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THE COMORBIDITY BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND OTHER NEURODEVELOPMENTAL DISORDERS: AETIOLOGY, TREATMENT AND OUTCOMES

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The comorbidity between attention-deficit/hyperactivity disorder and other neurodevelopmental disorders: aetiology, treatment and outcomes

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To mum and dad

ABSTRACT

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder (ND) defined by the presence of impairing levels of inattentiveness, hyperactivity, and impulsivity. These symptoms are often accompanied by impairment in several functional domains, and by the presence of symptoms or diagnoses of other disorders, especially other NDs, including Autism Spectrum Disorder (ASD). In addition, risky behaviours and health issues are more common among individuals with ADHD, as compared to their peers who do not display ADHD symptoms. The overall aim of this thesis is to investigate the comorbidity between ADHD, ASD and other NDs, in order to clarify shared aetiology, treatment effectiveness and adverse health outcomes.

Study 1 examined the association between clinically diagnosed ASD and ADHD across different types of relatives and explored potential differences between low- and high-functioning ASD (that is, with or without intellectual disability) in the link with ADHD. Data for the study came from a linkage of national Swedish registers in order to identify different types of relatives, from twins to cousins, and clinical diagnoses of ASD and ADHD. Logistic regression was used to estimate the association between ASD and ADHD within the same person (within-individual association) and within relative pairs (within-family association). Results demonstrated that individuals diagnosed with ASD and their relatives had an increased risk of ADHD. The association in twins and siblings was higher than the association in cousins. The magnitude of the association was larger in high-functioning ASD.

Study 2 focused on the phenotypic and aetiological overlap between traits related to ADHD and ASD in young adult twins from the general population. Data for the study came from a web-based survey within the Swedish Twin Registry. Four different trait dimensions were considered: inattention (IA), hyperactivity/impulsivity (HI), repetitive and restricted behaviours (RRB), social interaction and communication difficulties (SIC). Structural equation modelling was used to decompose the covariance across these trait dimensions into genetic and non-genetic influences. Results showed that at the phenotypic level, the correlation between IA and RRB was similar to the one between IA and SIC, while the correlation between HI and RRB was stronger than the one between HI and SIC. Genetic and non-genetic contributions accounted for a similar amount of the covariation across all trait dimensions under study. The largest genetic correlation between traits related to ADHD and traits related to ASD was between HI and RRB.

Taken together, results from Study 1 and 2 suggest that comorbidity between ADHD and ASD may reflect shared aetiological factors, which are in part of genetic origin and which may be specific to certain symptom domains.

Study 3 tested the association between use of ADHD medication and risk of unintentional injuries in children and adolescents with ADHD, including those with co-occurring NDs. Data for the study came from a linkage of national Swedish registers. All residents in Sweden with at least one diagnosis of ADHD and one diagnosis of unintentional injury were included and followed during the study period. Follow-up time was divided into consecutive periods, which may be on-treatment or off-treatment, and the rate of injuries during periods on-treatment was compared to the rate of injuries during periods off-treatment within the same individual, using stratified Cox regression. Results indicated that ADHD medication use was associated with a lower rate of all unintentional injuries, among children and adolescents, among males and females, and among individuals with NDs, as well as among the subgroup with ASD.

Study 4 investigated the association between different NDs and the risk of violent victimization in adolescents and young adults, considering the role of familial and mediating factors. Similarly to Study 1 and 3, a linkage of national Swedish registers was used to identify diagnoses of different NDs and inpatient or outpatient visits or deaths due to assault in the study population. The association between the NDs and violent victimization was explored using Cox regression. Results revealed that being diagnosed with any ND was associated with an increased risk of later violent victimization in males and females. After adjustment for familial factors and mediators, all the associations were attenuated and only ADHD was associated with an increased risk of violent victimization among males and females.

Taken together, results from Study 3 and 4 suggest that comorbidity between ADHD and other NDs does not seem to affect treatment effectiveness with regard to ADHD medication and injuries. On the other hand, risk of violent victimization, which seemed to be related to NDs as a group, may be specifically linked to ADHD.

In conclusion, the work presented in this thesis supports the notion that NDs are a group of disorders characterised by both general and specific aspects in terms of aetiology, treatment effectiveness and negative outcomes.

LIST OF SCIENTIFIC PAPERS

I. Ghirardi L, Brikell I, Kuja-Halkola R, Freitag CM, Franke B, Asherson P, Lichtenstein P, Larsson H.The familial co-aggregation of ASD and ADHD: a register-based cohort study. *Molecular Psychiatry.* 2018 Feb 23(2):257-262.

II. Ghirardi L, Pettersson E, Taylor MJ, Freitag CM, Franke B, Asherson P, Larsson H, Kuja-Halkola R. Genetic and environmental contribution to the overlap between ADHD and ASD trait dimensions in young adults: a twin study. *Psychological Medicine.* 2019 Jul;49(10):1713-1721.

III. Ghirardi L, Chen Q, Chang Z, Kuja-Halkola R, Skoglund C, Quinn PD, D'Onofrio BM, Larsson H. Use of medication for attention-deficit/hyperactivity disorder and risk of unintentional injuries in children and adolescents with co-occurring neurodevelopmental disorders. (*Accepted for publication)*

IV. Ghirardi L, Kuja-Halkola R, Pettersson E, Sariaslan A, Arseneault L, Fazel S, D'Onofrio BM, Lichtenstein P, Larsson H. Neurodevelopmental disorders and risk of violent victimization: a nation-wide sibling-comparison study in Sweden. (*Manuscript)*

CONTENTS

LIST OF ABBREVIATIONS

A	Additive genetic influences
ADHD	Attention-deficit/hyperactivity disorder
ASD	Autism spectrum disorder
ATC	Anatomical therapeutic chemical
C	Shared environmental influences
CD	Conduct disorder
CDR	Cause of death register
CI	Confidence interval
D	Dominant genetic influences
DAG	Directed acyclic graph
DZ	Dizygotic (twins)
DSM	Diagnostic and Statistical Manual of Mental Disorders
E	Unique environmental influences
GWAS	Genome-wide association study
h^2	Heritability
HI	Hyperactivity/impulsivity
HKD	Hyperkinetic disorder
HR	Hazard ratio
IA	Inattention
ICD	International Classification of Diseases and Related Health Problems
ID	Intellectual disability
IQ	Intelligence quotient
MBR	Medical birth register
MGR	Multi-generation register
MZ	Monozygotic (twins)
NCR	National crime register
ND	Neurodevelopmental disorder
NPR	National patient register
OR	Odds ratio

PDR	Prescribed drug register
PGC	Psychiatric Genomics Consortium
PIN	Personal identification number
PRS	Polygenic risk score
r	Correlation
rg	Genetic correlation
RRB	Repetitive and restricted behaviors
RCT	Randomized controlled trial
SEM	Structural equation modelling
SIC	Social interaction and communication difficulties
SNP	Single nucleotide polymorphism
STR	Swedish twin register
TBI	Traumatic brain injury
TPR	Total population register
WHO	World Health Organization
YATSS	Young Adult Twin Study in Sweden

1 INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder (ND) characterized by age-inappropriate levels of inattentiveness, hyperactivity, and impulsivity.[1,2] Individuals diagnosed with ADHD often present with some features or a diagnosis of other NDs, including autism spectrum disorder (ASD),[3-6] intellectual disability (ID),[7] learning disability,[3,6] and language problems.[3,8] Furthermore, ADHD is associated with several risky behaviours and adverse health outcomes.[9-12]

The heritability of ADHD is estimated to be one of the highest among psychiatric disorders.[13] However current knowledge about aetiology and pathophysiology of the disorder is limited. In addition, it remains unclear the extent to which aetiological factors underlying liability to ADHD are shared with other NDs and whether certain symptoms of ADHD may be more strongly linked to other NDs.

Several treatment options are available for the management of ADHD symptoms, including pharmacological[14,15] and non-pharmacological interventions.[15-17] However, little is known about whether such treatment options remain equally effective for individuals who present with both ADHD and other NDs.

Furthermore, considering the high rates of co-occurrence with other disorders, especially NDs, an important aspect that remains unclear is whether the association between ADHD and risky behaviours and adverse health outcomes is specific to ADHD or is present also among other NDs.

This thesis seeks to extend previous knowledge about the comorbidity between ADHD, ASD and other NDs, focusing on shared aetiology, treatment effectiveness and adverse health outcomes.

2 BACKGROUND

2.1 ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD)

The term "Attention Deficit/Hyperactivity Disorder" dates back to 1980, when it was introduced in the revised third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R).[18] DSM-III-R listed a number of separate symptoms for for inattention, impulsivity, and hyperactivity. With the fourth edition of DSM (DSM-IV), published in 1994, ADHD was described as a disorder characterized by two separate dimensions: the deficit in attention and the component related to hyperactivity/impulsivity. In addition, DSM-IV introduced ADHD subtypes, based on symptoms manifestation: predominantly inattentive, predominantly hyperactive-impulsive, and combined.[19] The fifth edition of DSM (DSM-5), published in 2013 has implemented a change in the terminology used for ADHD subtypes.[1] The term "subtype" has now been replaced by the term "presentation". This implies that ADHD presentation may, for example, change during development.[20] The "combined type" presentation of ADHD described by DSM-5 is similar to, but does not completely overlap with, "hyperkinetic disorder" (HKD), as defined by International Classification of Disorders, Tenth Edition (ICD-10).[2] Although the descriptions of behavioural symptoms in DSM and ICD are essentially the same, a diagnosis of HKD in the ICD-10 requires greater pervasiveness of symptoms in different domains (that is, across inattention, hyperactivity and impulsivity) and across different settings (for example, both at home and at school or at work). Therefore, HKD can be regarded as a more severe subcategory of ADHD (or even of the combined presentation of ADHD). In the new revision of ICD (ICD-11), the name of the disorder has changed to "Attention deficit hyperactivity disorder", which is now listed in the "Neurodevelopmental disorders" category. The description of ADHD in ICD-11 resembles DSM-5 criteria and describes the same presentations as DSM-5.[21]

2.1.1 Diagnostic assessment

According to European guidelines, clinical assessment of ADHD usually includes: an evaluation of clinical symptoms and psychosocial functioning in different domains and settings; a physical examination; an investigation of medical and of developmental history; reports from different informants, such as parents and teachers for children.[22-24]

Although ADHD is defined as a single disorder, there is great variability in the symptom profile of diagnosed individuals, as well as in the degree of impairment in daily functioning. Further, in recent years, evidence has accumulated supporting the view of ADHD as a set of symptoms representing the extreme end of normally distributed traits in the population.[25] Several rating

scales are available for the assessment of ADHD symptoms and they have been used in community and in clinical samples.[26] These inventories assess possibly problematic behaviours, which are usually rated by an informant, such as a parent or a teacher, in the case of children. Examples of widely used scales for ADHD evaluation are Conners' Rating Scales (CRS) [27,28] and ADHD Rating Scale-IV (ADHD-IV).[29,30] However, for individuals who seek help and come in contact with health-care for the first time as adults, self-report is often the main source of information. The Adult Self-Report Scale (ASRS) and the ASRS Screener (a shorter version of the ASRS including only six items) are official instruments of the World Health Organization, which have been developed to evaluate ADHD symptoms in adults.[31,32] Another instrument used to assess symptoms in adults is the Conners' Adult ADHD Rating Scales (CAARS),[33] which includes both a version for self-report and a version for observer-report. These scales are often used in research to collect more detailed information on traits related to ADHD in the general population and investigate whether the variability at the phenotypic level may reflect heterogeneity in the aetiological architecture of the disorder.

2.1.2 Epidemiology

ADHD is among the most common psychiatric disorders in childhood. According to the most recent meta-analysis on the prevalence of mental disorders in childhood and adolescence, the estimated worldwide prevalence of ADHD is 3.4% (95% CI 2.6–4.5).[34] However, pooled prevalence estimates indicate great heterogeneity, due to differences in study methods. The factors that seem to influence prevalence estimates are diagnostic criteria (that is, DSM vs ICD), requirement of functional impairment, and source of information (that is, one vs multiple informants).[35] The prevalence of ADHD is higher in males than in females, with a male-to-female ratio of 4:1 in studies based on clinical samples and 2.4:1 in studies based on population-derived samples.[36]

Increasing attention has been given to how ADHD manifests in adults in the last decade. A meta-analysis of six published studies based on adult samples found a pooled estimate of ADHD prevalence equal to 2.5% (95% CI 2.1–3.1),[37] with a lower estimate in the European sample.[38] In addition, a recent study has shown that, although there may be differences in clinical presentation of ADHD between women and men, rates of persistent ADHD seem to be comparable across sexes.[39] Despite the increased interest in ADHD in adults, the disorder is still under-diagnosed and more research is needed to understand better its manifestations and associated impairment.[40,41]

2.1.3 Developmental course

Symptoms of ADHD usually have their onset during childhood and most individuals are diagnosed after starting school.[42] Among those children who are diagnosed with ADHD during pre-school years, the majority seem to continue to meet criteria for ADHD later in childhood,[42-46] while some of them may remit partially or completely.[42,47] The available longitudinal research indicates that both some level of stability and some level of change characterize the trajectory of ADHD throughout development. In general, symptoms of inattentiveness seem to be more persistent than symptoms of hyperactivity and impulsivity.[48,49]

Although historically conceived as a childhood condition, in the last decade there has been increased recognition that ADHD is a life-long condition that can be reliably diagnosed in adults.[37,38,50-52] A substantial proportion of individuals diagnosed in childhood continue to suffer from impairing levels of symptoms in adulthood and a minority of them meet criteria for a diagnosis.[53-55] More recently, a number of studies have reported that individuals manifesting ADHD symptoms as adults may not have presented these symptoms as children.[54,56] This line of evidence is in contrast with the current conceptualization of ADHD as a childhood-onset disorder, as described by current diagnostic criteria. Whether these findings may be explained by the action of protective factors during childhood that would mitigate the impact of the symptoms or by the existence of an "adult-onset" form of ADHD is still debated.

