From the DEPARTMENT OF CLINICAL NEUROSCIENCE
Karolinska Institutet, Stockholm, Sweden

CHILDHOOD SIGNS OF ADHD AND PSYCHOSOCIAL OUTCOMES IN ADOLESCENCE - A LONGITUDINAL STUDY OF BOYS AND GIRLS

Eva Norén Selinus

Stockholm 2015

CHILDHOOD SIGNS OF ADHD AND PSYCHOSOCIAL OUTCOMES IN ADOLESCENCE - A LONGITUDINAL STUDY OF BOYS AND GIRLS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

The public defense (in Swedish) will take place at Karolinska Institutet, Karolinasalen, Tomtebodavägen 18A, Solna

Friday the 13th of November 2015, at 10.00 a.m.

By

Eva Norén Selinus
MD

Principal Supervisor:
Clara Hellner Gumpert, MD, Ph.D.,
Associate professor
Karolinska Institutet
Department of Clinical Neuroscience
Centre for Psychiatry Research & Education

Co-supervisor(s):
Henrik Anckarsäter, MD, Ph.D.,
Professor
University of Gothenburg
Centre for Ethics, Law, and Mental Health
(CELAM)

Paul Lichtenstein, Ph.D.,
Professor
Karolinska Institutet
Department of Medical Epidemiology and
Biostatistics

Yasmina Molero, Ph.D.,
Karolinska Institutet
Department of Medical Epidemiology and
Biostatistics

Opponent:
Bruno Hägglöf, MD, Ph.D.,
Professor
University of Umeå
Department of Clinical Science

Examination Board:
Carl Göran Svedin, MD, Ph.D.,
Professor
University of Linköping
Department of Clinical Sciences

Kent Nilsson, MD, Ph.D.,
Professor
University of Uppsala
Centre for Clinical Research, County of
Västmanland

Vladislav Ruchkin, MD, Ph.D.
Associate professor
University of Uppsala
Department of Neuroscience, Child and
Adolescent Psychiatry

To all the children, adolescents and adults who struggle daily with their symptoms of ADHD

PROLOGUE

Working as a child and adolescent psychiatrist has been a most exciting, rewarding and challenging venue of my life. I have always loved meeting children and adolescents, trying to understand each one's personality and situation. That is how my interest for neuropsychiatric problems started. Each individual is always unique, whatever symptoms or personality traits he or she might have.

I have met quite a few children and adolescents with ADHD throughout the years, and each one of them has been truly unique. Many have had a creative capacity in fields like music, acting, performing, drawing, painting or handicraft. It is not possible for me to cover this aspect of their creativity in my thesis, but I am most aware of its existence!

In 2008, the twin study 'Developmental Outcomes in a Genetic Twin Study in Sweden' (DOGSS) was just starting up at the three study sites: Stockholm, Gothenburg and Malmö. The aim of this project was to study psychosocial outcomes in adolescents who screened positive for neurodevelopmental problems in childhood. It was a 3-year project, studying three yearly cohorts of twins born between 1993 and 1995.

At the time, I was a senior child and adolescent psychiatrist, with extensive experience in the neuropsychiatric field, and I was searching for new challenges in life in the form of research. I was lucky to become the child psychiatrist involved in the DOGSS study, meeting all the psychologists conducting the assessments in the three cities, and going through the 452 assessments of twins. Through this start in scientific research, I got inspired to embark on the PhD student journey, which I have not regretted!

ABSTRACT

Childhood neurodevelopmental problems (NDPs; encompassing attention deficit hyperactivity disorder [ADHD], autism spectrum disorder [ASD], tic disorder [TD], learning disorder [LD], and developmental coordination disorder [DCD]), affect around 10% of children worldwide. ADHD is the most common disorder, with an estimated prevalence between 5 and 10%. Based on its relatively high prevalence and associated impairments and adverse outcomes, ADHD is considered a major public health problem. The etiology of ADHD is multifactorial, including both genetic and environmental factors. ADHD affects both boys and girls in various areas of functioning; including academic, cognitive, psychosocial, and mental health. Previous longitudinal research on ADHD has rarely included aspects of comorbidity in relation to such outcomes. Also, it remains unclear how genetic and environmental factors influence the association between ADHD and internalizing problems during childhood and adolescence. To avoid the potentially artificial demarcation of a diagnostic cut-off, several studies have assessed the degree of core ADHD-symptoms rather than the clinical diagnosis. Such work indicates that subthreshold levels of ADHD may also be associated with negative outcomes such as poorer academic achievements, lower self-esteem, and relationship problems. A particular challenge for society lies in the fact that only children who are clinically assessed and diagnosed with ADHD may be entitled to care and support, when in fact individuals with subthreshold level symptoms might also benefit from such interventions. The general aim of this thesis was to investigate how childhood symptoms of ADHD affect psychosocial outcomes in adolescence, with a special focus on gender differences. We used data from a population-based cohort of twins, who were assessed for the presence of NDP symptoms during childhood and followed up at age 15.

Study I investigated the diagnostic predictive validity of the screening-interview A-TAC, an instrument that is used throughout all studies in this thesis. The results demonstrated that A-TAC is an effective screening tool for NDPs, and that it can be used for the purpose of predictive assessment in the general population. Overall, A-TAC demonstrated satisfactory psychometric properties as a screening instrument.

Study II examined the association between childhood signs of ADHD and/or other NDPs (at age 9 or 12) and psychosocial outcomes at age 15. The results demonstrated that symptoms of NDPs or other mental health problems at the age of 9 or 12 were associated with a higher degree of psychosocial problems during adolescence. Despite the presence of comorbidity, childhood ADHD symptoms stood out as the most important risk factor for later antisocial development and impaired daily functioning.

Study III examined if different levels of ADHD symptoms were differentially associated with psychosocial problems in adolescent boys and girls. ADHD symptoms as well as their associated negative outcomes were dimensionally distributed in the study cohort. Girls and boys displayed somewhat different risk profiles, even after controlling for other neuropsychiatric symptoms.

Study IV explored the relative contribution of genetic and environmental influences associated with childhood ADHD and internalizing problems to symptoms of internalizing problems during adolescence. ADHD and internalizing problems were associated. There was

a gender difference in the genetic explanation of internalizing problems at age 15. In both boys and girls, both new genetic and new environmental factors emerged in adolescence.

In summary, childhood symptoms of ADHD turned out to be the most important risk factor for adolescent antisocial behavior and impaired daily functioning, despite the presence of comorbid symptoms. During adolescence, increasing levels of ADHD-related symptoms were associated with increasing levels of psychosocial problems. Girls and boys displayed somewhat different risk profiles, e.g. girls displayed more internalizing symptoms and seemed to have a higher risk for drug misuse. The finding that ADHD symptoms were associated with higher drug misuse in girls motivates particular attention and active screening routines. The findings also point to the need for increased awareness and further study of the complex etiologic and developmental relationship between internalizing symptoms and ADHD.

SAMMANFATTNING PÅ SVENSKA

Det övergripande syftet med denna avhandling var att undersöka hur ADHD-symptom i barndomen påverkade utvecklingen av psykosociala problem i tonåren. Arbetet delades upp i fyra delarbeten: I delarbete I ville vi se om vår screening-intervju A-TAC på ett tillfredsställande sätt kunde förutsäga diagnoser och problem tre till sex år senare i ett urval individer ur befolkningen. I delarbete II ville vi studera om barndomssymptom på ADHD och andra neuropsykiatriska problem var förknippade med psykosociala problem vid 15 års ålder. I delarbete III fördjupade vi oss ytterligare genom att undersöka om det fanns könsskillnader med avseende på psykosociala problem vid 15 års ålder för de som haft ADHD-symptom i barndomen, och om det också fanns något samband mellan grad av ADHD-symptom man haft i barndomen och hur mycket psykosociala problem man fick i tonåren. I delarbete IV, slutligen, försökte vi klargöra hur genetiska och miljömässiga faktorer förknippade med ADHD och ångest/depression i barndomen kunde förklara ångest och depressivitet i tonåren. Vi undersökte också om det fanns några skillnader mellan flickor och pojkar. Här följer en presentation av de olika delarbetena och vad de visat.

I **delarbete I** ville vi se om vår screening-intervju A-TAC på ett tillfredsställande sätt kunde förutsäga diagnoser och problem tre till sex år senare, i ett urval individer i befolkningen. Detta urval fick vi genom det svenska tvillingregistret. I delarbete I och II ingick de tvillingar födda 1993-1995 som var screen-positiva för en neuropsykiatrisk diagnos, och som tackade ja till att delta både i telefonintervjun vid 9 (eller 12) års ålder och i en omfattande klinisk uppföljning tillsammans med sina co-tvillingar samt slumpmässigt utvalda kontroller vid 15 års ålder (totalt 450 individer). Vid 15 års ålder jämförde vi de diagnoser som ställdes vid den kliniska uppföljningen med de "screening-diagnoser" vi fått fram vid telefonintervjun med A-TAC. 'Screening' betyder att man 'gallrar ut' viss problematik och vissa individer, för att ha möjlighet att studera det man vill ha reda på mer om. När man använder "screening-diagnoser" har man bestämt sig för hur man definierar varje diagnos. Någon som är "screen-positiv" har symptom som uppfyller kraven för en viss diagnos, medan någon som är "screen-negativ" *inte* har det. Det visade sig att sensitiviteten (förmågan att identifiera de som hade en diagnos) och specificiteten (förmågan att utesluta de individer som *inte* hade diagnos) hos A-TAC att förutsäga en senare klinisk diagnos, på det hela taget var god till utmärkt. Bland de som var screen-positiva för ADHD och/eller autism i barndomen, fick hälften en klinisk ADHD-diagnos respektive autism spektrum-diagnos vid uppföljningen vid 15 års ålder. För inlärningssvårigheter var motsvarande andel en sjättedel och för ticsstörningar drygt hälften. En del av de screen-positiva fick inga diagnoser vid uppföljningen vid 15 års ålder, medan några av de initialt screen-negativa fick en diagnos vid uppföljningen.

