and comorbidity in ADHD, and lends support to the hypothesis that ADHD may be considered part of broader continuum of psychopathology that is underpinned by partly shared genetic liability. Based on evidence thus far, this shared genetic liability appears less strongly related to epilepsy.

8.1 FUTURE DIRECTIONS

8.1.1 Are all psychiatric disorders the same thing?

Increasing evidence for a shared genetic liability towards virtually all common psychopathology has widespread implications for future research. In general, it suggests that the efficiency of future etiological studies may be considerably improved by studying more dimensional, multivariate phenotypes. With rapid developments in multi-trait GWAS methods,[264] future directions is psychiatric genomics will likely include efforts to identify genetic variants with pleiotropic effects across disorder, and possibly GWAS focused on broad dimensional phenotypes such as the general factor of psychopathology.[10,245] Based on recent findings linking white matter development and frontotemporal connectivity to broad childhood psychopathology dimensions,[103,244] it seem likely that most studies aiming to identify biological markers of psychiatry will benefit from taking a more trans-diagnostic approach.

Considering the widespread genetic sharing in psychiatry, can we even expect to find disorder specific markers? Although debated,[265] evidence from this thesis suggest so. Results from Study 2 indicted that about 1/3 of the ADHD PRS association was specific to hyperactivity/impulsivity and not shared with general childhood psychopathology. We are aware of at least one other study reporting genetic specificity in ADHD by showing that ADHR

PRS, but not PRS for other psychiatric conditions, are associated with developmental trajectories of ADHD.[65] Similarly, results from Study 3 showed only a moderate genetic overlap between ADHD and epilepsy. Considered together with previous studies reporting limited genetic associations across neurology and psychiatry,[135] these findings should stimulate research on other non-genetic factors that underpin comorbidity.

Together, findings from this thesis suggest that by studying what is shared across disorders etiologically, we may also gain insight into factors that are disorder specific. Future studies aiming to parse disorder-specific genetic factors from genetic factors with more general effects across psychopathology will be very important. Although methods development will be needed to do so at the level of specific variants, the issue may be partly addressed at the phenotypic level. Study 2 in this thesis provides one such example, together with several recent genetic and neuroimaging studies.[82,103,244]

8.1.2 What causes disorder specificity?

If genes are largely responsible for influencing a general liability to psychiatry, non-genetic factors along the pathway from genotype to phenotype must influence disorder specific expression. Yet, most non-genetic and environmental risk factors identified so far for ADHD, such as birth complications and childhood SES, do not seem to be disorder specific. To advance understanding of causal non-genetic factors in psychiatry, longitudinal epidemiological samples with both dense and deep phenotyping will be needed. Further, such data will need to be combined with genomic information, or analyzed using genetically informative designs, to understand the interplay between genetic and environmental factors across development.[245] Large-scale efforts to study pre- and perinatal, non-genetic and environmental factors in consortia settings are making headway,[266,267] and many of them include biological data. Yet, data harmonization for diverse environmental measures remains a challenge. As in genetics, its seem that studying single disorder exposure-outcome associations may be hampering identification of potential risk factors, and that research on environmental and non-genetic risk factors would also benefit from taking a more dimensional and multi-disorder approach. By doing so, causes of disorder specificity may also be identified.

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