2.2 COMORBIDITIES OF ADHD

In children and adolescents, ADHD is often associated with other neuropsychiatric disorders.[3,22,57] In addition, there is some evidence indicating that the presence of co-occurring disorders may lead to poorer functioning in several domains.[3,10] Nevertheless, individuals who meet diagnostic criteria for ADHD and other conditions, or even just display some symptoms of other disorders, are often excluded from studies in order to compare groups that are more homogenous. For example, randomized controlled trials (RCTs) aimed at testing efficacy of interventions for ADHD symptoms and large genetic studies aimed at identifying genetic variants associated with the disorder, such as the Psychiatric Genomics Consortium (PGC), have typically excluded individuals with other neuropsychiatric disorders or low intelligent quotient (IQ). Therefore, it is not clear whether findings based on samples defined by such strict exclusion criteria may generalize to the larger group of ADHD patients, who often present with symptoms or a diagnosis of another disorder.

2.2.1 Neurodevelopmental disorders

ADHD often co-occurs with other neurodevelopmental disorders (NDs). According to DSM-5, NDs are a group of disorders that typically have their onset early during development and are characterized by developmental deficits that cause impairment in one or more areas of funtioning.[1] In addition to ADHD, NDs include: ASD, intellectual disability (ID), communication disorders, learning disorders, motor disorders, tic disorders and other/unspecified ND.

2.2.1.1 ASD

The co-occurrence of ADHD and ASD has received increased attention during the last decade.[4,58-64] ASD is a group of neurodevelopmental disorders affecting 1-2% of the general population[65-67] and it is characterized by impairments in social interaction and communication and by the presence of repetitive and stereotyped patterns of behaviours, interests and activities.[1,2] Although ADHD and ASD do not appear to share a lot in terms of core symptoms, these NDs have some important features in common. ASD symptoms, similarly to ADHD symptoms, seem to represent the extreme end of traits that are normally distributed in the population.[68,69] In addition, alike ADHD, ASD is highly heritable[70] and more prevalent in males than in females.[65-67]

Several studies have reported that children and adolescents diagnosed with ADHD may display autistic symptoms.[4,58-61] Likewise, symptoms of ADHD are common among children and adolescents diagnosed with ASD.[62-64] In a community sample from the United Kingdom, a standardized interview was used to evaluate the rates of psychiatric disorders based on DSM-IV symptoms in children with ASD. It was found that 70% of the sample met criteria for at least one other disorder listed by DSM-IV and ADHD was among the most common, with a point estimate for the prevalence slightly below 30%.[64] It is noteworthy to mention that DSM-IV and ICD-10 did not allow diagnosing ADHD in children with ASD. However, this has changed with DSM-5. In fact, in the fifth version of DSM, ASD is no longer an exclusionary diagnosis for ADHD.

2.3 AETIOLOGY OF ADHD

ADHD aetiology is multifactorial, and a complex interplay between several genetic and non-genetic factors is probably implicated. The heritability of ADHD has been repeatedly estimated to be between 70 and 90% in large twin and family studies.[71-74] Heritability refers to the proportion of variation in the liability to ADHD in the population attributable to genetic variation (see section 5.2.2). A substantial proportion of this quantity is accounted for by

common genetic variants, commonly known as single nucleotide polymorphisms (SNPs; see section 2.6.4), each of which has a very small effect.[75,76] In a large study including several population-based samples, SNP-based heritability for ADHD symptom scores was estimated to be between 5 and 34%.[76] In addition, a meta-analysis of genome-wide association studies (GWAS; see section 2.6.4), which included over 20,000 individuals diagnosed with ADHD and over 35,000 controls, has recently identified the first 12 genome-wide significant risk loci associated with ADHD and calculated a SNP-based heritability for ADHD around 22%.[75]

Furthermore, it has been shown that the risk alleles for ADHD discovered in GWAS, which were based on case-control comparison, also contribute to individual differences in the general population in traits that are related to symptoms of hyperactivity, impulsivity, and inattentiveness.[75-77] Therefore, it seems that overlapping genetic factors may contribute to both continuous variations of ADHD symptoms in the general population and dichotomous measures of ADHD, that is, the clinically diagnosed cases vs controls.

Several studies have reported associations between environmental factors and ADHD, including pre- and postnatal factors, environmental toxins, diet and psychosocial adversities.[78-80] However, only a few studies have attempted to examine whether these associations may be consistent with a causal hypothesis or primarily due to unmeasured familial confounders. For example, there is some evidence that the association between paternal age at childbearing,[81] family income,[82] and low-birth weight[83,84] and ADHD may be consistent with a causal interpretation. On the contrary, the association between maternal smoking during pregnancy and offspring ADHD[85,86] seems to be explained by shared familial confounding, that is, factors shared between the mother and the offspring that predispose the mother to smoke and the child to develop ADHD (see sections 2.6.1 and 2.6.2 on causal inference and confounding).[87-89]

2.3.1 Shared aetiology between ADHD and ASD

Based on the observation that individuals diagnosed with ADHD also tend to display symptoms of ASD and vice versa, several twin studies have evaluated the relative importance of genetic and environmental factors for the overlap between traits related to ADHD and ASD.[90-94] Although moderate genetic correlations between traits related to ADHD and ASD have been reported by several studies, the genetic overlap between clinically ascertained cases of ADHD and ASD remains largely unclear.

The familial transmission of the disorders has been investigated in large samples from the general population. One study found that offspring of mothers with clinically diagnosed ADHD

were at increased risk of ASD.[95] Similarly, a more recent study found an increased risk of ADHD in siblings of ASD cases.[96]

A GWAS on ASD published earlier this year has reported for the first time a positive genetic correlation between ADHD and ASD (around 0.36),[97] while previous studies had failed to detect a genetic correlation between the disorders.[98] Other studies have found an overlap between ADHD and ASD in rare chromosomal deletions and duplications.[99,100]

2.4 ADVERSE OUTCOMES OF ADHD

Individuals diagnosed with ADHD suffer from impairments in several aspects of their functioning. During childhood and adolescence, they are more likely to experience problems in social and school functioning[101,102] and to be bullied.[103,104] Furthermore, they are less likely to complete high school and continue toward post-secondary education.[9,105,106] As adults, they are more likely to struggle with work and social environment.[9,37,50,52,106,107] Moreover, ADHD is associated with a higher risk of substance abuse,[108-110] criminality,[12,111,112] victimization,[113-115] different types of injuries,[116-120] and suicide.[10,121,122]

Despite the high rate of comorbidity between ADHD and other NDs and the link between ADHD and several negative outcomes are well documented, it remains unclear if and how comorbidity with NDs may influence the risk of these negative outcomes, which may be specifically related to ADHD or, more generally, to the broader diagnostic group of NDs.

2.5 TREATMENT OF ADHD

According to the European clinical guidelines, the management of ADHD symptoms involves several types of interventions, including "psychological interventions, educational change, medication and diet", which should be optimally combined into a multimodal approach.[22] These guidelines define a treatment hierarchy, which recommends the use of medication when "psychological treatments are insufficient alone" or in the most severely disabled cases.[22]

2.5.1 Non-pharmacological treatment of ADHD

When diagnosed with ADHD, patients and their families should be informed about how ADHD symptoms may impact their life and how to identify and further develop strengths in the patients and in their families. Several simple changes in the environment or routines may help improving ADHD symptoms. Other non-pharmacological approaches for the management of ADHD symptoms include group- or individual-based behavioural interventions at the family level, such as parent-training programmes. Schools may also be involved (for school-aged children). For pre-school children, interventions are mainly directed to parents or carers.

Cognitive-behavioural therapy is usually offered to older children who have benefitted from medication, but may have residual symptoms that cause some level of impairment. Among adults, psychosocial interventions are recommended in case of reduced adherence to medication, due to ineffectiveness or poor toleration, or in the case of informed decision to decline medications.[22,23]

2.5.2 Pharmacological treatment of ADHD

Stimulants are the main type of medication approved and used for the management of ADHD symptoms. European guidelines recommend methylphenidate as the first drug of choice.[22] Other stimulant medications commonly used in European countries are dexamfetamine and pemoline.[22] Non-stimulant medications (for example atomoxetine) have also been used to treat ADHD, although their efficacy seems to be inferior to stimulants.[123]

Findings from RCTs indicate that these medications have beneficial short-term effects on the core symptoms of ADHD and may lead to improvements in several functional domains.[14,123,124] Likewise, observational studies have found that ADHD medication use is associated with reduced risk of adverse outcomes.[125-133] A recent meta-analysis of observational studies has reported an increased risk of different types of injuries among individuals with ADHD and a lower risk of injuries in association with use of ADHD medication.[134] Unintentional injuries, such as traffic accidents, falls and poisoning, represent a leading cause of disability in Europe.[135,136] Therefore, it is clinically important to understand whether pharmacological treatment of ADHD symptoms, may also help to reduce the occurrence of adverse health outcomes associated with ADHD.

2.5.3 Pharmacological treatment of ADHD in the context of other NDs

Although there is consistent evidence indicating general safety and efficacy of pharmacological interventions from RCTs and meta-analyses, less is known about their effect in ADHD patients with other NDs. For example, in the case of co-occurrence of ADHD and ASD, guidelines recommend the use of methylphenidate and cognitive-behavioural therapy in combination,[22] however, very few studies have directly evaluated safety and efficacy of such interventions among individuals with both ADHD and ASD.[137] In addition, despite the increasing evidence from observational studies showing that ADHD medication use is associated with a decreased risk of several adverse outcomes, no previous study has explored whether the association may be different among those with other NDs. For example, Man and colleagues investigated the association between methylphenidate use and risk of trauma in a large population-based cohort and found that methylphenidate use was associated with a lower risk of trauma. In the study, it

was reported that over 12% of the sample had been diagnosed with ASD and a similar proportion had been diagnosed with specific developmental delays. However, the authors did not provide separate estimates for groups with different diagnoses.[130]

2.6 AN EPIDEMIOLOGICAL APPROACH

Classic epidemiologic research deals with the distribution of diseases and other health states in the population, their predictors and their consequences.[138] On a more descriptive level, epidemiological studies can estimate prevalence or incidence of diseases and compare them across groups and populations, or describe time trends. Epidemiology often focuses on identifying causes of diseases or factors that may prevent them, that is, rather than describing patterns of diseases, the aim is to understand the mechanisms underlying diseases. For instance, in psychiatry, epidemiological studies have addressed crucial questions on the role of demographic characteristics and environmental exposures in influencing the risk of a disorder, or if certain disorders tend to cluster in families, or which genetic variants are associated with one or more disorders.[139] Other epidemiological studies focus on the evaluation of treatment or prevention strategies on one or several outcomes, including, for example, risks, benefits and costs.

2.6.1 Causal inference in epidemiology

Ideally, evaluation of the causal effect of an exposure on an outcome would require observing the outcome of each study participant under the different levels of the exposure at the same time. In other words, in the simple case of an exposure that has only two possible levels (that is, a person is either exposed or unexposed), the best test to establish whether there is a causal relationship between an exposure and an outcome would be the comparison between the outcome of a study participant exposed vs the outcome of the same study participant, had this person not been exposed. The latter scenario is often referred to as the counterfactual outcome, as it is not observable. However, if it were possible to observe and measure both outcomes for each subject (that is, the outcome when exposed and the outcome when unexposed), the exposure effect for each individual could be easily calculated by contrasting these quantities.[140]

In RCTs, random allocation of study participants to the different levels of the exposure of interest ensures that exposure does not depend on observed or unobserved characteristics. Random allocation tends to create groups that are, on average, comparable in terms of background characteristics. In other words, randomization ensures sufficient exchangeability between different exposure groups. Therefore, in RCTs the effect of an exposure can be estimated by comparing outcomes between exposed and unexposed.[141]

Causality often has to be inferred from observational data, that is, data obtained without any manipulation of the allocation of the exposure. This is because random assignment of individuals to certain exposures may not always be feasible or ethical, as in the case of exposures that have already been established as risk factors for human health. In observational studies, the lack of randomization may lead to systematic differences between exposed and unexposed individuals. In fact, the probability of being exposed or unexposed to a certain factor may be influenced by several observable or unobservable characteristics, which may also be related to the outcome under study. Consequently, a major challenge in observational studies is to remove the effect of these observable and unobservable differences between exposed and unexposed, in order to estimate the causal effect of the exposure on the outcome. In fact, when a factor influences both the probability of having a certain level of the exposure and the probability of having the outcome of interest, it creates an association between the exposure and the outcome, which is not due to their causal relationship. Such factor is referred to as a confounder. A confounder may be defined as any variable U, influencing both the exposure and the outcome, but not being on the causal path going from the exposure to the outcome.[138] An illustration of confounding is given in the Directed acyclic graph (DAG) depicted in Figure 2.6.1.