Slutsatsen blev att A–TAC var ett tillförlitligt instrument för att screena för neuropsykiatriska svårigheter i vår populationsbaserade studie. A-TAC hade goda till utmärkta psykometriska egenskaper, med en utmärkt förmåga att urskilja neuropsykiatrisk problematik från icke-neuropsykiatrisk tre år efter screeningen. Det är dock värt att notera att vissa individer inte fick samma diagnos vid uppföljningen som vid screeningen med A-TAC, dvs.

symptombilden ändrade sig över tid men de hade fortfarande neuropsykiatriska problem av något slag.

I **delarbete II** undersökte vi sambandet mellan att som barn ha varit screen-positiv för en neuropsykiatrisk diagnos och hur den psykosociala problematiken yttrade sig i tonåren (med särskilt fokus på ADHD). Baslinjedata samlades in via den ovan beskrivna telefonintervjun med föräldrar till 9 år (eller 12 år) gamla tvillingar (ATAC-intervjun). Psykosocialt fungerande, såsom kamratrelationer, skolgång, internaliserande problem (ångest/depression), antisocialt beteende, alkoholmissbruk, drogmissbruk och nedsatt daglig funktionsnivå, undersöktes vid 15 års ålder. Vi fann att den som var screen-positiv för någon neuropsykiatrisk diagnos i barndomen hade en tydligt förhöjd risk att uppvisa psykosociala problem i tonåren. Om man varit screen-positiv för ADHD fördubblades eller tredubblades oddsen för senare psykosociala problem, även efter att vi tagit hänsyn till annan neuropsykiatrisk samsjuklighet. När vi tog hänsyn till föräldrarnas utbildningsnivå i analysen, kvarstod signifikanta resultat endast för antisocialt beteende och nedsatt daglig funktionsnivå. Vår slutsats blev att symptom på neuropsykiatriska funktionshinder eller annan psykisk ohälsa vid 9 eller 12 års ålder var associerat med en mer problemtyngd tonårsutveckling. Oberoende av annan samsjuklighet var ADHD-symptom vid 9 eller 12 års ålder den mest betydelsefulla riskfaktorn (av de riskfaktorer som vi studerade) för utveckling av antisocialt beteende och nedsatt daglig funktionsnivå i denna studie.

I **delarbete III** studerade vi könsskillnader mellan olika nivåer av ADHD-symptom i barndomen och psykosociala utfall i tonåren. Ett större urval av svenska tvillingar (totalt 4635 stycken) screenades för neuropsykiatriska symptom med hjälp av A-TAC-intervjun (se ovan). I delarbete III och IV inkluderas alla tvillingar, även de som var screen-negativa för någon neuropsykiatrisk diagnos. Dessa barn och deras föräldrar erbjöds sedan att delta i en enkät vid 15 års ålder, med frågor avseende aktuell psykosocial situation. För att urskilja effekten av att ha haft olika nivåer av ADHD-symptom i barndomen delades kohorten in i tre grupper: de som varit screen-negativa för ADHD vid baslinjeintervjun, de som varit screen-intermediära (dvs visat upp vissa drag på ADHD men inte över tröskelvärdet för en diagnos), och de som var screen-positiva (dvs uppvisat symptom över tröskelvärdet för en diagnos). I samband med uppföljningsintervjun vid 15 års ålder fyllde både barn och föräldrar i skattningsformulär gällande: 1) aktuella symptom på hyperaktivitet/ouppmärksamhet, 2) kamratproblem, 3) skolproblem, 4) internaliserande problem (ångest/depression) problem, 5) antisocialt beteende, 6) alkoholmissbruk och 7) drogmissbruk.

Våra resultat visade att en högre nivå av ADHD-symptom i barndomen var associerat med mer hyperaktivitet/ouppmärksamhet vid 15 års ålder samt med mer psykosocial problematik. Detta gällde inte bara den screen-positiva gruppen, utan även den screen-intermediära gruppen (båda kön) rapporterade avsevärda psykosociala problem. Flickor uppgav dock mer internaliserande problem än pojkar oavsett ADHD-symptomnivå. Flickor som varit screen-positiva för ADHD uppvisade högre problemnivåer än de screen-positiva pojkarna för flera av de psykosociala utfallen och särskilt gällande drogmissbruk. Liknande resultat

observerades också för screen-intermediära flickor jämfört med screen-intermediära pojkar. Våra slutsatser blev att fynden stödjer uppfattningen att ADHD-symptom, såväl som deras associerade negativa psykosociala utfall, är normalfördelade i befolkningen och att flickor och pojkar uppvisar olika riskprofiler. Att ADHD-symptom är associerade med större risk för drogmissbruk hos flickor är värt att uppmärksamma. Detta skulle kunna motivera aktiva drogscreening-rutiner.

ADHD och internaliserande problem kan ofta förekomma samtidigt, kunskapen är dock bristfällig när det gäller mekanismerna kring hur internaliserande problem påverkas av samtidig ADHD från barndom till tonårstid. I **delarbete IV** undersökte vi hur internaliserande problem och ADHD i barndomen påverkade internaliserande problem i tonåren. Samma urval av svenska tvillingar som i delarbete III (totalt 4635 stycken) screenades för symptom på ADHD och internaliserande problem då tvillingarna var 9 eller 12 år gamla. Vi använde oss av en modell där vi kunde särskilja effekten av både gener och miljöfaktorer vid båda tidpunkterna. Vi fann ett samband mellan ADHD och internaliserande problem, där sambandet mellan ADHD och internaliserande problem i barndomen var lika starkt som sambandet mellan ADHD i barndom och internaliserande problem i tonåren. Gener och miljöfaktorer som var unika för just internaliserande problem i tonåren hade dock ett större inflytande än gener och miljöfaktorer som delades med ADHD och internaliserande problem i barndomen. Vi hittade vissa könsskillnader i sambandet mellan ADHD i barndomen och internaliserande problem i tonåren. Hos flickor fanns ett genetiskt överlapp mellan ADHD och internaliserande problem, vilket tyder på att flickor med ADHD-symptom i barndomen har en högre risk för att utveckla internaliserande problem i tonåren. Vi kunde inte se ett motsvarande samband hos pojkar. Den här studien belyser att sambandet mellan ADHD och internaliserande problem är komplext och det finns ett behov av mer kunskap kring detta.

Sammanfattningsvis kom denna avhandling fram till att:

- A-TAC är ett tillförlitligt instrument för att screena för neuropsykiatriska svårigheter över tid. A-TAC har goda till utmärkta psykometriska egenskaper, med en utmärkt förmåga att urskilja neuropsykiatrisk problematik från icke-neuropsykiatrisk tre till sex år efter screeningen.

- Symptom på neuropsykiatriska funktionshinder eller annan psykisk ohälsa vid 9 eller 12 års ålder var associerat med en mer problemtyngd tonårsutveckling. Oberoende av annan samsjuklighet var ADHD-symptom vid 9 eller 12 års ålder den mest betydelsefulla riskfaktorn för utveckling av antisocialt beteende och nedsatt daglig funktionsnivå i denna studie.

- ADHD-symptom såväl som deras associerade negativa psykosociala utfall är dimensionellt fördelade i befolkningen, och flickor och pojkar uppvisar olika riskprofiler. Att ADHD-symptom är associerade med större risk för drogmissbruk hos flickor är värt att uppmärksamma. Detta skulle kunna motivera aktiva drogscreening-rutiner.

- Vi fann ett samband mellan ADHD och internaliserande problem. Gener och miljöfaktorer som var unika för just internaliserande problem i tonåren hade dock ett större inflytande än gener och miljöfaktorer som delades med ADHD och internaliserande problem i barndomen. För flickor fanns det ett genetiskt överlapp mellan ADHD och internaliserande problem, vilket tyder på att flickor med ADHD-symptom i barndomen har en högre risk att utveckla internaliserande problem i tonåren.

Illustration by Bengt Gullbing

LIST OF SCIENTIFIC PAPERS

I. Larson T, Lundström S, Nilsson T, Selinus EN, Råstam M, Lichtenstein P, Gumpert CH, Anckarsäter H, Kerekes N.
Predictive properties of the A-TAC inventory when screening for childhood-onset neurodevelopmental problems in a population-based sample
BMC Psychiatry 2013, 13:233

II. Selinus EN, Molero Y, Lichtenstein P, Larson T, Lundström S, Anckarsäter H, Gumpert CH.
Childhood Symptoms of ADHD Overrule Comorbidity in Relation to Psychosocial Outcome at Age 15: A Longitudinal Study.
PLOS ONE September 11, 2015, 1-18.

III. Selinus EN, Molero Y, Lichtenstein P, Anckarsäter H, Lundström S, Bottai M, Gumpert CH.
Childhood signs of ADHD and gender differences in adolescent outcomes.
(Manuscript)

IV. Selinus EN, Kuja-Halkola R, Rydell M, Molero Y, Lichtenstein P, Lundström S, Anckarsäter H, Gumpert CH.
Internalizing problems and ADHD: A longitudinal twin study of etiology and gender effects.
(Manuscript)

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
A-TAC	Autism-Tics, ADHD, and other Comorbidities inventory
AUC	Area Under receiver operating characteristic Curve
BIC	Bayesian Information Criterion
CATSS	The Child and Adolescent Twin Study in Sweden
CD	Conduct disorder
CGAS	Children's global assessment scale
DCD	Developmental coordination disorder
DOGSS	Developmental Outcomes in a Genetic Twin Study in Sweden
DOR	Diagnostic odds ratio
DSM	Diagnostic and Statistical Manual of Mental Disorders
DZ	Dizygotic
ED	Eating disorder
ESSENCE	Early symptomatic syndromes eliciting neurodevelopmental clinical examinations
FN	False negative
FP	False positive
ICC	Intra-class correlation coefficient
KIDDIE-SADS	Schedule for Affective Disorders and Schizophrenia for School-Age Children
LD	Learning disorder
MZ	Monozygotic
NDP	Neurodevelopmental problems
NPV	Negative predictive value
OCD	Obsessive compulsive disorder
ODD	Oppositional defiant disorder
PPV	Positive predictive value
PR	Parent-report

ROC	Receiver operating characteristic
SDQ	Strengths and Difficulties Questionnaires
SR	Self-report