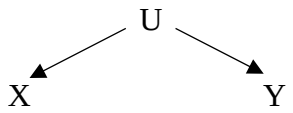

Figure 2.6.1 DAG illustrating confounding. The DAG illustrates that U is a confounder, because it influences the exposure X and the outcome Y and is not on the causal path going from the exposure X to the outcome Y. Because of the causal relationship of U with both X and Y, U induces an association between X and Y, even if there is no direct causal relationship between X and Y.

Traditionally, confounding in observational studies has been addressed by controlling for those variables that are known to influence both the exposure and the outcome and that can be measured. Controlling for a confounder often implies adjusting for it in a statistical model or matching the groups who are compared on the relevant confounders. However, sometimes there might be relevant confounders that researchers are unaware of or that are not easily measurable. An example of such factors are genetic influences on human traits and diseases, which are often unknown or unmeasured.

2.6.2 Causation in genetically informative studies

Genetic influences can often represent confounders for a putative causal relationship of interest. This phenomenon is commonly referred to as genetic confounding. For example, if the genetic factors that influence the risk of ADHD also influence the risk of being victimized,[142] such

genetic overlap will induce a spurious association between ADHD and risk of victimization. An illustration of this phenomenon is given in the DAG depicted in Figure 2.6.2.

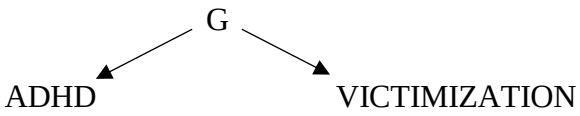

Figure 2.6.2 DAG illustrating genetic confounding. The DAG illustrates that G, genetic influences, is a confounder, because it influences the exposure ADHD and the outcome VICTIMIZATION and is not on the causal path going from ADHD to VICTIMIZATION. Because of the causal relationship of G with both ADHD and VICTIMIZATION, G induces an association between ADHD and VCTIMIZATION, although there is no direct causal relationship between ADHD and VICTIMIZATION.

One way to assess and adjust for genetic confounding, when data on measured genetic markers are not available, is to use of information on individuals who are genetically related. For example, sibling-comparison design is a type of genetically informative design in which unmeasured potential confounders that are shared by memebrs of a cluster of siblings, including genetic and non gentic factors, are adjusted for. Of note, sibling-comparison design can adjust for only part of the potential genetic confounding, as siblings are not genetically identical, but it can adjust for other non-genetic factors that are shared by siblings and that may be relevant confounders. A special case of genetically informative design that attempts to control for unmeasured potential confounders in order to ask a causal question, is the within-individual comparison. In this type of study the aim is to adjust for all the background characteristics of an individual, including genetic and non-genetic factors that are stable within the person. These approaches will be described in section 5.1.3.

2.6.3 Quantitative genetic studies

Information on individuals who are genetically related may also be used to examine the relative importance of genetic and environmental influences on human traits and diseases or on the potential overlap between traits and diseases. For example, familial co-aggregation studies and twin studies take advantage of the different degree of sharing of genetic and environmental factors between different types of biological relatives in order to better understand the role of such factors in causing a disorder. Familial co-aggregation studies and twin studies will be described in sections 5.1.1 and 5.1.2.

2.6.4 The role of genomics in epidemiology

In the last fifteen years, genomic research has provided new tools to explore the role of genetic factors in the aetiology of human traits and diseases. Since the first GWAS in 2005,[143] thousands of loci have been reported in association with traits and disorders.[144] In addition to that, summary statistics from GWAS have been used to calculate the so-called genome-wide

polygenic scores. These measures correspond to the aggregated effect of all the SNPs associated with the phenotype under study.[145] Therefore, these scores represent a way to measure genetic liability to a trait or a disorder, without having information on related individuals. Genome-wide polygenic scores may be used to explore associations across phenotypes, similarly to family and twin studies. In addition, if the polygenic scores were good predictors of a phenotype, they could be used as proxies for phenotypes that have not been measured, but that may be an important confounder.

In general, genetic information is becoming an integrated part of observational studies.[146] It may come from measured genetic markers or it may be inferred from familial relationships. It may shed light on the relative importance of genetic and non-genetic factors for a phenotype or for the covariation between phenotypes. It may also help to identify causal mechanisms behind observed associations. As each approach makes different assumptions and has inherent limitations and advantages, convergence from studies using different designs is a crucial goal to advance the understanding of diseases' causes and consequences.[147,148]

3 AIMS

3.1 OVERARCHING AIM

The overarching aim of this thesis is to extend previous knowledge about the comorbidity between ADHD, ASD and other neurodevelopmental disorders, focusing on possible shared aetiology, treatment effectiveness and adverse health consequences.

3.2 SPECIFIC AIMS

- To evaluate to what extent ADHD and ASD may be caused by shared and specific aetiological factors (Study 1 & 2).
- To examine the impact of ADHD, other NDs and ADHD medication on health adverse outcomes. (Study 3 & 4).

4 DATA AND MEASURES

Studies 1, 3, and 4 were all based on data derived from a linkage of several Swedish nationwide registers. Study 2 included data from the Young Adult Twin Study in Sweden (YATSS).

4.1 SWEDISH NATIONAL REGISTERS

The personal identity number (PIN)[149] consists of the date of birth and a four-digit number and was introduced in Sweden in 1947 (the fourth digit was added in 1967). Therefore, since then, every person residing in Sweden on a permanent basis (that is, recorded in the Total population register, TPR) is assigned a PIN. The PIN is routinely used by governmental agencies (e.g., tax agency, health care providers, prison services, schools, etc.). Governmental agencies (such as Statistics Sweden) can merge data from different registers using the PIN. The following nationwide registers were the main sources of data for the present thesis.

Total population register (TPR). TPR includes information on demographics (date of birth, sex, country of birth, migration, date of death) on all individuals residing in Sweden who were born after 1932 and were alive in 1968 or later.[150]

Multi-generation register (MGR). MGR provides information on biological (and, when applicable, adoptive) parents of all individuals born after 1932, alive and living in Sweden after 1961, with the exception of those whose parents died or migrated out of the country before 1947.[151] For individuals born since 1950 information on mothers is complete while the coverage of information on fathers is slightly lower.

National patient register (NPR). NPR contains information on all in-patient care in Sweden from 1987 and on outpatient visits from 2001.[152] Data from primary care are not included in the NPR. When the register was started by the National Board of Health and Welfare in the 1960's, it only contained information about patients treated in psychiatric care and a small proportion of patients in somatic care. The diagnoses in the NPR are classified according to the International Classification of Diseases; ICD-8 (1969-1986), ICD-9 (1987-1996) and ICD-10 (1997-2013).

Medical birth register (MBR). The MBR includes information on a wide range of pre-, peri- and post-natal factors of nearly all births in Sweden since 1973. It also includes information on several measures about the mothers.[153]

Prescribed drug register (PDR). The PDR includes information on all dispensed prescribed drugs in Sweden since June 1st 2005.[154] All medicines are classified according to the

Anatomical Therapeutics Chemical (ATC) classification system. The PDR does not include information on drugs used in hospitals or on the indication for treatment.

Longitudinal integration database for health insurance and labour market studies register (LISA). The LISA register includes data on all individuals aged 16 or older registered in Sweden as of December 31st of each year since 1990. It covers information on marital status, residential relocations, educational attainment, income, unemployment, and social benefits.[155,156]

National crime register (NCR). The NCR contains records of all criminal convictions in Swedish lower courts since 1973, including non-custodial sentences and fines. The legal age of responsibility in Sweden is 15 years, so no data on criminal convictions for individuals younger than this age are available.[157,158]

Cause of death register (CDR). The CDR provides information on all deaths among individuals registered in Sweden from 1952.[159] The CDR does not include information on stillbirths, individuals who died on a temporary visit to Sweden, asylum seekers without residence permit and Swedish citizens who have emigrated and are not registered in Sweden. Underlying causes of death are coded according to ICD classification system.

Swedish twin registry (STR). The STR was established in 1959 and contains information on approximately 200,000 twins born in Sweden after 1886.[160-162] The register is managed by Karolinska Institutet. Currently, twins are invited to be part of the register when they turn nine. In addition to information on zygosity, information from surveys and from collection of biological samples are available for several cohorts of twins.

4.1.1 Main measures in the registers

4.1.1.1 ADHD

There are two main sources of information on ADHD in the registers. First, the presence of a diagnosis in the NPR according to ICD classification system can be used to identify individuals who were ever diagnosed with HKD. To define ADHD, we used the ICD-9 code 314 ("Hyperkinetic syndrome of childhood") and the ICD-10 code F90 ("Hyperkinetic disorders").[163] Second, it is possible to identify all dispensed medications approved in Sweden for the management of ADHD from the PDR.[158] The following medications were approved in Sweden for the management of ADHD during the time period relevant for the studies included this thesis (ATC codes in parentheses): Methylphenidate (N06BA04); Amphetamine (N06BA01); Dexamphetamine (N06BA02); Lisdexamfetamin (N06BA12); Atomoxetine

(N06BA09). Information on ADHD from the NPR was used in all the studies. In Study 1, information on ADHD medication from the PDR was additionally used to define ADHD cases.

4.1.1.2 ASD

In order to identify individuals with ASD, information from the NPR was used. The ICD-9 code 299 ("Pervasive developmental disorders") and the ICD-10 code F84 ("Pervasive developmental disorders") were used to identify individuals with ASD.[66,164] This information was used in all the studies. Furthermore, information from the NPR on diagnoses of ID according to ICD-9 (codes 317-319) and ICD-10 (codes F70-F79) was used in Study 1 to identify individuals with ASD and ID, which was defined as low-functioning ASD, vs ASD without ID, which was defined as high-functioning ASD.

4.1.1.3 Other NDs

Information from the NPR was used to define other NDs in Study 3 and in Study 4. We grouped NDs similarly to the classification proposed by DSM-5. In addition to ADHD and ASD, other NDs were: ID, communication disorders, specific learning disorder, motor disorders, and other/unspecified neurodevelopmental disorders. A complete list of all the ICD-9 and ICD-10 codes used for NDs can be found in Table 4.1.1.3. These diagnoses were used to define NDs in Study 3 and in Study 4.

Disorders	**ICD-9 codes**	**ICD-10 codes**
ADHD	314	F90
ASD	299	F84
ID	317-319	F70-F79
Communication disorders	315.3	F80
Specific learning disorder	315.0, 315.1,315.2	F81, R48
Motor disorders	315.4, 307.2, 307.3	F82, F95, F984
Other neurodevelopmental disorders	315.8, 315.9	F88-F89

Table 4.1.1.3 ICD Codes for NDs. Abbreviations: NDs=neurodevelopmental disorders; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICD-9=The International Classification of Diseases, Ninth Revision; ICD-10=The International Classification of Diseases, Tenth Revision.

4.1.1.4 Treatment status by ADHD medication

In Study 3, we used information from the PDR on all medications approved in Sweden for the management of ADHD during the study period (January 1st 2006 – December 31st 2013). Based on dispensations of these medications, we divided the study period into on-treatment and off-treatment periods. Prescriptions for ADHD medication are usually refilled within 3 months. In the case of low adherence or treatment cessation during weekends or holiday, time between dispensations may be longer. Consequently, on-treatment periods were defined as the time between two consecutive medication dispensations that were no longer than 122 days apart (122-days interval), similarly to previous studies.[112,127,165,166] On-treatment periods started with

the first dispensation date and ended with the last dispensation date. The remaining follow-up time was defined as off-treatment.

4.1.1.5 Unintentional injuries

Information from the NPR was used to identify unintentional injuries. Unintentional injuries were defined as inpatient and outpatient visits reporting an injury as the main diagnosis (ICD-10 codes: S00-T78) and an unintentional cause (ICD-10 codes: V01-X59). This definition was used for the outcome of Study 3. Moreover, because there was a concern that the same injury may be recorded several times, as the same injury may be associated with several visits, we only included unplanned visits longer than 14 days apart to reduce the risk to count the same event multiple times.

4.1.1.6 Violent victimization

Information from the NPR and the CDR was used to identify violent victimization events. Violent victimization events were defined as any inpatient visit, outpatient visit or death reporting assault as cause (ICD-9 codes: E960-E969; ICD-10 codes: X85-Y09). Violent victimization was the outcome in Study 4.

4.2 YATSS

Study 2 was based on the Young Adult Twin Study in Sweden (YATSS). The survey was initiated in 2013. Using information from the STR, approximately 17,000 twins born in Sweden between May 1st 1985 and June 30th 1992 were identified. Individuals who had opted out of the STR, died, migrated, or acquired a secret identity were excluded. Individuals who were invited to participate in the study (N=16,237) were asked to fill out an online questionnaire. A paper version was available upon request. Seven individuals who had requested to be re-included in the STR were included at a later stage. The final target population included 16,244 individuals. Among them, 6,866 (42%) filled out the questionnaire, either the on-line or the paper version. Among them, the response rate for all the ADHD and ASD traits was 74% (N=5,082). Information on zygosity was obtained using a set of physical similarity questions, which has been validated through genotyping.

4.2.1 Measures of ADHD and ASD trait dimensions in YATSS

In Study 2, the focus was on ADHD and ASD trait dimensions, which were self-reported by study participants. ADHD trait dimensions were assessed via the WHO Adult ADHD Self-Report Scale (ASRS).[31,167] This questionnaire consists of 18 items that resemble DSM-IV symptoms. Each item has a five-point answer format (0=‘never’, 1=‘rarely’, 2=‘sometimes’,

3=‘often’ and 4=‘very often’). Answers to each items were summed in order to create two scores reflecting the two symptom-dimensions of ADHD: inattention (IA, nine items), and hyperactivity/impulsivity (HI, nine items). ASD trait dimensions were assessed via a set of 12 items, which are part of the Autism – Tics, AD/HD, and other Comorbidities inventory (A-TAC).[168] The items are based on DSM-IV symptoms. A-TAC has been developed for assessment of a wide range of behaviours, cognitive domains and psychiatric symptoms in children. Therefore, some of the items were adapted for adults. Each item has a three-point answer format (0=‘no’, 0.5=‘yes, to some extent’, and 1=‘yes’). Answers to each item were summed to create two scores reflecting the two symptom-dimensions of ASD, based on DSM-5 classification: social interaction and communication difficulties (SIC, eight items), and repetitive and restricted behaviours (RRB, four items). A complete list of the items used in Study 2 is reported in Table 4.2.1.

Items	Subscale
How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?	IA
How often do you have difficulty getting things in order when you have to do a task that requires organization?	IA
How often do you have problems remembering appointments or obligations?	IA
When you have a task that requires a lot of thought, how often do you avoid or delay getting started?	IA
How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?	HI
How often do you feel overly active and compelled to do things, like you were driven by a motor?	HI
How often do you make careless mistakes when you have to work on a boring or difficult project?	IA
How often do you have difficulty keeping your attention when you are doing boring or repetitive work?	IA
How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?	IA
How often do you misplace or have difficulty finding things at home or at work?	IA
How often are you distracted by activity or noise around you?	IA
How often do you leave your seat in meetings or other situations in which you are expected to remain seated?	HI
How often do you feel restless or fidgety?	HI
How often do you have difficulty unwinding and relaxing when you have time for yourself?	HI
How often do you find yourself talking too much when you are in social situations?	HI
When you are in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish themselves?	HI
How often do you have difficulty waiting your turn in situations when turn taking is required?	HI
How often do you interrupt others when they are busy?	HI
Do you have difficulties expressing emotions and reactions with facial gestures, pronunciation, or body language?	SIC
Have you difficulties to get and keep friends?	SIC
Are you disinterested in sharing joy, interests, and activities with others?	SIC
Can you only be with other people on your terms?	SIC
Was your language development delayed?	SIC
Do you have difficulties participating in discussions with others?	SIC
Do you like to repeat words and expressions or do you use words in a way other people find strange?	SIC
Do you have difficulty imitating other people or to play charades?	SIC
Do you get absorbed by your interests in such a way as being repetitive or too intense?	RRB
Do you get absorbed by routines in such a way as to produce problems for yourself or for others?	RRB
Have you some body movements that come automatically when you are happy or upset?	RRB
Do you get absorbed by details?	RRB

Table 4.2.1 List of items used to assess ADHD and ASD traits. The table reports the English translation of the items used to assess ADHD and ASD trait dimensions in YATSS. Abbreviations: IA=inattention; HI=hyperactivity/impulsivity; RRB=repetitive and restricted behaviours; SIC=social interaction and communication difficulties.

5 METHODS

5.1 STUDY DESIGNS

5.1.1 Familial co-aggregation studies

Familial aggregation studies often represent the first step to understand if familial influences (of genetic and non-genetic origin) have a role in the occurrence of one disorder or in the co-occurrence of two or more disorders.[169,170] Family members share a higher amount of genetic and environmental factors as compared to unrelated individuals. Consequently, whenever a disorder is more common among relatives of individuals who have the disorder as compared to relatives of individuals who do not have the disorder, genetic and environmental factors shared by family members may be assumed to play a role in the aetiology of the disorder. Similarly, whenever a disorder A is more common among relatives of individuals who have the disorder B as compared to relatives of individuals who do not have the disorder B, genetic and environmental factors shared by family members may be assumed to play a role in the aetiology of the co-occurrence of the disorders A and B.

In addition, it is possible to compare the magnitude of the association across different types of relatives in order to assess the importance of genetic and non-genetic factors that influence familial co-aggregation. For example, it is possible to compare the association of two disorders in full siblings, who share on average 50% of their co-segregating alleles, with the association of two disorders in half siblings, who share on average 25% of their co-segregating alleles. A higher association among full siblings compared to half siblings provides evidence for the importance of genetic influences. However, it should be noted that different types of relatives might share other non-genetic influences to a different extent. For example, it may be assumed that maternal half siblings share more pre-natal environmental factors than paternal half siblings, as there will be more similarities between two different pregnancies in the same woman than between two pregnancies in different women.

5.1.2 Twin studies

Twin study design capitalizes on the comparison of the resemblance on a trait between monozygotic (MZ) and dizygotic (DZ) twins.[171] The difference between MZ and DZ twins is that MZ twins are genetically identical, while DZ twins share, on average, half of their co-segregating alleles, just like full siblings. Furthermore, it is assumed that MZ and DZ twins share the same amount of common environmental influences. For this reason, by using information on the degree of resemblance between members of MZ twin pairs on a certain trait vs the degree of resemblance between members of DZ twin pairs on the same trait, it is possible

to understand whether genetic influence may be important for such trait or not. In other words, if a trait is influenced by genetics, the correlation between the members of a twin pair on this trait (usually referred to as intra-class correlation, ICC) is expected to be greater in MZ than in DZ twins. Similarly, it is possible to examine cross-trait correlations to understand the relative importance of genetic and environmental influences for the covariation between two traits. To this purpose, a correlation between trait A for twin 1 and trait B in twin 2 (usually referred to as cross-twin cross-trait correlations, CTCT) is calculated in MZ and DZ twin pairs separately and CTCT correlations are then contrasted. Higher CTCT correlations among MZ twins than among DZ twins indicate that the covariation between the traits under study is influenced by overlapping genetic effects. In Study 2, information on ADHD and ASD trait dimensions reported by MZ and DZ twins was used to decompose the observed variation and covariation of such traits into the genetic and non-genetic influences. Structural equation modelling (SEM) was used to estimate the contribution of these influences.[172] A description this method is given in section 5.2.2.

5.1.3 Within-cluster comparison

A common strategy to adjust for confounding in observational studies is to match on one or several potential confounders. For example, in cohort studies, it is possible to select a number of unexposed individuals with the same level of the covariate(s) that we want to adjust for as the exposed individuals. By doing so, the association between the potential confounder(s) and the exposure is broken. In other words, matching ensures that exposed and unexposed are conditionally exchangeable. Similarly, in case-control studies, controls can be selected so that they are matched to cases on the level of covariate(s) that we want to adjust for.

Matching occurs naturally in a number of instances. For example, members of a MZ twin pair are matched on virtually all their genetic background and pre-natal environment. Thus, by comparing the members of a MZ twin pair where one member experiences a certain exposure and the other does not, the association between the aforementioned potential confounders and the exposure of interest is broken. In other words, comparing differentially exposed members of a cluster allows for matching for all the factors that members of a cluster share, without the need of measuring such factors, and, therefore, it approximates conditional exchangeability within the cluster.

5.1.3.1 Within-sibling comparison

In a within-sibling comparison study, members of clusters of siblings, who are differentially exposed to a risk (or protective) factor, are compared in terms of the outcome(s) of interest. In

this way, sibling-comparison design adjusts for all the sources of confounding that are shared between siblings.[80,173] For example, in full siblings, such comparison will be adjusted for half of their genetic make-up, since full siblings share, on average, 50% of their co-segregating alleles, and for those environmental exposures shared by siblings, such as parental education level or medical history. In Study 4, sibling-comparison design was used to test whether a member of a sibling pair who was diagnosed with NDs had a different risk of violent victimization compared to a member of the same sibling pair who was not diagnosed with NDs. This was done in order to adjust for shared familial factors that may be associated with risk of being diagnosed with NDs and with risk of being victimized.

5.1.3.2 Within-individual comparison

Within-individual comparison is a special case of within-cluster comparison, in which the same individual is compared to him- or her-self under two different levels of the exposure.[174] As a consequence, this design requires at least two measurements of the exposure for an individual to contribute to the analysis. This type of comparison adjusts for all the factors that do not change within the same person during the time of the study, such as the genetic background or previous experiences. In Study 3, within-individual comparison design was used to estimate the association between ADHD medication use and unintentional injuries by comparing the rate of unintentional injuries during periods on-medication with the rate of unintentional injuries during periods off-medication within the same person.

5.2 STATISTICAL METHODS

5.2.1 Logistic regression

Logistic regression is a statistical method commonly used to analyze binary outcomes. This method allows for estimating the change in the log-odds of the outcome for every unit increase in the exposure variable, while controlling for a set of covariates. The measure of association between the exposure and the outcome is given by the odds ratio. Odds are defined as the ratio of the probability of an event divided by the probability of that event not occurring. An odds ratio is the ratio between odds of the event under study in the two different groups that are compared. Logistic regression was used in Study 1 to estimate the association between a diagnosis of ASD and a diagnosis of ADHD within the same person and within families.

5.2.2 Structural equation modelling

Structural equation modelling (SEM) is an approach that incorporates and combines statistical methods that can be expressed as models of covariance matrices. SEM is commonly used to

estimate the relative contribution of unobserved constructs (traditionally referred to as latent variables) in explaining the variance of observable variables or their covariance.[172]

SEM is used in quantitative genetics to estimate the contribution of the latent components: additive genetic influences (A); environmental influences shared by the members of the twin pair (C); dominance genetic effects (D); and other sources of variation that make members of a twin pair less similar (E), including non-shared environmental influences and random error. A univariate model allows to estimate the contribution of A, C, D, E to the total variance of a phenotype. The univariate model can be written as:

$$X_i = \mu + A_i + C_i + D_i + E_i$$

where X_i is the observed trait in the i^{th} individuals in the population and μ is the population mean. Assuming that latent components are independent of each other, the variance in a trait is defined as:

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

It follows that, in order to estimate the relative contribution of each component to the variance of the trait in the population, the ratio between the variance of that component and the total variance of the observed trait is taken. For example, the contribution of additive genetics, usually referred to as narrow-sense heritability (h^2), is given by:

$$h^2 = Var(A)/Var(X)$$

It should be noted that it is not possible to estimate the C and the D components simultaneously, together with A and E components, when only data from twin pairs are available. In other words, the information from MZ and DZ twins is not sufficient to estimate all the parameters in the model. Usually an ADE model (that is, a model including A, D, and E as sources of variance and covariance) and ACE model (that is, a model including A, C, and E as sources of variance and covariance) can only be fitted to the data separately and then compared in order to establish which one fits the data better.

In a multivariate model, it is possible to estimate the contribution of each of these latent components to the total variance of more than one phenotype as well as to the covariance between the phenotypes. A multivariate model was used in Study 2.

5.2.3 Cox regression

Cox regression is a statistical method commonly used to analyze time-to-event data. It allows for comparing the rate of events between different levels of the exposure of interest while

controlling for other covariates included in the model and for the selected underlying time-scale. The rates in each level of the exposure are hazard rates, which can be thought as "instantaneous rates of occurrence". The hazard function is obtained by, first, calculating the ratio between the conditional probability that the event will occur in a certain time interval, given that it has not occurred before, and the width of the time interval, and, second, by taking the limit as the width of the interval goes down to zero. The hazard ratio (HR) is then given by the ratio between the hazard functions under the different levels of the exposure.

5.2.3.1 Stratified Cox regression model

When data are clustered, within individuals as in Study 3 or within families as in Study 4, it is possible to exploit the structure of the data to adjust for factors that are shared across different observations within the cluster.[175] Stratified Cox regression can be used to compare the hazards across different levels of the exposure within the same cluster (also referred to as stratum). In this model, the coefficients of the different levels of the exposure are the same for each stratum, while the baseline hazards (i.e., the hazard for the baseline level of the exposure) are free to differ across strata.

In Study 3, stratified Cox regression was used to compare the hazard between on- and off-medication periods within the same individual. Each individual is considered as a separate stratum and the comparison between exposure categories (on- versus off-medication) is done within each stratum.

In Study 4, stratified Cox regression was used to compare the hazard within each cluster of full siblings between a sibling who is diagnosed with NDs and a sibling who is not diagnosed with NDs. Thus, each cluster of full siblings is entered in the model as a separate stratum.

6 STUDY SUMMARIES AND RESULTS

6.1 SHARED AETIOLOGY BETWEEN ADHD AND ASD

Study 1 and 2 were designed to address the knowledge concerning shared aetiology of ADHD and ASD both as clinical diagnoses and as trait dimensions.