1 INTRODUCTION

1.1 NEURODEVELOPMENTAL PROBLEMS (NDP)

Childhood neurodevelopmental problems affect around 10% of all children (C. Gillberg, 2010). Included among the NDPs are attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), tic disorder (TD), learning disorder (LD), and developmental coordination disorder (DCD). ADHD is the most common disorder, with a prevalence ranging between 5 and 10%, while the prevalence of ASD is between 1% and 2.6 % (Baird et al., 2006; Idring et al., 2012; Kim et al., 2011). Around 1.5% of the children meet the criteria for LD (C. Gillberg & Soderstrom, 2003; Landerl & Moll, 2010), and 1% to 6.6% are considered to have TD (Bitsko et al., 2013; Cubo, 2012; Khalifa & von Knorring, 2003; Walkup, Ferrao, Leckman, Stein, & Singer, 2010). Finally, DCD has a prevalence of around 5% (Kadesjo & Gillberg, 1999; Kirby, Sugden, & Purcell, 2014)). The presence of neurodevelopmental problems often means a higher risk of functional and psychosocial problems, increased mortality and risk for mental health problems and often require lifelong interventions (Biederman, Faraone, et al., 2006). Children with NDPs often need a wide selection of interventions from medical and social services, sometimes life-long (Biederman, Faraone, et al., 2006). Studies that have investigated psychosocial problems in other NDPs than ADHD are rather scarce (Gilmour, Hill, Place, & Skuse, 2004; Kanne, Christ, & Reiersen, 2009). The few studies examining associated problems of ASD, LD, TD, and DCD, have focused on psychiatric comorbidities (Piek, Barrett, Smith, Rigoli, & Gasson, 2010; Simonoff et al., 2013), academic difficulties (St Clair, Pickles, Durkin, & Conti-Ramsden, 2011; Westendorp, Hartman, Houwen, Smith, & Visscher, 2011), and peer victimization (Tseng, Howe, Chuang, & Hsieh, 2007; Twyman et al., 2010). Less attention has been paid to antisocial behavior and substance misuse (Gaub & Carlson, 1997; Lundstrom et al., 2014). Most studies to date are restricted by small samples, short-term follow-up or cross-sectional data (Einarsson, Sigurdsson, Gudjonsson, Newton, & Bragason, 2009; Siponmaa, Kristiansson, Jonson, Nyden, & Gillberg, 2001).

Children with one NDP diagnosis often show comorbidity with other NDP diagnoses (Hurtig et al., 2007; Reiersen, Constantino, & Todd, 2008; Simonoff et al., 2008). It has also been shown that individuals drift between NDP diagnoses (C. Gillberg, 2010; Reiersen, 2011), suggesting that these diagnoses are not discrete disorders or syndromes.

NDP comorbidity is an important clinical feature, which might have implications for diagnosis and treatment. For example, individuals with comorbid NDPs can present a more severe form of the disorders (Anckarsater et al., 2011), and they can also have a poorer long-term prognosis (De Alwis et al., 2014; Reiersen, 2011). Few studies have taken NDP comorbidity into account when examining long-term outcomes, as most studies have examined outcomes of ADHD, ASD, LD, TD, and DCD separately. Given that NDPs are not entirely discrete disorders, NDP comorbidity needs to be taken into account both at baseline and at follow-up in longitudinal studies in order to understand its impact at different time-points. It is important to examine how NDP comorbidity influences a wide range of psychosocial outcomes, as different symptom profiles may be linked to different outcomes.

1.1.1 Psychiatric diagnoses

There are two classification systems used to differentiate between the different psychiatric conditions: The ICD-10, published by the World Health Organization, includes both somatic and psychiatric diagnoses (WHO, 1992). ICD-10 is the official system in Sweden for recording disease and mortality rates. The Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association (APA), is often used for research purposes and also commonly applied parallel to ICD-10 in clinical psychiatric practice in Sweden. The latest version, DSM-5 (APA, 2013), was published in 2013 but in this thesis the previous version, DSM-IV (APA, 2000) was used.

It is important to bear in mind that psychiatric diagnoses are criteria-based and descriptive. Hence, no assumption of etiology can be made based on such classifications. Criteria-based diagnoses have been criticized for relying solely on superficial symptoms, which may be subject to interpretation and/or cultural bias. Another criticism is the artificial divide between what is healthy or "normal" versus "pathological". Still, the systems are viewed as offering a common language and a means of standardizing complex conditions. Given its limitations, the demands on case ascertainment and symptom assessment in research are usually higher than in clinical practice.

1.1.2 ADHD

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder of childhood affecting between 5 and 10% of all children (Faraone, Sergeant, Gillberg, & Biederman, 2003; Kessler et al., 2006; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007), and often persisting throughout life (Barkley, 2002). Developmentally inappropriate symptom levels of inattention, hyperactivity, and impulsivity constitute the core symptoms of ADHD. The etiology is considered multifactorial with multiple genetic and environmental factors (Larsson, Anckarsater, Rastam, Chang, & Lichtenstein, 2012). ADHD is considered a major public health problem in view of its prevalence, and its' associated impairments and adverse outcomes.

Table 1 presents the symptoms of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) (APA, 2000). According to DSM-IV, individuals with ADHD have a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with their development or functioning. Based on the prominence of the types of symptoms, three subtypes of ADHD are defined: predominantly inattentive type, predominantly hyperactive-impulsive type, and combined type.

Table 1. The DSM-IV diagnostic criteria for ADHD

A. Either (1) or (2) or both:

(1). Six (or more) of the following symptoms of inattention have been present for at least six months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

1. Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
2. Often has difficulty sustaining attention in tasks or play activities
3. Often does not seem to listen when spoken to directly
4. Often does not follow through on instruction and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
5. Often have difficulty organizing tasks and activities
6. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
7. Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
8. Is often easily distracted by extraneous stimuli
9. Is often forgetful in daily activities

(2). Six (or more) of the following symptoms of hyperactivity/impulsivity have been present for at least six months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

1. Often fidgets with hands or feet or squirms in seat
2. Often leaves seat in classroom or in other situations in which remaining seated is expected
3. Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings or restlessness)
4. Often has difficulty playing or engaging in leisure activities quietly
5. Is often "on the go" or often acts as if "driven by a motor"
6. Often talks excessively

Impulsivity

7. Often blurts out answers before questions have been completed
8. Often has difficulty awaiting his/her turn
9. Often interrupts or intrudes on others (i.e., cuts into others' conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7

C. Some impairment from the symptoms is present in two or more settings (e.g. at school or work and at home).

D. There must be clear evidence of clinically significant impairment in social, academic or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

In DSM-5 (APA, 2013), some of the criteria have been changed; the symptoms must be present before the age of 12 (instead of age 7) and from the age of 17 years, 5 out of 9 criteria in each subgroup are required for a diagnosis (instead of 6 out of 9). These changes have been made based on the increasing knowledge base on ADHD, for example that some individuals develop symptoms later during childhood, and that the functional impairment may remain over time even though symptoms have declined.

1.1.3 NDPs, ADHD and long-term outcome

1.1.3.1 Comorbidity.

Comorbidity among the NDP diagnoses is common (Hurtig et al., 2007; Reiersen et al., 2008; Simonoff et al., 2008). Many children with ADHD also exhibit symptoms of ASD (Antshel, Zhang-James, & Faraone, 2013; Kotte et al., 2013; Matson & Cervantes, 2014; Reiersen, Constantino, Volk, & Todd, 2007; Ronald, Edelson, Asherson, & Saudino, 2010), TD may co-exist with LD, ASD and ADHD (Canitano & Vivanti, 2007; Ringman & Jankovic, 2000; Rizzo, Gulisano, Pellico, Cali, & Curatolo, 2014; Sturm, Fernell, & Gillberg, 2004), and LD, ADHD or ASD overlaps with DCD in up to 50% of the cases (Missiuna et al., 2014; Moruzzi, Ogliari, Ronald, Happe, & Battaglia, 2011; Polatajko & Cantin, 2005). Individuals may drift between NDP diagnoses, a circumstance that has led to the suggestion that the diagnoses should not be seen as discrete disorders but rather as spectrum disorders. Children with ADHD are at increased risk of displaying or developing a range of problems such as poor peer relationships, school failure, emotional difficulties, antisocial behavior, and substance misuse in adolescence (Biederman, Petty, Evans, Small, & Faraone, 2010; Biederman, Petty, O'Connor, Hyder, & Faraone, 2012; Elkins, McGue, & Iacono, 2007; Loe & Feldman, 2007; Molina & Pelham, 2003; Zulauf, Sprich, Safren, & Wilens, 2014). Children with ADHD are often more impaired in psychosocial, educational, and neuropsychological functioning as adults (Biederman, Faraone, et al., 2006). Most longitudinal studies of NDPs have focused on ADHD, and those that have examined long-term problems associated with ASD, TD, LD, and DCD, have focused on either psychiatric comorbidity (Piek et al., 2010; Simonoff et al., 2008), academic difficulties (St Clair et al., 2011; Westendorp et al., 2011), and peer victimization (Tseng et al., 2007; Twyman et al., 2010). Follow-ups focusing on substance abuse and antisocial behavior are less common (Anckarsater et al., 2011; Geluk et al., 2012; Lundstrom et al., 2014) in relation to these conditions.

1.1.3.2 Gender differences.

ADHD affects both boys and girls in all areas of functioning; academic, cognitive, psychosocial, and psychiatric (Bauermeister et al., 2007; Biederman, Ball, et al., 2008; Biederman et al., 2002; Biederman, Monuteaux, et al., 2006; Biederman et al., 2012; Disney, Elkins, McGue, & Iacono, 1999; Gross-Tsur et al., 2006; Hinshaw, Owens, Sami, & Fargeon, 2006; Mick et al., 2011; Nussbaum, 2012; Rucklidge, 2010; Washbrook, Propper, & Sayal, 2013; Yoshimasu et al., 2012). However, sex differences concerning the prevalence of ADHD are affected by many uncertain sources. Teachers have been found to be more prone to report ADHD symptoms in boys than in girls (Bauermeister et al., 2007; Staller & Faraone, 2006), often due to more hyperactivity symptoms. It has been suggested that many studies

4

that rely on clinical populations have overestimated ADHD in boys due to referral bias (Gaub & Carlson, 1997). Furthermore, the symptom criteria have been criticized for being more appropriate for boys than for girls. Girls have been found to be as impaired as boys, despite not filling all the diagnostic criteria (Smalley et al., 2007).

Girls with ADHD are more likely to display internalizing symptoms than are boys with ADHD (Biederman et al., 1994; Bussing, Mason, Bell, Porter, & Garvan, 2010; Levy, Hay, Bennett, & McStephen, 2005; Staller & Faraone, 2006). Girls with ADHD also display more externalizing symptoms, eating disorders (ED), and substance dependence than girls without ADHD (Biederman, Monuteaux, et al., 2006; Dalsgaard, Mortensen, Frydenberg, & Thomsen, 2014; Hinshaw et al., 2006). Prospective studies focusing on gender differences indicate that childhood ADHD may predict more steeply rising symptoms of anxiety and depression in girls than in boys during adolescence (Lahey et al., 2007). Most longitudinal studies of girls with ADHD, of which the majority are from North America, have used clinical samples and case-control designs.

1.1.3.3   Heritability.

Twin studies of liability for ADHD among children and adolescents have found strong genetic influences, with heritability estimates around 60-90% (Burt, 2009; Faraone et al., 2005), whereas both genetic and shared environmental influences seem to be important for internalizing problems (Ask, Waaktaar, Seglem, & Torgersen, 2015; McAdams et al., 2015). On the other hand, non-shared environmental influences like differential parental treatment, differential sibling interactions, and differences in peer characteristics seem to be important for explaining severity and comorbidity in children with ADHD (Buschgens et al., 2008). Environmental stressors can also have a causative effect on the emergence of internalizing disorders (Arseneault et al., 2008; Hicks, DiRago, Iacono, & McGue, 2009). Further, there is evidence that the co-occurrence of internalizing and externalizing (such as ADHD) psychopathology in adolescence results from both genetic and environmental influences (Cosgrove et al., 2011).

Longitudinal twin studies have suggested that continuity in ADHD-like traits (Chang, Lichtenstein, Asherson, & Larsson, 2013) and internalizing traits (Garcia et al., 2013) are mainly due to the same genetic effects involved over time. Developmental change in internalizing traits seems to be due to new genetic effects that emerge from childhood to young adulthood (Waszczuk, Zavos, Gregory, & Eley, 2014).

1.1.3.4   Subthreshold symptoms of ADHD.

To avoid the potentially artificial demarcation of a diagnostic cut-off, several studies have assessed the degree of core ADHD-symptoms rather than the clinical diagnosis. Such work indicates that subthreshold levels of ADHD also may be associated with negative outcomes such as poorer academic achievements, lower self-esteem, and relationship problems (for a review, see Balazs 2014) (Balazs & Kereszteny, 2014). Previous research on ADHD has also suggested that both ADHD diagnoses and subthreshold symptoms of ADHD are genetically linked (Larsson et al., 2012). A particular challenge for society lies in the fact that only children who are clinically assessed and diagnosed with ADHD may be entitled to care and

support, when those with subthreshold level symptoms would also benefit from such interventions.

1.2 THE CONCEPT OF PSYCHOSOCIAL HEALTH

The term 'psychosocial', which is defined as "relating to the interrelation of social factors and individual thought and behavior" (Oxford Dictionaries), is widely used in the literature in connection with health outcomes. It has been suggested that the root of this concept stems from the World Health Organization's definition of health as "a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity" (Martikainen, Bartley, & Lahelma, 2002)(p.1091). Thus, psychosocial health outcome implies the use of a broader perspective, focusing not only on the individual but also on how the individual relates to society.

It must be kept in mind that longitudinal studies focusing on psychosocial or other outcomes cannot determine causality, only associations. A number of factors influence individual health, many of which are not amenable to systematic assessment. Still, the need for prospective studies that assess the same individuals several times are of importance (Ruchkin & Schwab-Stone, 2003), in that they may increase our understanding of the development and dynamics of childhood psychopathology.

Given that the ADHD diagnostic criteria involve both behaviors, and an evaluation of whether these behaviors cause individual impairment, it is not surprising that many prospective follow-ups of ADHD have focused on psychosocial outcomes (Bauermeister et al., 2007; Biederman, Monuteaux, et al., 2006; Biederman, Petty, Dolan, et al., 2008).

Bellow is a description of some important aspects of psychosocial health.

1.2.1 Peer interaction.

To have and to develop good peer relations is of utmost importance for the growing and maturing child and adolescent. This is an important step in developing social skills needed throughout life. If this process is partially hampered or prevented, it might influence an individual's whole lifetime and future possibilities of having sound and healthy relationships. Being bullied in childhood or being the one who bullies others is one example of such negative peer interaction. Difficulties in peer functioning have been shown to predict future anxiety, global impairment, delinquency and cigarette smoking in adolescents with childhood ADHD (Mrug et al., 2012).

1.2.2 School performance.

A crucial aspect of growing up is participating in educational activities. Education is an important stepping-stone for gaining knowledge as well as establishing oneself in society, gaining self-esteem, and getting a sense of meaning with one's life. ADHD has been shown to be associated with increased risk of poor academic achievements and grade retention (Barbaresi, Katusic, Colligan, Weaver, & Jacobsen, 2007; Loe & Feldman, 2007), as well as a higher risk of not being employed fulltime as an adult (Biederman & Faraone, 2006).

1.2.3 Internalizing problems.

Internalizing problems is a collective term often used to describe emotional problems such as anxiety, depression as well as certain psychosomatic symptoms, for example headache and stomachache. Through assessment of an individual's symptoms of anxiety, depression and psychosomatic problems, it becomes possible to evaluate the burden these symptoms may cause in everyday life. Previous research has shown that girls with ADHD have a higher risk than controls to manifest mood and anxiety disorders (Biederman, Monuteaux, et al., 2006). To our knowledge, no previous study has explored gender differences in genetic and environmental contributions to internalizing problems in adolescence in a longitudinal twin design.

1.2.4 Antisocial behavior.

Antisocial behavior during adolescence may be viewed as the most severe sign of maladjustment in that it may indicate risk of future criminal behavior. Although many adolescents engage in acts that violate some societal norm, early onset of more severe antisocial behavior (e.g. violent acts) indicate worse outcomes (Odgers et al., 2008). Previous research has shown that girls with ADHD have a higher risk than controls to manifest oppositional defiant disorder (ODD) (Biederman, Monuteaux, et al., 2006), and that persistent ADHD in boys was associated with higher rates of ODD as well as conduct disorder (CD) compared with male controls (Biederman et al., 2010).

1.2.5 Alcohol or drug misuse.

Excessive use/misuse of alcohol, i.e. both binge drinking and/or frequent use of alcohol, may lead to the development of dependency (Viner & Taylor, 2007). Alcohol, as well as drug misuse, is also associated with antisocial behavior and violence (Compton, Thomas, Stinson, & Grant, 2007; Pulay et al., 2008). Children diagnosed with ADHD who have been followed-up in adolescence have reported higher levels of alcohol use than controls (Molina & Pelham, 2003). ADHD is also associated with an increased risk for substance use and abuse (Elkins et al., 2007; Zulauf et al., 2014).

1.2.6 Level of functioning.

Even if not all symptom criteria of a diagnosis are present, or not considered to be so severe, they may still cause impairment that is of significant importance in everyday life (Biederman et al., 2010; Biederman et al., 2012). Therefore, assessment of global functioning, e.g. how well one can perform daily activities such as getting out of bed, attending school, interacting with others, leading a 'normal' life may add important information. Measurement of functional levels has also proved valuable as a predictor of future outcomes (Lundh, 2012).

1.3 KNOWLEDGE GAPS

Yet, there are still knowledge gaps regarding the association between ADHD and psychosocial outcomes, and these include: 1) Failure to examine how comorbidity with other NDPs affects the longitudinal association between ADHD and several psychosocial

outcomes; 2) a paucity of population-based cohorts that include information on several NDPs, as most studies have been based on clinical samples and have focused on only one or few specific NDP diagnoses separately; 3) few studies have simultaneously examined a wide range of psychosocial outcomes in a population-based cohort, and; 4) most of the previous studies have been based on North American samples, and it is uncertain whether their results can be generalized to other cultural settings.

This thesis aims to address some of these knowledge gaps by: 1) Taking NDP comorbidity into account when examining the longitudinal association between ADHD and a wide range of psychosocial outcomes; 2) using a population-based cohort that includes information on several NDPs to provide a more comprehensive picture of how NDP symptoms, and their associated psychosocial consequences are distributed in the population; 3) choosing a broad span of psychosocial outcomes that represent several important aspects of an adolescent's life, and; 4) using a cohort of Swedish twins to represent a different setting and culture.

2 AIMS

The general aim of this thesis was to investigate how childhood symptoms of ADHD are associated with psychosocial outcomes in adolescent boys and girls in a population-based cohort.

Specific objectives:

1. To investigate the validity of the screening-interview A-TAC, specifically its diagnostic predictive properties (**Study I**).
2. To examine the association between childhood signs of ADHD and/or other NDPs (at age 9 or 12) and psychosocial outcomes at age 15 (**Study II**).
3. To examine if different levels of ADHD symptoms were differentially associated with psychosocial problems in adolescence with special attention given to gender differences (**Study III**).
4. To explore the relative contribution of genetic and environmental influences connected to both ADHD and internalizing problems in childhood to symptoms of internalizing problems in adolescence in boys and girls, respectively (**Study IV**).

3 MATERIAL AND METHODS

3.1 MATERIAL

3.1.1 The Swedish Twin Registry

The Swedish Twin Registry (STR) was established in the late 1950s' with the capacity to control for genetic liability for disease (Lichtenstein et al., 2002). At present it includes information on more than 95 000 twin pairs born in Sweden since 1886 (Lichtenstein et al., 2002; Magnusson et al., 2013).