6.1.1 Familial co-aggregation of ASD and ADHD (Study 1)

6.1.1.1 Rationale

Previous family studies using data on clinical diagnoses of ADHD and ASD have found an increased risk of ASD in offspring of mothers with ADHD,[95] and an increased risk of ASD in siblings of individuals with ADHD[176], and vice versa[96]. However, no previous study has examined the association of these disorders in different types of relatives, who share familial factors to a different extent. Therefore, Study 1 aimed at testing whether ASD and ADHD co-aggregate in families and at examining potential differences between low- and high-functioning ASD in the link with ADHD.

Study	Musser et al., 2014	Jokiranta-Olkoniemi et al., 2016	Jokiranta-Olkoniemi et al., 2018
Sample	Kaiser Permanente Northwest Health Plan members (United States)	Finnish general population	Finnish general population
Association	OR= 2.5(95%CI=1.28-4.94)	RR = 3.7 (95%CI=2.9-4.7)	RR = 3.9 (95%CI=3.3-4.6)
Relatives	Mother-offspring	Full siblings	Full siblings

Figure 6.1.1.1. Family studies on ADHD and ASD. The figure summarizes results from recent studies on the association between clinical diagnoses of ADHD and ASD. Abbreviations: OR=odds ration; RR=risk ratio; 95%CI=95% confidence interval. Note: In Musser et al., 2014, the OR refers to the risk of being diagnosed with ASD in offspring of mothers diagnosed with ADHD, as compared with offspring of mothers not diagnosed with ADHD. In Jokiranta-Olkoniemi et al., 2016, the RR refers to the risk of being diagnosed with ADHD in siblings of individuals diagnosed with ASD, as compared with siblings of individuals not diagnosed with ASD. In Jokiranta-Olkoniemi et al., 2018, the RR refers to the risk of being diagnosed with ASD in siblings of individuals diagnosed with ADHD, as compared with siblings of individuals not diagnosed with ADHD.

6.1.1.2 Methods

All individuals born in Sweden between 1987 and 2006 were identified from the MBR. After exclusion of stillbirths, individuals diagnosed with congenital malformations, individuals who died or migrated before their 7th birthday, and individuals who were adopted away or whose biological parents were not identifiable, 1,899,654 individuals were included in the study. Furthermore, using information from the MGR, each individual included in the study was linked to their biological relatives and seven cohorts of different types of relatives were created. The following cohorts were included in the study: MZ twins, DZ twins, full siblings, maternal half siblings, paternal half siblings, full cousins and half cousins. Information from the NPR was used to identify individuals with a diagnosis of ASD (low- and high-functioning), ADHD,

or both, at any time between age one for ASD and age three for ADHD and December 31st 2013.

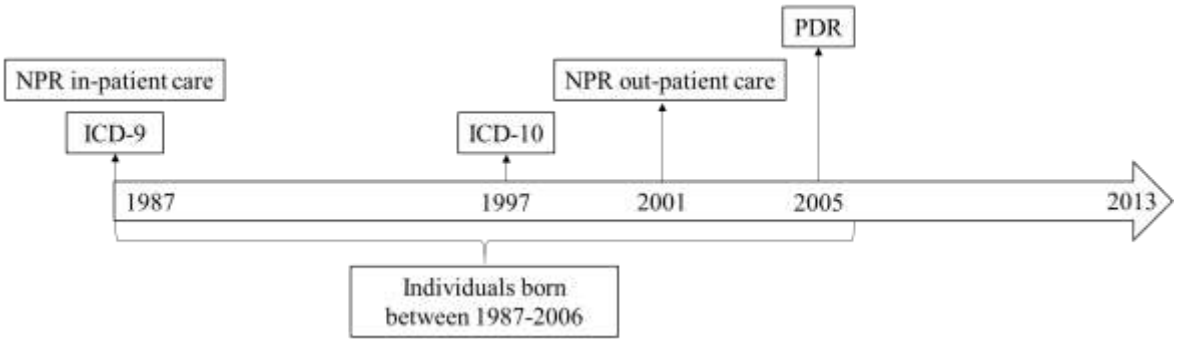

Figure 6.1.1.2. Timeline Study 1. The figure illustrates the timeline for the main data sources and for the sample included in Study 1. Abbreviations: NPR=national patient register; ICD=International Classification of Diseases; PDR=prescribed drug register.

Logistic regression was used to estimate the odds of receiving a diagnosis of ADHD in individuals with a diagnosis of ASD, as compared with individuals who did not have a diagnosis of ASD, among those included in the study (within-individual association). Furthermore, logistic regression was used to estimate the odds of receiving a diagnosis of ADHD in relatives of individuals with a diagnosis of ASD, as compared with relatives of individuals who did not have a diagnosis of ASD, among those included in the study (within-family association). This analysis was performed in each cohort of relatives separately. In all the analyses, we adjusted for sex and year of birth. Separate estimates for high- and low-functioning ASD were obtained for within-individual association and within-family associations in full siblings and full cousins. All the analyses were performed using Stata 14.0 (StataCorp., College Station, TX, USA).

6.1.1.3 Results

Individuals diagnosed with ASD and their relatives had an increased risk of ADHD, as displayed in Figure 6.1.1.3. Within-family associations indicated that MZ twins of individuals diagnosed with ASD had an increased risk of having a diagnosis of ADHD (OR=17.77; 95% CI=9.80-32.22). The association in MZ twins was higher than the associations in DZ twins (OR=4.33; 95% CI=3.21-5.85) and in full siblings (OR=4.59; 95% CI=4.39-4.80), which, in turn, were higher than the associations estimated in half siblings. The association in maternal half siblings (OR=2.25; 95% CI=2.07-2.43) was higher than the one found in paternal half siblings (OR=1.68; 95% CI=1.54-1.84). The risk of having ADHD was increased both in full cousins (OR=1.64; 95% CI=1.58-1.71) and half cousins (OR=1.30; 95% CI=1.23-1.38) of ASD cases.

The magnitude of the association was larger when considering high-functioning ASD both in full siblings (OR=4.93; 95% CI=4.70-5.17) and in full cousins (OR=1.68; 95% CI=1.62-1.75), as compared to low-functioning ASD (full siblings: OR=1.17; 95% CI=1.03-1.32; full cousins (OR=0.93; 95% CI=0.85-1.02).

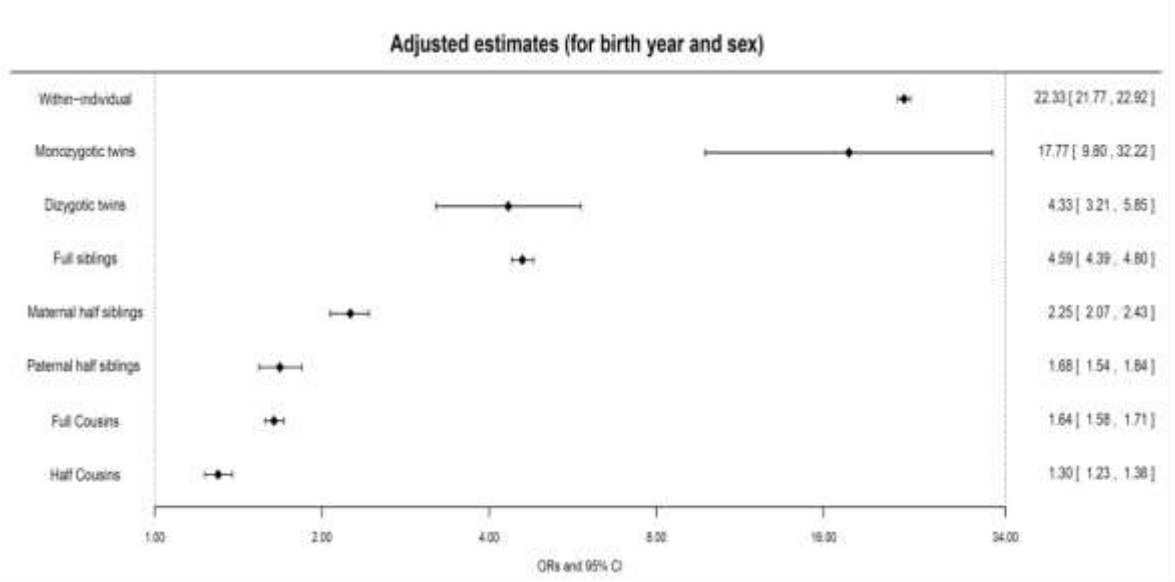

Figure 6.1.1.3. Within-individual and within-family associations between ASD and ADHD. The plot illustrates ORs (diamonds) and 95% CI (bars) expressing the association between ASD and ADHD obtained from the within-individual analysis performed in the whole study sample and from the within-family analyses performed in the different cohorts of relatives. Abbreviations: OR=odds ratios; 95% CI=95% confidence interval.

6.1.2 ADHD and ASD trait dimensions in adults (Study 2)

6.1.2.1 Rationale

Previous twin studies support the presence of a genetic link between traits related to ADHD and traits related to ASD.[90,91,177-179] Furthermore, some traits related to ADHD seem to be more strongly associated with certain traits related to ASD.[94,180,181] However, studies in children[94,180] and in adults[181] have led to partially different conclusions. Considering the paucity of studies on the link between specific ADHD and ASD traits in adults, Study 2 aimed at estimating phenotypic and aetiological overlap between ADHD and ASD trait dimensions in young adults.

Study	Pinto et al., 2016	Taylor et al., 2015	Polderman et al., 2014
Sample	Study of Activity and Impulsivity levels	Twins Early Development Study	Swedish Twin Registry
rg(CI)	HI-SIC: 0.44(0.33-0.55) IA-SIC: 0.52(0.39-0.65)	HI-C: 0.50(0.44-0.56) IA-C: 0.48(0.41-0.49)	HI-RRB: 0.64(0.63-0.65) IA-RRB: 0.61(0.56-0.64) IA-SIC: 0.50 (0.48-0.53)
Age	7-10 years old	12 years old	20-46 years old

Figure 6.1.2.1. Twin studies on ADHD and ASD trait dimensions. The figure reports genetic correlations between ADHD and ASD trait dimensions from previous twin studies from childhood to adulthood.

Abbreviations: rg=genetic correlation; IA=inattention; HI=hyperactivity/impulsivity; RRB=repetitive and restricted behaviours; SIC=social interaction and communication difficulties; C=communication difficulties.

6.1.2.2 Methods

First, a saturated model and several sub-models were fitted to the data to obtain age-adjusted estimates of means, variances, and correlations, and to perform assumption testing using likelihood ratio tests. Then, SEM was used to estimate the phenotypic correlation between IA, HI, RRB, SIC, to decompose the observed correlations into genetic and non-genetic contributions, and to estimate correlations between genetic and non-genetic factors influencing each trait dimension. To examine the relative contribution of A, D, and E to the phenotypic correlations between trait dimensions, a model that allowed the sources of variation and covariation to correlate between trait dimensions (correlated factors model) was fitted to the data. The choice of an ADE model was motivated by the observation that most correlations were more than twice as higher in MZ twins than in DZ twins. Potential sex differences were investigated in a set of sex-limitation models, which tested for quantitative and qualitative sex differences. Quantitative differences refer to differences between males and females in the relative importance of each component in influencing correlations, while qualitative differences refer to differences between males and females in the sets of genes influencing correlations.

In addition, a set of sub-models (AE and E models) were fitted to the data in order to evaluate whether a more parsimonious model would explain the data significantly worse. More specifically, comparing the AE model to the ADE model is a way to test whether disregarding the influence of D causes a significant loss in the indexes measuring the fit of the model. Similarly, the comparison of the E model to the AE model allows testing whether disregarding any genetic source of variation/covariation causes a significant loss in the fit of the model. Likelihood ratio test and Akaike Information Criterion were reported in order to evaluate the fit of the models. All the analyses were conducted using OpenMx.[182]

6.1.2.3 Results

Main results were obtained from the AE model not allowing for sex differences, since this was the most parsimonious solution that did not lead to a significant loss in the fit of the model. At the phenotypic level, the correlation (rP) between IA and RRB (rP=0.33; 95% CI=0.31-0.36) was similar to the one between IA and SIC (rP=0.32; 95% CI=0.29-0.34), while the correlation between HI and RRB (rP=0.38; 95% CI=0.35-0.40) was stronger than the one between HI and SIC (rP=0.24; 95% CI=0.21-0.26). A and E components accounted for a similar amount of the

phenotypic correlations across all trait dimensions under study. Phenotypic correlations and A and E contributions are reported in Figure 6.1.2.3.

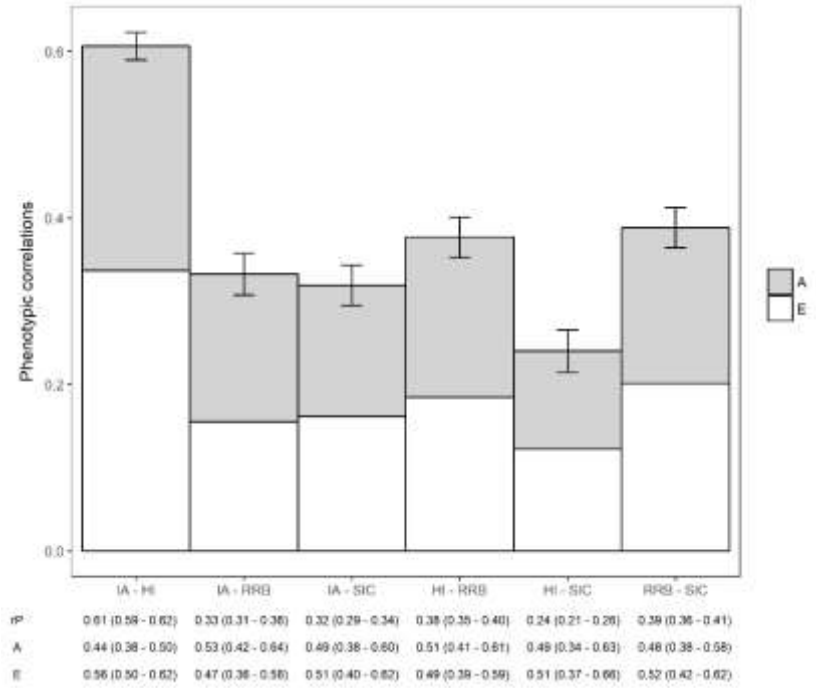

Figure 6.1.2.3. Phenotypic correlations and relative contribution of A and E. The plot illustrates rP (phenotypic correlations) and the proportion of rP explained by A (additive genetic influences) and E (non-shared environmental influences) for the following trait dimensions: IA=inattention; HI=hyperactivity/impulsivity; RRB=repetitive and restricted behaviours; SIC=social interaction and communication. Note: 95% confidence intervals in parentheses.

Aetiological correlations are presented in Table 6.1.2.3. Among the cross-trait genetic correlations (rg), the largest one was between HI and RRB (rg=0.56; 95% CI=0.46-0.65) and the smallest one was between HI and SIC (rg=0.33; 95% CI=0.23-0.43).

	IA	HI	RRB	SIC
	r (95% CI)	r (95% CI)	r (95% CI)	r (95% CI)
IA		0.57 (0.53-0.61)	0.25 (0.19-0.30)	0.28 (0.23-0.33)
HI	0.66 (0.60-0.71)		0.26 (0.21-0.31)	0.19 (0.14-0.24)
RRB	0.49 (0.39-0.58)	0.56 (0.46-0.65)		0.29 (0.24-0.35)
SIC	0.42 (0.33-0.51)	0.33 (0.23-0.43)	0.59 (0.49-0.70)	

Table 6.1.2.3. Additive genetic and non-shared environmental correlations. The table reports correlations between additive genetic influences (below the diagonal) and non-shared environmental influences (above the diagonal) influencing the following trait dimensions: IA=inattention; HI=hyperactivity/impulsivity; RRB=repetitive and restricted behaviours; SIC=social interaction and communication. Other abbreviations: r=correlation coefficient; 95% CI=95% confidence intervals.

6.2 ADHD AND OTHER NDS: OUTCOMES AND TREATMENT EFFECTIVENESS

Study 3 and 4 were designed to investigate whether the high comorbidity between ADHD and other NDs may have implications in terms of treatment effectiveness and if ADHD is specifically related to adverse health outcomes or if NDs as a group are associated with such outcomes.

6.2.1 ADHD medication and injuries and the role of co-occurring neurodevelopmental disorders (Study 3)

6.2.1.1 Rationale

Meta-analytic evidence has demonstrated that treatment with ADHD medication is associated with a 12% reduction in the risk of injuries.[134] However, no previous study has tested if use of ADHD medication may prevent adverse health outcomes in children with other NDs, which often co-occur with ADHD in children.[3-8] Considering the burden of injuries in this age group,[135] Study 3 aimed at estimating the association between ADHD medication use and the risk of unintentional injuries in children and adolescents with ADHD, including those with co-occurring NDs.

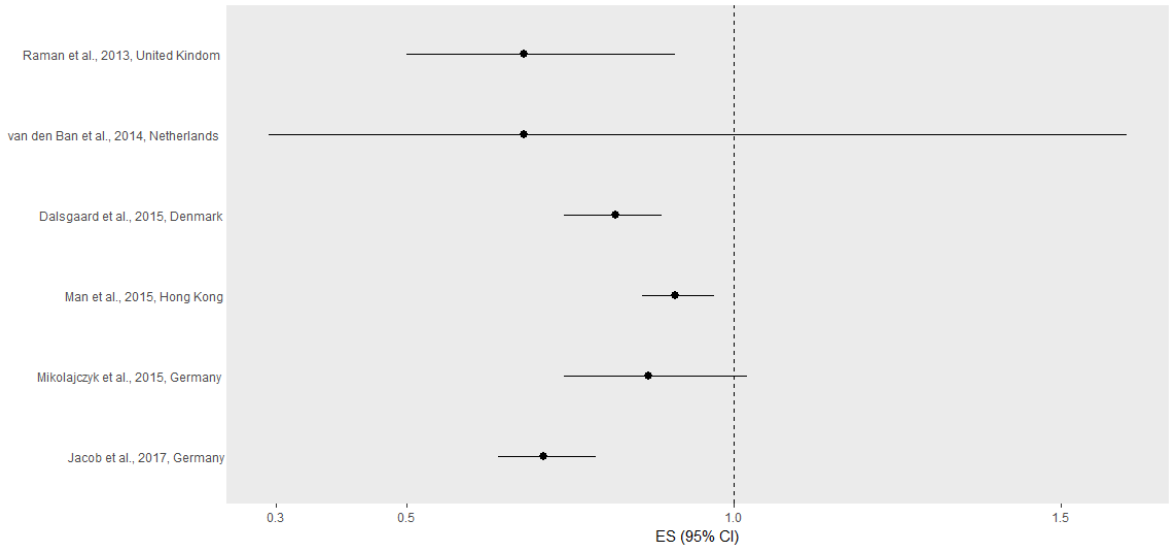

Figure 6.2.1.1. Short-term association between ADHD medication use and injuries. The forest plot illustrates a summary of recent observational studies using data from population-based health-care databases on the short-term association between ADHD medication use and injuries. Abbreviations: ES=effect size; 95% CI=95% confidence intervals.

6.2.1.2 Methods

To be included in the study, individuals had to reside in Sweden and have a diagnosis of ADHD and a diagnosis of unintentional injury. All individuals were followed from January 1st 2006 or their 5th birthday or the date of the first unintentional injury, whichever came last, to December 31st 2013 or their 18th birthday or death, whichever came first.

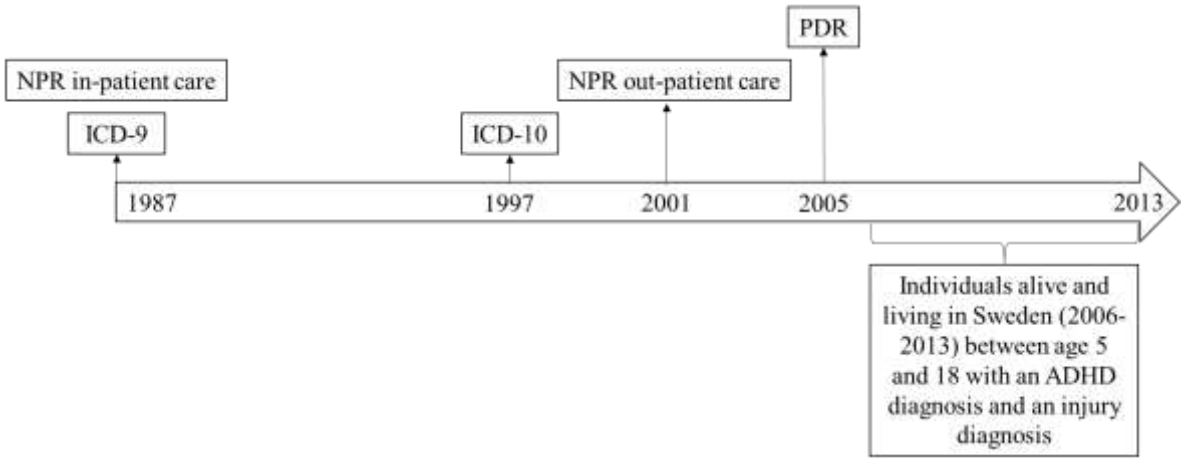

Figure 6.2.1.2. Timeline Study 3. The figure illustrates the timeline for main data sources and for the sample included in Study 3. Abbreviations: NPR=national patient register; ICD=International Classification of Diseases; PDR=prescribed drug register.

For each individual included in the study, follow-up time was divided into consecutive periods and the rate of injuries during periods on-treatment was compared to the rate of injuries during periods off-treatment (baseline). The comparison was within each individual. Stratified Cox regression was used to estimate the HR and 95% CIs for time to unintentional injury. The underlying time scale was time since last event (i.e., the last unintentional injury). Therefore, follow-up time was reset to zero whenever there was an event. The analyses were adjusted for age and seasonal pattern as time-varying covariates. As a secondary outcome, additional analyses were performed focusing on traumatic brain injuries (TBIs). Furthermore, separate analyses were performed in children and adolescents, in males and females, and in individuals with co-occurring NDs and ASD. Stata 15.1 (StataCorp., College Station, TX, USA) was used for all the analyses.

6.2.1.3 Results

There were 9,421 individuals included in the main analyses. Among them, more than 30% had been diagnosed with another ND (N=2,986) and the most common was ASD (N=1,390). Approximately 80% of the sample had at least one period on-medication and one period off-medication.

Main results on the association between ADHD medication use and injuries are presented in Table 6.2.1.3. ADHD medication use was associated with a lower rate of all unintentional injuries (HR=0.85; 95% CI=0.78-0.92), and of TBIs specifically (HR=0.27; 95% CI=0.20-0.38). A negative association between ADHD medication use and injuries was observed among children (HR=0.66; 95% CI=0.58-0.74) and adolescents (HR=0.85; 95% CI=0.74-0.97), among males (HR=0.88; 95% CI=0.80-0.96) and females (HR=0.77; 95% CI=0.67-0.90),

among individuals with any co-occurring ND (HR=0.88; 95% CI=0.77-1.01), and among the subgroup with co-occurring ASD (HR=0.77; 95% CI=0.62-0.96).

	N of events	Person-years at risk	HR	95%CI
Overall	16,344	53,069	0.85	(0.78-0.92)
TBIs	1,696	9,075	0.27	(0.20-0.38)
Age				
Children	7,525	23,086	0.66	(0.58-0.74)
Adolescents	6,572	13,715	0.85	(0.74-0.97)
Sex				
Males	11,472	37,951	0.88	(0.80-0.96)
Females	4,872	15,118	0.77	(0.67-0.90)
Co-occurring disorders				
Co-occurring NDs	5,212	17,313	0.88	(0.77-1.01)
Co-occurring ASD	2,344	8,125	0.77	(0.62-0.96)

Table 6.1.2.3. Association between ADHD medication use and injuries. The table reports number (N) of events, person-years at risk, hazard ratios (HRs), 95% confidence intervals (95%CIs) expressing the association between use of medication for ADHD and rate of unintentional injuries. Separate associations are reported for different age groups, sexes, individuals with co-occurring NDs, and for TBIs.

6.2.2 Neurodevelopmental disorders and victimization (Study 4)

6.2.2.1 Rationale

NDs are associated with several adverse outcomes, including bullying and victimization. However, it remains unclear if all NDs or only some of them are associated with these outcomes. Therefore, Study 4 aimed at investigating the association between different NDs and the risk of violent victimization in adolescents and young adults, considering sex differences and the role of shared familial factors and mediating factors.

6.2.2.2 Methods

Information from NPR was used to identify diagnoses of ADHD, ASD, ID and other NDs after age two. All the exposures were time-varying. Individuals who were diagnosed with NDs before their 15th birthday were considered exposed for the entire follow-up. Individuals who were diagnosed with NDs after their 15th birthday were considered unexposed from their 15th birthday until the first diagnosis, and exposed afterwards. We defined violent victimization as any inpatient or outpatient visit (as recorded in the NPR) or death (as recorded in the CDR) due to any type of assault. The outcome date was defined as the date of first registered diagnosis (or the date of death).

All individuals born in Sweden between 1985 and 1997 were followed from their 15th birthday until the first violent victimization event, death, migration outside Sweden, or December 31st 2013, whichever came first.

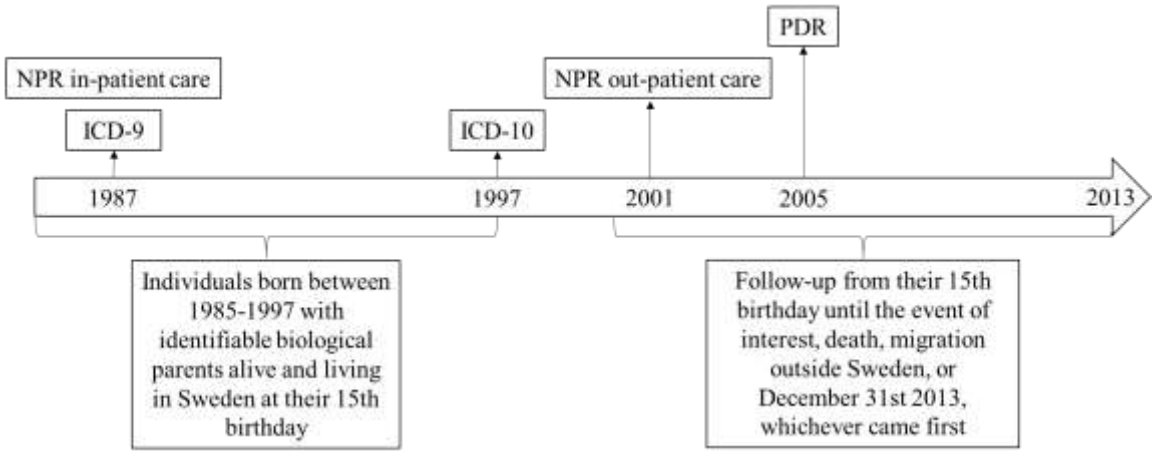

Figure 6.2.2.2. Timeline Study 4. The figure illustrates the timeline for the main data sources and the sample included in Study 4. Abbreviations: NPR=national patient register; ICD=International Classification of Diseases; PDR=prescribed drug register.