3.1.2 The Child and Adolescent Twin Study in Sweden (CATSS)

The Child and Adolescent Twin Study in Sweden – CATSS - is an ongoing longitudinal, nation-wide twin study targeting all twins born in Sweden since July 1992. Two different sets of data from the CATSS are used in all four studies in this thesis [for a detailed description of the entire CATSS, see (Anckarsater et al., 2011)]. Since 2004, the STR has systematically invited parents of 9-year old twins (CATSS-9/12) to participate in a telephone interview regarding their children's somatic and mental health, and social environment. During the first three years of the study, parents of twins aged 12 years (born 1992-1994) were invited to participate; since then, the interview has been performed with parents of 9-year old twins. Part of the CATSS telephone interview consists of the Autism-Tics, ADHD, and other Comorbidities inventory (A-TAC). The A-TAC screens for a range of neuropsychiatric and other child psychiatric disorders (for further description, see below under Measures).

By September 2015, parental interviews for approximately 27 092 twins in CATSS were completed, with an overall response rate of 70%. An analysis of differences between non-responders and responders based on data from approximately 11 000 twins from CATSS demonstrated that non-responders more often belong to a low socio-economic stratum and have more neuropsychiatric problems such as ADHD and ASD (Anckarsater et al., 2011). The CATSS is currently the largest child psychiatric twin study in the world. For an overview of CATSS, see Figure 1. Several follow-ups and extensions have been initiated, such as a follow-up at age 15 and 18, and other cohorts with the aims to study more disease-specific questions (Magnusson et al., 2013).

3.1.2.1 *Zygosity determination.*

Zygosity in CATSS is determined by DNA (in saliva) or by using answers to questions about similarity such as "Are your twins like two peas in a pod, or more like siblings in general?", which have shown an accuracy of about 95% (Lichtenstein et al., 2002).

3.1.3 Study samples

3.1.3.1 CATSS-9/12 (Study I-IV)

Data collected in the CATSS telephone interview was used in each study (Study I-IV) in this thesis (baseline data collection). The twins were either 12 (1992-1994) or 9 (1995 and forward) years old at the time of the parent interview. Throughout the thesis, these datasets are referred to as CATSS-9/12.

3.1.3.2 Developmental Outcomes in a Genetic Twin Study in Sweden (DOGSS)
(Study I-II)

Families with one or two twins born 1993 to 1995, who were screen-positive (assessed by the A-TAC) for ADHD, ASD, LD, TD, DCD, CD, OCD, or ED in the CATSS-9/12 or who were selected as random controls, were contacted for the CATSS-15/ Developmental Outcomes in a Genetic Twin Study in Sweden (DOGSS) at twin-age 15. Only same-sex twin pairs were eligible to participate. The inclusion criteria were an A-TAC cut-off score based on previous validations (see below under Table 2) (Hallerod et al., 2010).

3.1.3.3 Sample and Response Rate in DOGSS.

Out of all twins born in Sweden 1993-1995, 7% of the children, and 13% of all the twin pairs, and an additional random sample of control twin pairs (5%, i.e. one out of 20 interviews), were included in the DOGSS study. In November 2008 (the 1995 birth cohort), the inclusion criteria had to be modified due to financial restraints and only included children who were screen-positive for ADHD and/or ASD, regardless of whether they indicated dysfunction or suffering, and controls. The selected cohort (i.e. the screen-positive subsample of the entire CATSS cohort) consisted of 860 twins eligible for inclusion in the DOGSS follow-up. The final sample consisted of 450 twins (participation rate 52%); 247 screen-positive for NDP and/or NDP related behavioral disorder (144 boys, 103 girls), 157 screen-negative (88 boys, 69 girls), and 46 randomly selected sex-matched controls (30 boys, 16 girls). There were 38 twin pairs where both twins were NDP-cases: 23 pairs of boys and 15 pairs of girls. For two subjects (included as co-twins) full A-TAC information was lacking, why they were not included in the study (Figure 1).
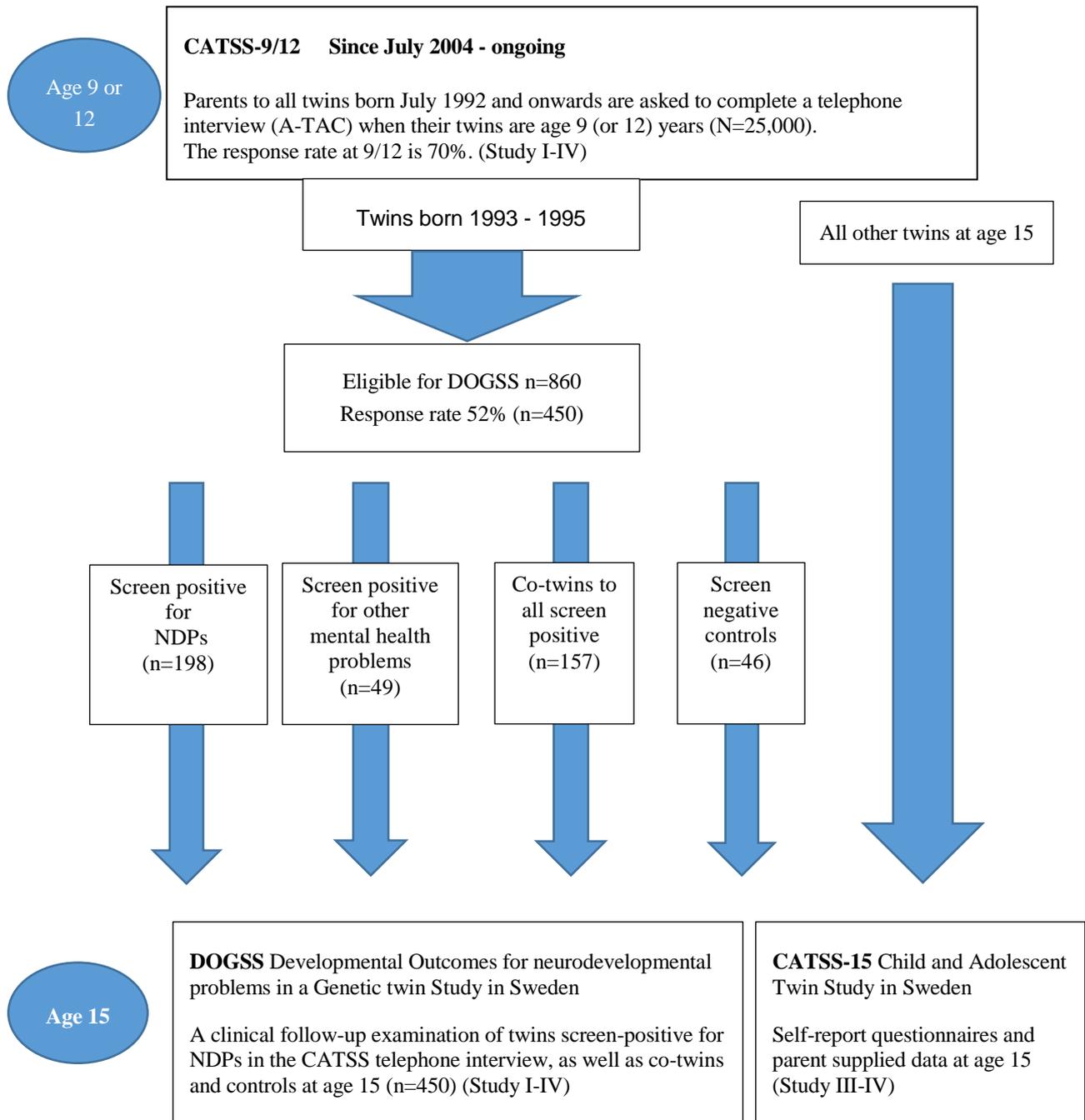
Figure 1. Study I-II: Flow-chart of the Child and Adolescent Study in Sweden (CATSS)/ DOGSS.

Representativeness of the sample

An analysis of the attrition to the DOGSS cohort shows that the attrition group included fewer girls, more ADHD screen-positive children, and that parental education levels were lower (Table 2).

Table 2. Descriptive statistics. Comparison of frequencies in the DOGSS cohort and the attrition cohort.

		DOGSS cohort (N=450)	Attrition cohort (N=410)	*P**
Sex	Girls	41.8 %	31.7 %	<0.001
Screen-positives	Cases (NDP+non-NDP)	54.9 %	58.5 %	0.28
ADHD	ADHD screen-positive	21.1 %	30.0 %	<0.001
Screen-negatives	Screen-negative cotwin	34.9 %	32.7 %	0.38
	Screen-negative control	10.2 %	8.8 %	0.47
Parental education level[A]	Both parents have primary school or less (9 years of school)	3.1 %	0.5 %	0.01
	At least one of the parents has secondary school (10-12 years)	35.6 %	41.2 %	0.04
	At least one parent with university studies or equivalent	39.1 %	35.1 %	0.24

Note: Missing information on 22.2% of the DOGSS cohort, and 23.2% of the attrition cohort.

* P value for comparison of distribution of qualitative variables between the DOGSS cohort and the attrition cohort with a Chi-square test

[A] Parental education level: A combination of both parents' education levels.