First, the crude association between the NDs and violent victimization was explored by estimating the cumulative incidence of being violently victimized in exposed and unexposed groups, separately for males and females. Then, Cox regression was used to estimate the HR and 95% CIs for time to violent victimization. The underlying time scale was time since the start of the follow-up, that is, the 15th birthday. Then, adjusted estimates were obtained. Year of birth was included in the model as covariate and stratified Cox regression, entering each cluster of full siblings as a separate stratum, was used to control for unmeasured familial factors. Last, the following externalizing problems were added as covariates to the previous model (that is, the model adjusted for year of birth and unmeasured familial factors) in order to explore their possible mediating role: diagnosis of substance use disorder (SUD), diagnosis of conduct disorder (CD), and crime conviction. These covariates were time-varying and date of the first diagnosis or first crime was used as the starting date of the exposed time.

All the analyses were performed separately for males and females, for NDs combined, as well as for ADHD, ASD and ID separately and then for ADHD, ASD and ID included in the same model, that is, adjusted for other NDs. Stata 15.1 (StataCorp., College Station, TX, USA) was used to perform all the analyses.

6.2.2.3 Results

Among 1,344,944 individuals included in the study, 74,487 were diagnosed with a ND. ADHD was the most common diagnosis (N=45,991). There were 37,765 individuals who experienced violent victimization during the follow-up.

At the end of the follow-up, 10.2% (95%CI=9.7-10.8) of males experienced violent victimization after being diagnosed with an ND, as compared to 6.0% (95%CI=5.9-6.1) of males who were not diagnosed with any ND. Among females, 9.2% (95%CI=8.6-9.9)

experienced violent victimization after being diagnosed with an ND, as compared to 2.4% (95%CI=2.4-2.5) among those who were not diagnosed with ND. ADHD was associated with the largest difference in the cumulative difference of violent victimization between those diagnosed and those who were not diagnosed, both in males and in females.

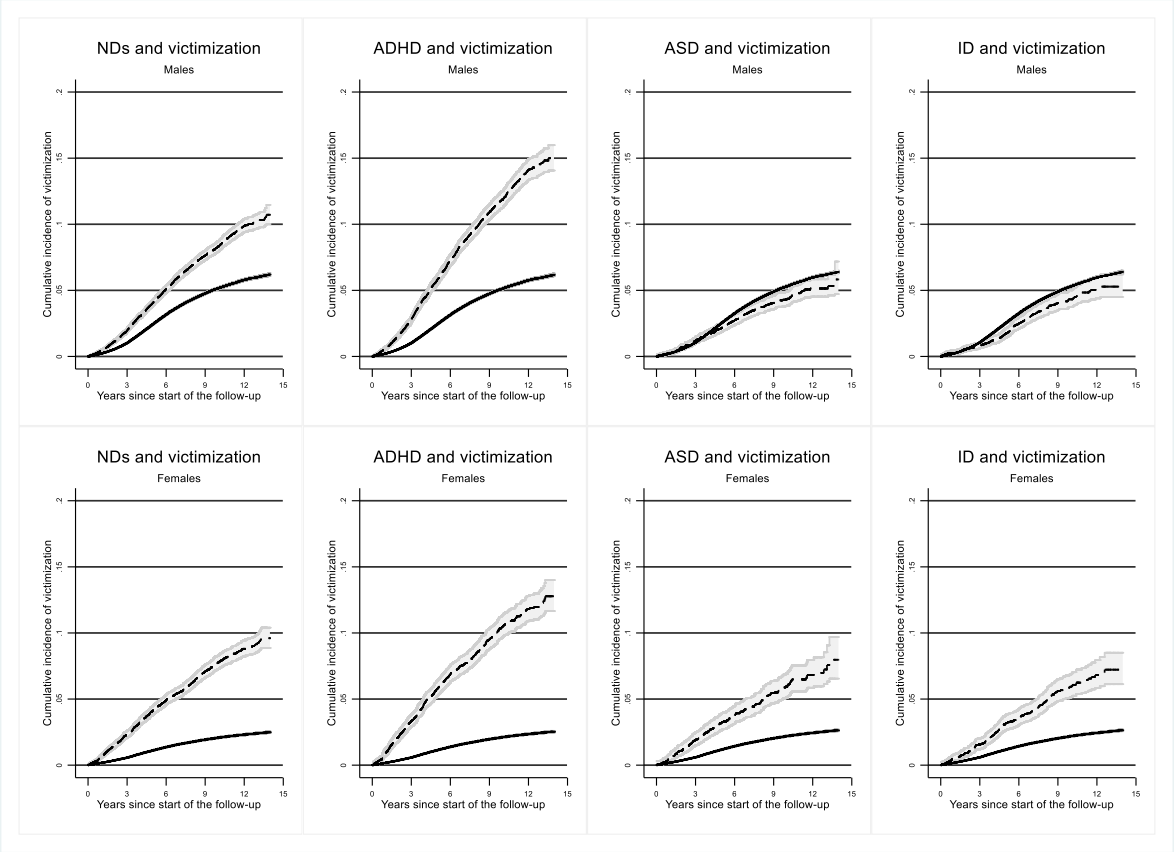

Figure 6.2.2.3. Cumulative incidence of violent victimization. Figure 6.2.2.3 depicts the cumulative incidence of violent victimization among individuals diagnosed and not diagnosed with NDs. The top part of the figure reports the estimates in in males and the lower part of the figure reports the estimates for females. Note: Dashed line=exposed to NDs; solid line=unexposed to NDs. Abbreviations: NDs=neurodevelopmental disorders; ASD=autism spectrum disorder; ID=intellectual disability.

Estimates from the crude model, showed that being diagnosed with any ND was associated with an increased risk of later violent victimization in males (HR=1.68; 95%CI=1.61-1.76) and females (HR=3.81; 95%CI=3.57-4.07). However, when analyzing specific disorders while adjusting for the other NDs, only ADHD was associated with an increased risk of later violent victimization in both sexes. ASD and ID were positively associated with violent victimization only in females, although adjusting for other NDs, attenuated these estimates.

In the model adjusted for unmeasured familial factors, being diagnosed with any ND was associated with an increased risk of later violent victimization in males (HR=1.12; 95%CI=0.98-1.27) and females (HR=1.68; 95%CI=1.34-2.10). When considering specific disorders, only ADHD was associated with an increased risk of violent victimization in males (HR=1.46; 95%CI=1.25-1.70) and females (HR=2.11; 95%CI=1.57-2.83). Furthermore, there

was a positive association with ID among females, but the CI included one (HR=1.25; 95%CI=0.78-2.01). All the associations were attenuated when compared to the unadjusted model, which suggests that familial factors shared by siblings may explain at least part of the association.

Thereafter, when externalizing problems were added to the previous model (that is, adjusted for familial confounding) as covariates, all the associations attenuated, confirming that externalizing problems may mediate at least part of the association between NDs and violent victimization. When considering specific disorders, only ADHD was associated with an increased risk of violent victimization among males (HR=1.23; 95%CI=1.05-1.45) and females (HR=1.61; 95%CI=1.17-2.21). Furthermore, there was a positive association with ID in females, however the CI included one (HR=1.24; 95%CI=0.78-1.98).

	Crude association	**Adjusted for other NDs**	**Adjusted for familial factors**	**Adjusted for familial factors and mediators**
	HR (95% CI)	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Males				
Any ND	1.68(1.61-1.76)	-	1.12(0.98-1.27)	0.99(0.86-1.12)
ADHD	2.45(2.33-2.58)	2.69(2.55- 2.84)	1.46(1.25-1.70)	1.23(1.05-1.45)
ASD	0.84(0.75-0.95)	0.61(0.54-0.69)	0.81(0.60-1.10)	0.82(0.61-1.10)
ID	0.81(0.70-0.93)	0.66(0.57-0.76)	0.52(0.37-0.72)	0.55(0.40-0.76)
Females				
Any ND	3.81(3.57-4.07)	-	1.68(1.34-2.10)	1.40(1.10-1.78)
ADHD	5.12(4.73-5.55)	4.67(4.27-5.10)	2.11(1.57-2.83)	1.61(1.17-2.21)
ASD	2.80(2.42-3.24)	1.24(1.05-1.47)	0.89(0.55-1.43)	0.83(0.52-1.33)
ID	2.72(2.37-3.13)	1.75(1.50-2.04)	1.25(0.78-2.01)	1.24(0.78-1.98)

Table 6.2.2.3. NDs and risk of violent victimization. Table 6.2.2.3 reports the estimates from the different models testing the association between NDs and risk of victimization. Abbreviation: HR=hazard ratio; CI=confidence interval; ND=neurodevelopmental disorder; ADHD=attention-deficit/hyperactivity disorder; ASD=autism spectrum disorder; ID=intellectual disability.

7 DISCUSSION

7.1 MAIN FINDINGS AND IMPLICATIONS

Overall, results from the four studies presented in this thesis demonstrate that comorbidity between ADHD and ASD may be attributable to common aetiological factors, which are, at least in part, of genetic origin. Comorbidity seems to be a key aspect of NDs as a diagnostic group, and it does not seem to affect treatment effectiveness with regard to ADHD medication and injuries. In addition to commonalities between ADHD and other NDs, there are some specific features regarding certain negative outcomes, as in the case of violent victimization, which seems to be more specifically associated with ADHD.

7.1.1 Shared aetiology between ADHD and ASD

When the work included in this thesis was initiated, there was a large body of evidence from twin studies supporting the existence of a genetic overlap between ADHD and ASD traits,[90-94,177-181,183] however little was known on the overlap between ADHD and ASD as clinically diagnosed disorders, with the exceptions of few family studies.[95,96] Furthermore, only a few twin studies had investigated the association between ADHD and ASD traits in adults,[91,92,179] and only one[181] had explored how specific trait dimensions related to one disorder may be associated with specific trait dimensions related to the other disorder. Results from molecular genetic studies, based on the comparison between clinically diagnosed patients vs controls, had provided support for shared rare chromosomal deletions and duplications between ADHD and ASD,[99,100] but the only available study on the overlap in common genetic variants had failed to detect a genetic association.[98] Therefore, it was unclear if the link between ADHD and ASD was limited to traits associated to the disorders as measured in the general population or it was also present between clinically diagnosed disorders.

Results from Study 1 confirmed evidence from previous family studies, which had included only first degree relatives,[95,96] that ADHD is more common among individuals with ASD and their relatives (up till half cousins). In addition, the association estimated in pairs of relatives who were more genetically similar (for example, twins and full siblings) was stronger than the association estimated in pairs of relatives who were less genetically similar (for example, half siblings and cousins). Furthermore, the associations were larger for high-functioning than for low-functioning ASD. New evidence has been accumulating in the last year on the overlap between ADHD and ASD, both from family studies[176] and from molecular genetics studies,[97] in agreement with the findings presented in this thesis. The most recent GWAS of ASD,

published earlier in 2019, has, for the first time, reported a positive genetic correlation between ASD and ADHD, estimated to be equal to 0.36.[97]

Results from Study 2 converge with the only previous existing study on dimension-specific overlap between ADHD and ASD traits. Study 2 showed that, although there were phenotypic and genetic correlations across all traits examined, the size of the correlations varied. For example, the association between RRB and SIC (that is, between two traits within ASD) was similar to the association between RRB and HI (that is, between one trait related to ASD and one trait related to ADHD). The latter association was, in turn, higher than the association between SIC and HI.

In summary, findings from Study 1 and 2 indicate that the comorbidity between ADHD and ASD may be due to familial factors shared by the disorders and by the traits related to these disorders. These factors are likely to be of genetic origin, although non-genetic factors may also play a role. This is in line with recent findings supporting the existence of a heritable general factor of psychopathology, which includes ADHD.[184-186] Results from Study 1 on differences between low- and high-functioning ASD and results from Study 2 on different trait dimensions related to ASD and ADHD suggest that the overlap between these disorders may be explained by different links between specific manifestations or symptom dimensions related to each disorder.

These studies add to the increasing evidence on cross-disorder overlap and within-disorder heterogeneity in psychiatry, which is having an impact on diagnostic systems, and, hopefully, will continue to inform psychiatric nosology. For example, from the 4th to the 5th edition of DSM there was a change in the diagnostic criteria of ADHD. In the 4th version, ASD was an exclusion criterion for the diagnosis of ADHD, while DSM-5 has removed this exclusion criterion and allows a diagnosis of ADHD in individuals with ASD. However, this change has not been implemented in ICD-11, which has been recently released.[21] Our results, in combination with previous research, indicate that ICD-11 should probably adopt the DSM-5 approach on this.

Future research aimed at characterizing causes of ADHD, other NDs and their co-occurrence might benefit from combining different genetically informative designs and from the availability of rich phenotypic data, ideally including measures of continuous variation of traits in the population as well as clinically significant symptoms. In order to understand the genetic architecture of neuropsychiatric disorders, some studies have focused on parsing disorder-specific from cross-disorder[187] or general effects.[186] In addition, within-disorder phenotypic

and genetic heterogeneity has not only been given increased attention in genetic studies of psychiatric phenotypes,[97,188] but also in genetic studies of other complex traits.[189]

7.1.2 ADHD and other NDS: outcomes and treatment effectiveness

Most of the previous research on outcomes of ADHD and treatment effectiveness has neglected the role of comorbidity with other NDs, either by excluding individuals with co-occurring disorders or by lumping together individuals with and without co-occurring disorders.

Findings from Study 3 suggest that children and adolescents diagnosed with ADHD and co-occurring NDs may benefit from use of ADHD medication to the same extent in terms of prevention of unintentional injuries. While no previous observational study had examined the association between ADHD medication use and injuries in individuals with co-occurring NDs, these results are in line with evidence from RCTs, which suggests that ADHD medications are superior to placebo in reducing core symptoms of ADHD among children with co-occurring NDs.[190-192]

Results from Study 4 indicate that, although NDs as a group seem to be associated with an increased risk of being violently victimized, particularly among females, ADHD may be driving the association. In addition, results from the analyses adjusted for familial factors and for mediation via externalizing problems suggest that there may be a direct link between ADHD and victimization. These findings are in line with previous research on the association between NDs and other types of victimization.[114,115,193,194]

Altogether, Study 3 and 4 support the view of NDs as a diagnostic group characterised by homogeneity in terms of response to medications and adverse health outcomes. Results from Study 3 suggest that comorbidity with other NDs does not affect ADHD medication effectiveness in reducing the risk of injuries and results from Study 4 indicate that violent victimization seems to be associated with NDs as a group. Therefore, the risk of victimization should be assessed in this group of patients. On the other hand, Study 4 demonstrates that ADHD may be more specifically associated with an increased susceptibility to violent victimization. More research is needed to understand which aspects of ADHD may be stronger risk factors for this adverse outcome.

Future epidemiologic studies may expand current knowledge on outcomes of ADHD and treatment effectiveness by taking into consideration the presence of other symptoms or disorders or other aspects of the disorder such as severity and presentation. Furthermore, the role of familial factors, of genetic or non-genetic origin, and of possible mediating factors should be assessed in order to explore the mechanisms that may explain observed associations.

7.2 METHODOLOGICAL CONSIDERATIONS

7.2.1 Measures

7.2.1.1 Register measures

In Study 1, 3, and 4 the main exposure and outcome measures were derived from different Swedish nation-wide registers, in particular from the NPR, the PDR and the CDR. For diagnoses of NDs, we expect that the most severe cases are more likely to be captured from this data source. This may imply that, for example, individuals who have a recorded diagnosis of NDs in the NPR may be more likely to present with higher impairment and with co-occurring conditions. This may have caused an overestimation of comorbidity rates in Study 1. For Study 3 and 4 this may limit the representativeness of the observed associations between ADHD medication and reduced risk of injuries (Study 3) and between NDs and violent victimization (Study 4) to the most severe groups of patients only.

In study 3, information on frequency of medication dispensations was used to define ADHD treatment status. The choice of the maximum interval between medications was based on previous studies. In addition, sensitivity analyses using varying lengths of the interval (for example 3, 4 and 6 months) have supported the robustness of the results. However, non-adherence may lead to misclassification of the exposure. In other words, if the dispensation would cover a period of time longer than estimated, due to poor adherence, time that should have been classified as medicated would in fact be classified as non-medicated. One scenario in which this may be problematic is if the majority of events were to occur at the beginning of a new non-medicated period, which followed a previous medicated period. If this was the case, an alternative explanation for the protective effect of ADHD medication on the risk of injuries observed in Study 3 may be misclassification of time that was exposed to ADHD medication as unexposed time.

The definition of the outcome in Study 3 and 4 was based on ICD codes used to specify the causes of morbidity and mortality. In Study 3 the outcome of interest was on injuries with unintentional cause only, while in Study 4 the outcome of interest was assault. Currently, there is no evaluation of the quality of this specific information and validation studies are needed to assess reliability of these register measures. However, it can be assumed that when the cause of an event cannot be reliably ascertained, it will be recorded as "event of undetermined intent". Therefore, although some events that are in fact unintentional injuries or assault may be recorded as "event of undetermined intent", it is less likely that the cause of an event will be recorded as unintentional or assault if there is uncertainty about the real cause of the event.

7.2.1.2 Self-rated measures

ADHD and ASD trait dimensions used in Study 2 were self-rated using a web-based questionnaire (a paper version could be provided upon request). There are at least two key limitations to consider related to the data source for Study 2. First, the reliance on self-rating only. Cross-twin correlations based on self-rating (that is, when each twin rates themselves separately) tend to be lower than those based on parent's rating (that is, when the same parent rates both twins). As a consequence, cross-twin correlations based on self-rating may be underestimated. This, in turn, may lead to an inflation of the E component, which captures any source of dissimilarity between the members of the twin pairs, including rater bias, that is, a personal tendency (in this case not influenced by genetics) to provide similar answers to different items in a questionnaire. A second important issue is the low response rate. Supplementary analyses showed that non-participants were less likely to have higher education attainment and to be employed, and they were more likely to be diagnosed with a psychiatric disorder. These observations clearly limit the generalizability of our results to individuals with higher socio-economic status and less severe levels of ADHD and ASD symptoms.

Despite the aforementioned limitations, the convergence between results from Study 1, based on clinical diagnoses from the registers, which are likely to capture more severe cases, and results from Study 2, based on self-rated trait dimensions measured in the general population, supports the robustness of our conclusions on the phenotypic and genetic overlap between ADHD and ASD.

7.2.2 Methods

Various designs and analytical approaches have been applied in this thesis, each of which has inherent assumptions, advantages and limitations.

Study 1 and 2 are based on the notion that different clusters of relatives are characterised by different genetic sharing. For example, MZ twin pairs are genetically identical, while DZ twins and full siblings share, on average, half of their genetic background. In addition to this notion, Study 2 assumes that MZ and DZ twins share common aspects of rearing environment (that is, the C component) to the same extent (often referred to as Equal environment assumption). In other words, the only source contributing to higher resemblance on a trait within members of MZ twin pairs vs DZ twin pairs is genetics. This assumption has been demonstrated to be valid for several psychological traits and psychiatric disorders.[195,196] Another assumption of twin design is the absence of assortative mating for the traits under examination. Assortative mating has been reported for several psychiatric disorders, both within each disorder and between

different disorders, including ASD and ADHD.[197] Violation of this assumption in twin design may lead to underestimation of heritability, since higher similarity between parents will cause an increase in the average genetic resemblance between DZ twins. However, it is unclear if this may have caused an underestimation of the genetic contribution to the phenotypic correlations between ADHD and ASD trait dimensions in Study 2. Last, twin design assumes that the effects of gene-gene or gene-environment interaction, if any, are negligible. When these types of mechanisms are considered to be important, other genetic methods, may be adopted. For example, if gene-environment correlation or interaction is suspected, extensions of the classic twin method may be used. Depending on the nature of the environment (that is, shared or not by the members of the twin pairs) that correlate or interact with the genetic component, different types of data may be needed to test gene-environment interplay. And the nature of the relevant environment will also determine which parameters may be affected by such interplay. While the lack of a test of these aspects in Study 2 may be considered a limitation, this was not among the intended aims of the study. On the other hand, gene-gene and gene-environment interplay do represent interesting directions for future research, which may benefit from a combination of different methods of genetic epidemiology.

Study 3 and 4 have used within-cluster comparison to adjust for cluster-invariant confounders. When using this approach, only clusters with variation in the covariates included in the model are informative for the analysis. Therefore, two main limitations of this approach are generalizability of the results to the informative clusters only and the precision of the estimates. Of note, in Study 3 most of the study participants did have variation in their medication status throughout the follow-up. In Study 4 it remains unclear if sibling clusters with variation in the diagnostic status of NDs are representative of the source population. Another limitation related to within-cluster comparison is that, although cluster-invariant confounders are adjusted for by design, other confounders that vary within the cluster may be relevant for the research questions investigated in Study 3 and 4. In Study 3, for example, lack of data on psychosocial treatment during the follow-up is a limitation, as this may be both related to medication use and injury risk. In Study 4, factors non-shared by siblings that may increase vulnerability to ADHD and to being violently victimized may explain at least part of the association. For example, characteristics of the parents and/or of the offspring related to birth, such as parental age at childbearing or birth weight, may be additional factors to consider. Furthermore, it has been demonstrated that confounding by factors that are not perfectly shared by members of the clusters and random error related to exposure measurement may introduce bias.[198] Last, analytical methods applied in within-cluster comparison assume absence of carryover effect within the cluster. For example, in the case of the sibling-comparison design, used in Study 4,

the assumption implies that the exposure and outcome status of one sibling in the cluster does not affect the exposure and outcome status of the other siblings in the cluster. In many instances, this may lead to bias.[199] One scenario that may be problematic is when exposure status in one sibling may influence the outcome in the other siblings, or when there is an association between the outcome on one sibling and the outcome in the other sibling. Some of these associations may be more plausible than others, and some may be ruled out. For example, in Study 4, estimates may be biased by carryover effect if the diagnosis of a ND in one sibling would influence the subsequent vulnerability to violent victimization of the other sibling or if there was an effect of violent victimization in one sibling on subsequent vulnerability to violent victimization in the other sibling. These two potential associations were not formally tested in Study 4, and this may be considered a limitation of the study. On the other hand, they do not seem to be plausible alternative explanations for the associations observed.

7.3 ETHICAL CONSIDERATIONS

7.3.1 Data collection and handling

The work presented in this thesis includes studies based on data from a record linkage of several Swedish registers and from a survey within the STR. The record linkage has obtained approval by the Regional Ethical Review Board in Stockholm in 2013. In the case of national registers informed consent is not needed according to Swedish law. In contrast, individuals participating in the survey from the STR, YATSS, were asked informed consent to use the data for research purposes. Informed consent was asked after having provided relevant information about the study, in order to ensure that individuals were aware of possible risks and, therefore, to enable them to make an informed and independent decision about participation. Moreover, individuals may decide to be excluded from the STR and may decline invitation to participate to surveys within the STR. Ethical approval was obtained from the Regional Ethical Review Board in Stockholm for the YATSS study.

According to the Personal Data Act in Sweden (Swedish abbreviation: PUL) and to the European General Data Protection Regulation (GDPR), the information included in the record linkage of national registers is considered personal data. The definition of personal data includes any information that can be directly or indirectly attributed to a person. For the projects included in this thesis, data were anonymized and located in a protected server. Data handling was done following recommendations for good practice in data management and archiving formulated by the department.

7.3.2 Results communication and interpretation

In this thesis, results from four different studies are described. Therefore, there are aspects related to the communication and interpretation of the studies' results, both within the scientific community and with the wider audience, which should be considered. For example, in Study 1 we used the term "high-" vs "low-functioning" ASD to refer to ASD without or with ID, respectively. While this terminology has been extensively used in the literature on ASD, it has also been criticized based on the observation that intelligence alone may not be as important as other skills in predicting the level of functioning of individuals with ASD in daily activities.[200,201] On the other hand, the term "low-functioning" disregards individual strengths and may be perceived as stigmatizing. More reflection and debate on these aspects are needed in order to agree on language and terminology. Terminology should be appropriate for scientific purposes, where some level of simplification may be needed. However, it is vital to select terms that do not convey stigma and that promote inclusion and diversity.

Another potential issue concerns the interpretation of results from Study 4 on the increased vulnerability of individuals with NDs to violent victimization. Investigating whether NDs as a group or some specific disorders may increase the risk of being violently victimized should not be considered an attempt to shift the accountability for these acts from the perpetrators to the victims.[115] The goal of the study was to bring the attention of mental health professionals (and other health and social professionals too, ideally) on groups of individuals who may have experienced victimization, in order to provide specific support and prevent secondary effects. In addition, understanding mechanisms through which ADHD symptoms may increase the risk of victimization may help clinicians to monitor potential indicators of higher vulnerability to adverse events among ADHD patients.

8 CONCLUSIONS

The work presented in this thesis supports the view of NDs as a diagnostic group characterised by both general and specific aspects. Partially overlapping aetiological factors, of genetic and non-genetic origin, may explain the comorbidity between ADHD and ASD. Among children and adolescents with ADHD and co-occurring NDs, treatment with ADHD medication seems to be as effective in reducing the risk of adverse health outcomes as it is in the larger ADHD group. There is an association between NDs as a group and violent victimization in adolescence and young adulthood, but there is also a specific association with ADHD, which seems to be in part explained by shared familial factors and mediators and in part attributable to a direct link.

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