3.1.3.4 CATSS-15 (Study III-IV)

At twin age 15, all former participants in the CATSS study are invited to participate in a questionnaire-based follow-up; the CATSS-15. The CATSS-15 consists of written questionnaires for both parents and twins. Data from these surveys were used for Study III-IV, and were based on a cohort of 4635 twins (2252 boys and 2383 girls) who were born between 1993 and 1997. Thus, these participants had responded to both the initial telephone interview at 9/12 and the follow-up questionnaire at age 15. The follow-up questionnaires were the same as those used in the DOGSS cohort, and information from those who participated in the DOGSS study was also included in the analysis (i.e. twins born 1993-95, assessed at baseline to be screen-positive for an NDP). Figure 2 describes the cohort from CATSS-15 used in studies III and IV. We included only families who had participated in both the baseline interview and the follow-up questionnaire, leaving a response rate of 44%.
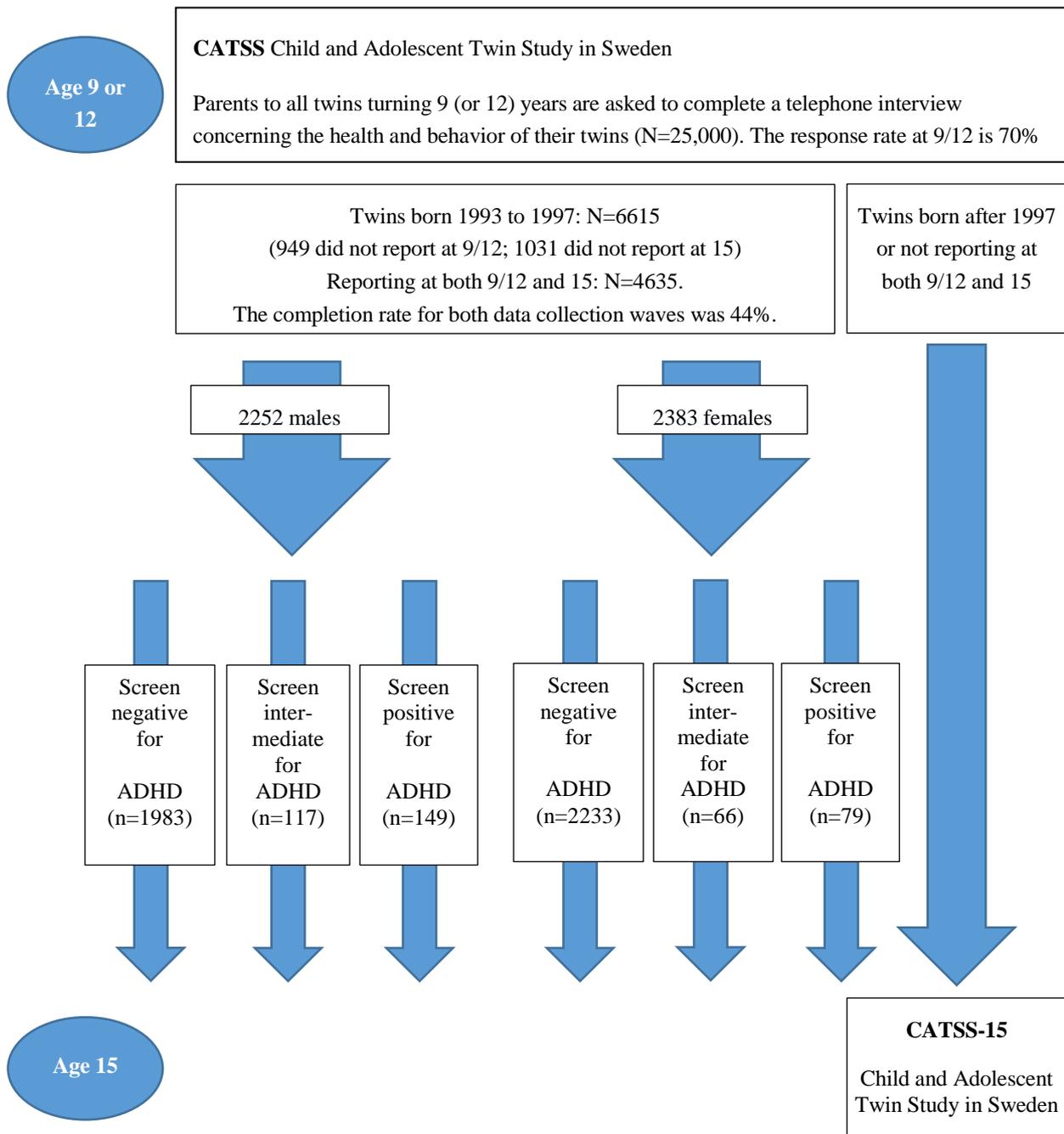
Figure 2. Study **III-IV**: Flow-chart of the Child and Adolescent Study in Sweden (CATSS).

Note: The same cohort and number of twins were included in both Study III and IV, but for Study III only, they were also categorized according to level of ADHD-symptoms.

3.2 MEASURES

3.2.1 Measures at baseline (age 9/12)

The autism-tics, ADHD and other comorbidities inventory (A-TAC) (Study I-IV)

The A-TAC is an open access instrument for researchers and clinicians. The original Swedish version has so far been translated into English, French, and Spanish. The English version is available at the BMC Psychiatry website (http://www.biomedcentral.com/bmcpsychiatry). At baseline (i.e. CATSS 9/12) investigators from a market research company ("Intervjubolaget") who have all been trained in using the computerized version of the A-TAC inventory administer the telephone interview. The interviewers do not have previous clinical training. The average interview time for the A-TAC in the CATSS is about 30 minutes. There are currently several established clinical instruments and rating scales to assess NDPs. The special feature of A-TAC however, is that it is administered as a telephone interview, thus nullifying the impact of geographical distances. It is also easily administered and covers the whole field of developmental disorders. The A-TAC is unique in its systematic assessment of all major overlapping and/or associated problem areas in child and adolescent psychiatry without letting the mutual exclusion criteria of the DSM obscure the overlap between problems. It is structured in separate modules and taps into different problem areas without diagnostic hierarchies. It presents not only dimensional scores of symptoms, but also the parent's perception of the child's suffering and dysfunction for a broad range of neurodevelopmental and psychiatric disorders, including ADHD, ASD, LDs, TDs, and DCD. It is structured and validated for administration by lay assessors as well as by clinicians. Unlike other instruments, it is validated for use over the telephone (Hansson et al., 2005).

The A-TAC inventory has shown good test-retest measures (Larson et al., 2014), excellent inter-rater reliability and construct validity (Hansson et al., 2005; Larson et al., 2010), and convergent validity with the Child Behaviour Check List (Hallerod et al., 2010). The Hansson et al study from 2005 showed excellent screening properties for ASDs and ADHD in a clinical sample. Hansson et al. found that *Areas under Receiver Operating Characteristics* curves (AUC; for a description of AUC, see Methods p.32) between interview scores and clinical diagnoses were approximately 0.90 for ADHD and ASD and above 0.70 for TD, LD, and DCD. Using optimal cut-off scores for ASD and ADHD, good to excellent kappa levels for interviews and clinical diagnoses were noted. Larson and colleagues replicated these results in 2010 (Larson et al., 2010) and screening cut-off scores for ASDs, ADHD, DCD, LD and TD, had sensitivities (sensitivity refers to an instrument's capacity to identify all individuals with a disorder) above 0.90 (0.95 for ASD and ADHD). Cut-off scores to identify proxies to clinical diagnoses had specificities (specificity refers to an instrument's capacity to rule out all individuals without a disorder) above 0.90 (0.95 for ASD and ADHD). Previous concurrent validations of the A-TAC generated *Receiver over characteristic* (ROC) curves for interview scores as predictors of clinical diagnoses were around 0.95 for most disorders, including ASD, ADHD, TD, DCD, and LD, indicating excellent screening properties (Larson et al., 2010). In Study I-IV, earlier validated cut-offs in A-TAC for NDPs were used (Hallerod et al., 2010; Hansson et al., 2005; Larson et al., 2010).

3.2.2 Measures at follow-up (age 15)

The DOGSS follow-up protocol (Study I, II)

Subjects participating in the DOGSS were assessed through a clinical examination at one of four sites: two locations in Stockholm, one in Malmö and one in Gothenburg. Two independent raters (experienced clinical psychologists) assessed case as well as control families. The raters were blind to the previous screening results and performed their assessments independently, following a structured assessment scheme. The protocol included the Schedule for Affective Disorders and Schizophrenia for School-Age Children: Kiddie – SADS – Present and Lifetime Version (Kaufman, Birmaher, Brent, Ryan, & Rao, 2000), and Wechsler Intelligence Scale for Children (Wechsler, 2003). In addition, the participants (twins and parents) had filled out several self-assessment forms, and records from previous contacts with the health care system were collected. As the final step, the results of the psychiatric diagnostic interviews were validated by a senior child psychiatrist (Eva Norén Selinus, author of this thesis) together with the rater, and compared with lifetime medical records (Table 3).

Table 3. Instruments included in the protocol of the Developmental Outcomes Genetic Twin Study in Sweden (DOGSS) used in the clinical assessment (Study I, II)[1]

Neurodevelopmental problems (based on examinations of parent & child)	Asperger Syndrome Diagnostic Interview (C. Gillberg, Gillberg, Rastam, & Wentz, 2001) Autism Diagnostic Interview (Lord, Rutter, & Le Couteur, 1994) Paris Autism Research International Sib pair study protocol (P.A.R.I.S proforma) (C. Gillberg, Coleman, M., 2000)
Clinical diagnoses (based on examinations of parent & child)	Kiddie-SADS-Present-Lifetime (Kaufman et al., 2000)
Psychosocial functioning (expert rating)	Children's Global Assessment Scale (C-GAS) (Shaffer et al., 1983)
Neurocognition (test of children)	Wechsler Intelligence Scale for Children (WISC-IV) (Wechsler, 2003) Qb-test (Bergfalk, 2006)

[1]Note: The scales used for self-and parent report in both DOGSS and CATSS-15 are listed below in Table 4.

CATSS-15

For the CATSS-15 follow-up, all families who previously had participated in the CATSS baseline interview (CATSS 9/12) were invited to participate. When twins were 15 years old, the twins and their parents were invited (by letter) to answer questionnaires about different aspects of mental health and lifestyle (two versions; parent- and self-report). The protocol used in CATSS-15 was the same as the one used in the DOGSS study (i.e. along with the clinical assessment in DOGSS). The list of outcome measures and scales in study II-IV is presented in Table 4.

Table 4. Diagnostic and Psychosocial outcomes in study I-IV (self- and parent report).

	Study I	Study II	Study III	Study IV
Diagnostic outcomes: ASD, ADHD, LD, TD, DCD	DSM-IV diagnoses according to K-SADS	--	--	--
Peer problems	--	SDQ Peer subscale (PR, SR) Being bullied (SR) Bullying (SR)	SDQ Peer subscale (PR, SR) Being bullied (SR) Bullying (SR)	--
School problems	--	Truancy (SR) Repeated school-year (PR) Failure in grades (PR)	Truancy (SR)	--
Internalizing problems	--	SDQ Emotion subscale (PR, SR)	SDQ Emotion subscale (PR, SR)	SDQ Emotion subscale (PR) (continuous scale)
Antisocial behavior	--	SDQ Conduct subscale (PR, SR) K-SADS diagnosis of CD Non-violent and violent criminal acts (SR)	SDQ Conduct subscale (PR, SR) Non-violent and violent criminal acts (SR)	--
Alcohol misuse	--	Alcohol intoxication (SR) Alcohol last month (SR)	Alcohol intoxication (SR) Alcohol last month (SR)	--
Drug misuse	--	Tried at least 1 illicit drug (SR)	Tried at least 1 illicit drug (SR)	--
Psychosocial impairment		Cut-off CGAS≤60 Yes/no	--	--
Hyperactivity/inattention		--	SDQ Hyperactivity subscale (PR, SR)	--

Note: PR = Parent Rated; SR = Self Rated

Strengths and Difficulties Questionnaires (SDQ)

The Strengths and Difficulties Questionnaires (SDQ) (Goodman, 2001) is a well-known, frequently used instrument in research, that can be completed in five minutes by parents, teachers and/or children for assessing psychological problems and prosocial behaviors among children aged 3–16 years. A unique aspect of the SDQ is that it assesses both problems and strengths in the child. SDQ consists of five subscales: hyperactivity/inattention, emotional, conduct, prosocial, and peer, with five questions in each subscale.

Self-Report Questionnaire on bullying, criminality, and substance misuse

All 15–year-old twins are invited to complete self-report questions on bullying, criminal acts, and alcohol and substance misuse. These questions are retrieved from two self-report measures: Olweus Bully Victim Questionnaire (Solberg & Olweus, 2003), and Self-reported delinquency (Elliot, Huizinga, & Ageton, 1985; Junger-Tas & Marshall, 1999; Junger-Tas, Terlouw, & W., 1994; Ring, 2000), and they are included in a questionnaire along with the self-report SDQ questions.

3.3 STATISTICAL METHODS (STUDY I-IV)

Statistics used in this thesis are presented in Table 5. Statistical analyses were performed in SPSS, STATA 12 and 13 (Rabe-Hesketh & Everitt, 2007) and R.

Table 5. An overview of statistical methods used in the different studies.

Study	I	II	III	IV
Receiver operating characteristic (ROC)	X			
Diagnostic Odds Ratio (DOR)	X			
Chi-square test		X		
Logistic regression		X	X	
Twin design				X

3.3.1 Study I

The A-TAC scores from the CATSS-9/12 were used as independent predictors, while the clinical diagnoses from the follow-up at 15 (CATSS/DOGSS) were used as dependent variables. To determine the optimal cut-off values, plotting sensitivity and specificity on receiver operating curve (ROC) can be helpful. On a ROC-curve, the true positive rate (sensitivity) is plotted against the false positive rate (1-specificity) for every possible threshold of the instrument (Figure 3). The ultimate instrument will have a cut-off value that gives both a sensitivity of 1 (100% identification of true cases) and a specificity of 1 (100% exclusion of non-cases). The score coming closest to that point determines the cut-off value. All inventories have ROC curves between two extremes, and the greater the area under the curve (AUC) is, the more ideal is the instrument. This means that an AUC of 0.50 reflects random prediction, an AUC of 0.60-0.70 indicates poor validity, 0.70-0.80 is fair, 0.80-0.90 is good, and AUC>0.9 shows excellent validity (Tape, 2004). The A-TAC cut-off values were determined and validated in earlier studies (Hansson et al., 2005; Larson et al., 2010), and used to assign screening-status from the A-TAC scores.

First, we compared the number of screen-positive children with a neurodevelopmental diagnosis identified in the screening at 9/12 to the number of children given a diagnosis in the assessment at follow-up three years later. Secondly, predictive psychometrics were calculated: a) Areas under receiver operating characteristic curve (AUCs); b) measures of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic odds ratio (DOR); using both the low cut-off (best for screening) and the high cut-off (as a proxy for clinical diagnosis), both cut-offs established in an earlier study (Larson et al., 2010). PPV is the ability of an instrument to correctly identify children who really have a

disorder, and NPV is its ability to identify the ones without the disorder. The DOR of a screening test is the ratio of the odds of those correctly identified with the disorder (screen-positive) to the odds of the ones without the disorder incorrectly being screen-positive in the test. The value of the DOR ranges from zero to infinity, where higher values indicate better discriminatory test performance. The DOR rises steeply when sensitivity and specificity come closer to perfect (Glas, Lijmer, Prins, Bonsel, & Bossuyt, 2003; Scott, Greenberg, & Poole, 2008).
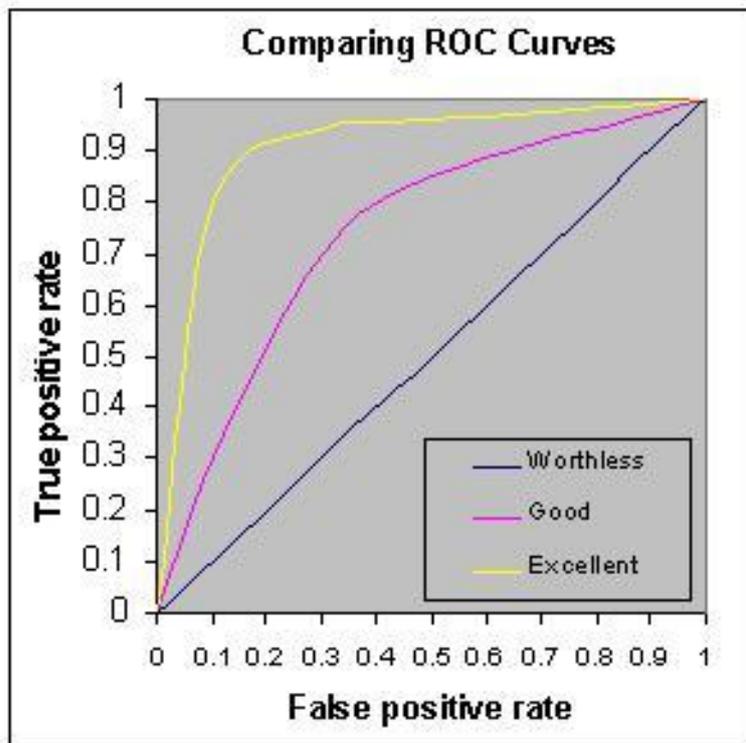
Figure 3. Graph showing three ROC curves. A perfect test has an Area Under ROC (AUC) of 1.0. The chance diagonal has an AUC of 0.5. Tests with some discriminating ability have AUCs between these two extremes. (By Thomas G. Tape, MD University of Nebraska Medical Center)

3.3.2 Study II

Frequencies for all seven psychosocial outcomes in adolescence were calculated, both for the whole cohort, for each baseline screen diagnosis, for screen-negative siblings, and screen-negative random controls. We distinguished between non-violent and violent antisocial behavior in a separate descriptive sub-analysis. Finally, we analyzed all cases and controls calculating the odds of each negative psychosocial outcome. The predictor of main interest was ADHD, with or without co-existing other NDPs and non-NDPs at baseline. The association between ADHD and each outcome was modeled with logistic regression, controlling for co-existing ASD, LD, TD, DCD, ODD, CD, OCD, and ED. In addition to this, we controlled for parental education level. Finally, since several correlated twin-pairs were included in the analysis, a robust sandwich estimator was used to adjust for the correlated data. The estimated associations are reported as odds ratios (OR) with 95% confidence intervals (CI).

3.3.3 Study III

The prevalence of the seven outcomes in adolescence was calculated for each ADHD symptom level, both for the genders combined and separately. The crude association between ADHD symptom level and each of the seven outcomes was modeled with logistic regression, also including the interaction between ADHD and gender. We also performed analyses adjusting for other baseline co-existing NDP and non-NDP diagnoses. These diagnoses were: ASD, LD, TD, DCD, ODD, CD, OCD, and ED. All regression models included: ADHD as a numeric predictor (0=screen-negative, 1=screen-intermediate, 2=screen-positive), gender (0=boy, 1=girl), and the interaction term between gender and ADHD. A cluster robust sandwich estimator was applied to adjust for the within twin-pair dependence when calculating CIs and p-values. The associations were reported as odds ratios (OR), separately for boys and girls. All p-values less than 0.05 were considered statistically significant.

3.3.4 Study IV

We explored the phenotypic association between ADHD and internalizing problems using linear regression. The predictors were *ADHD symptoms at 9/12* and *internalizing problems at 9/12* and the outcome variable was *internalizing problems at 15*. Both the predictors and the outcome variable were standardized to have mean 0 and standard deviation 1. First, we performed an analysis where each predictor was included separately and adjusted for sex. This analysis was performed stratified on sex to test whether estimates differed significantly between sexes. Then we included both predictors in one model and performed the same analyses as in the first step. Dependencies between twins were accounted for by using a cluster robust sandwich estimator for the standard errors.

The classic twin design compares the phenotypic resemblance between Monozygotic (MZ) and Dizygotic (DZ) twins, where MZ twins are genetically identical while DZ twins share on average 50% of their segregating genes. The design makes it possible to decompose the total variance of a specific phenotype into three latent variables: additive genetic (A), shared environmental (C), and non-shared environmental (E) effects (Figure 4). Shared environmental effects refer to environments that increase similarity within a twin-pair (the same for MZ and DZ twins), whereas non-shared effects refer to environments that make twins different from each other, including measurement errors (Plomin, 2013).
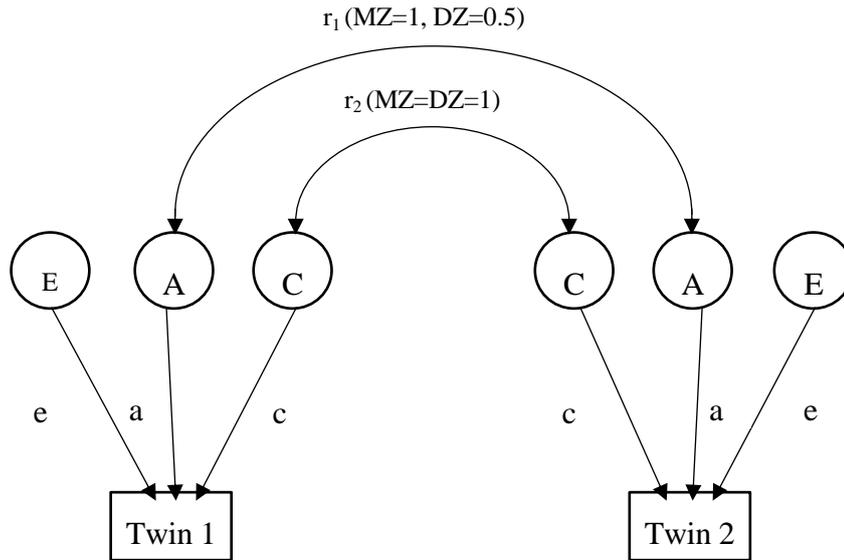
Figure 4. The Classic ACE twin model for one phenotype. r_1: genetic correlation; r_2: shared environmental correlation. Variables in shape of a square are observed variables, while circular shapes describe latent variables (non-measured values). Single headed arrows from latent to observed variables represent causal pathways, while a double headed arrow describes the covariance between two variables. The model assumes that the genetic correlation (r_1) is 1.0 between MZ pairs and 0.5 between DZ pairs. The shared environmental correlation (r_2) is set to 1.0 (MZ and DZ twin pairs are assumed to experience the shared environment to the same degree), and the correlation between non-shared environments is by definition 0.0. In addition, the model assumes that there is no co-variation between genes and environments and that there is no interaction between them.

Quantitative genetic analyses were used to estimate the relative importance of genetic and environmental factors for the variance in *internalizing problems at 15*.

Assumption testing: We fitted a series of models to the data and compared fit using the Bayesian Information Criterion (BIC) to assess appropriateness of data for quantitative genetic modeling. First, we fitted a saturated model where all parameters were allowed to vary freely across twin order, gender and zygosity. Second, we constrained the parameters to be equal across twin order, but allowed to vary across gender and zygosity. From this model, we estimated intra-class correlations and cross-twin cross-trait correlations with 95% profile likelihood CIs. For opposite sexed twins, means and within-individual variances and co-variances were allowed to differ between the male and the female twin, but the cross-twin cross-trait correlations were assumed to be equal within trait and gender. If all steps produced a smaller BIC, the data was acceptable for quantitative genetic analysis.

Quantitative genetic analyses: Since it was not possible for us to order the *ADHD symptoms at 9/12* and *internalizing problems at 9/12* measures temporally, we fitted a trivariate model. The trivariate model is a hybrid between the two most common parameterizations used in quantitative genetic modeling – the "correlated factors model" and the "Cholesky model" (Neale M., 2003). We used the correlated factors for *ADHD symptoms at 9/12* and

internalizing problems at 9/12, but their association with *internalizing problems at 15* followed the parameterization of a Cholesky model. We thus fitted models where A-, C-, and E- sources of variation in *ADHD symptoms at 9/12* and *internalizing problems at 9/12* were allowed to be correlated. In contrast to this, the association between *ADHD symptoms at 9/12* / *internalizing problems at 9/12* and *internalizing problems at 15* were modelled as the before mentioned A-, C-, and E-sources in variance (in *ADHD symptoms at 9/12* and *internalizing problems at 9/12*) explained the variation in *internalizing problems at 15*.

Furthermore, we allowed for A-, C-, and E-sources of variation unique for *internalizing problems at 15*. This made it possible for us to explain the variance in *internalizing problems at 15* using *ADHD symptoms at 9/12* and *internalizing problems at 9/12*, while adjusting for the correlation between *ADHD symptoms at 9/12* and *internalizing problems at 9/12*. Using the above setup, we fitted a series of models to see whether we could find a more parsimonious model than the model including A-, C-, and E-sources of variance, as well as quantitative and qualitative gender differences. Quantitative gender differences refer to allowing differences in the magnitude of explained variance and covariance by A-, C-, and E-sources in males and females. This is accomplished by letting male-male and female-female twin pairs estimate A-, C-, and E-parameters separately. Qualitative gender differences refer to allowing different genetic sources in males and females. This we can accomplish by allowing the female-male DZ twin pairs to have a lower covariation due to A-sources than expected from same-sex pairs (Neale, 2006). We then assessed fit of model by likelihood ratio tests. First, we fitted an ACE model with qualitative and quantitative gender differences. The ACE model indicates what proportion of variance in a trait is heritable (A), versus the proportions due to shared environment (C) or non-shared environment (E). Secondly, we omitted C in the model due to the fact that we expected minimal contributions of C. Thus, we fitted an AE model with qualitative and quantitative gender differences and tested whether this model explained the data significantly worse. Third, we used the previous result and fitted either ACE or AE models, first removing qualitative gender differences, then quantitative gender differences, and finally we fitted a model with no gender differences.

The model which most parsimoniously explained the data was then used to produce estimates of explained variance in *internalizing problems at 15*.

4 ETHICAL ASPECTS

Ethical aspects

All studies in this thesis had ethics approval. The CATSS-9/12 study had ethical approval from the Karolinska Institutet's Ethical Review Board No. 02-289, 03-672 and 2010/597-31/1; CATSS-15: No. 2009/739-31/5; DOGSS No. 03-672. All participants received written and oral information about the studies and they provided informed consent according to the ethical principles for medical research involving human subjects, developed by the World Medical Association (WMA) as part of the Declaration of Helsinki. Subjects were protected by the informed consent process, meaning they were informed of what type of data were to be collected and also that they could decline participation or cease participation at any time.

In the DOGSS study we were prepared to identify possible unmet health care and support needs among the participants. If the parents wished, they would get feedback and advice regarding their child. Also, if the research team came upon a child in need of support from the social services and/or police, the social services were contacted and informed about the case.

To protect the confidentiality and integrity of the participants in the studies in this thesis, all data was anonymized and the code keys were stored separately from the coded data. Analyses were performed using computer files that did not contain any identifying information.

5 RESULTS: SUMMARY OF FINDINGS

5.1 STUDY I

OBJECTIVE

In **Study I**, the aim was to validate the diagnostic predictive properties of the A-TAC interview.

METHODS

The study included NDP screen-positive twins from three birth year cohorts (1993-1995) in CATSS, along with their co-twins and randomly selected, healthy controls, who all were invited to a comprehensive clinical follow-up at age 15 ($N = 452$, participation rate 52%).

RESULTS

Sensitivity and specificity of the A-TAC scores for predicting later clinical diagnoses were good to excellent, with values of the area under the receiver operating characteristics curves ranging from 0.77 (ADHD) to 0.91 (ASDs). Among children who were screen-positive for an ASD at age 9/12, 48% received a clinical diagnosis of ASDs at 15. For ADHD, the corresponding figure was also 48%, for LDs 16%, and for TDs 60%. Between 4% and 35% of screen-positive children did not receive any diagnosis at the clinical follow-up three years later. Among screen-negative controls, prevalence of ASDs, ADHD, LDs, and TDs was 0%, 7%, 4%, and 2% respectively.

5.2 STUDY II

OBJECTIVE

The aim of **Study II** was to assess long-term psychosocial outcomes in adolescence associated with childhood NDPs, focusing on ADHD but considering other NDPs as well.

METHODS

We used the same cohort as in Study I: This included NDP screen-positive twins from three birth year cohorts (1993-1995) in CATSS, along with their co-twins and randomly selected, healthy controls, who all were invited to a comprehensive clinical follow-up at age 15 ($N = 450$, participation rate 52%, with two cases excluded due to incomplete data). The included psychosocial outcomes were peer problems, school problems, internalizing problems, antisocial behavior, alcohol misuse, drug misuse, and daily functioning.

RESULTS

Among the NDPs, antisocial behavior was the most common outcome across all NDP diagnoses. We performed a logistic regression which demonstrated that having been screen-positive for ADHD at 9/12 doubled the odds for school related and antisocial problems at age 15, and also increased the odds of risky alcohol use. Adjusting for ASD, LD, TD, DCD, and

also for ODD, CD, OCD and ED, did not change the odds substantially. When adjusting for parental education level, however, the significant association disappeared both for school problems and risky alcohol use, but remained for antisocial behavior. The significant association between ADHD and functional level remained in the adjusted model.

5.3 STUDY III

OBJECTIVES

The aim of **Study III** was to examine possible gender differences in psychosocial outcome at age 15. Moreover, we explored outcomes in relation to different levels of childhood ADHD symptoms.

METHODS

The CATSS-15 cohort from 1993-1997 was used for the follow-up. A sample of Swedish twins 9-12 years of age (*N*=4635) was screened for ADHD symptoms through a telephone interview with their parents. Participants were grouped into the following groups based on the degree of ADHD symptoms: screen-negative, screen-intermediate, and screen-positive. At follow-up (age 15), parents and teenagers completed questionnaires regarding: 1) ongoing hyperactivity/inattention, 2) peer problems, 3) school problems, 4) internalizing problems, 5) antisocial behavior, 6) alcohol misuse, and 7) drug misuse.

RESULTS

High levels of ADHD symptoms at age 9/12 were associated with high levels of hyperactivity and impulsivity at follow-up. After adjusting for baseline comorbidity, high levels of ADHD symptoms were also associated with higher probability for all outcomes in both genders, except for alcohol misuse in girls and drug misuse in boys. The results demonstrated a higher probability of the following outcomes among girls (but not boys) in the screen-positive group: peer problems, school problems (truancy), internalizing problems, and drug misuse. The probability of drug use was significantly higher in girls than in boys.

Girls reported more internalizing problems than boys across all ADHD symptom levels (OR: 1.50, 95% CI 1.20-1.87). Girls who had been screen-positive for ADHD displayed higher problem levels during adolescence than their male counterparts on several of the psychosocial outcomes, particularly for drug misuse (OR: 1.64, 95% CI 1.25-2.14).

In both genders, the screen-intermediate groups reported higher levels of psychosocial problems than the screen-negatives.

5.4 STUDY IV

OBJECTIVES

In **Study IV** we aimed to explore the association between ADHD and internalizing problems. Furthermore, we aimed to investigate the relative contribution of genetic and environmental influences to symptoms of ADHD and internalizing problems in childhood on symptoms of internalizing problems in adolescence, including gender differences.

METHODS

The CATSS-15 cohort from 1993-1997 was used for the follow-up. A sample of Swedish twins 9-12 years of age (*N*=4635) was screened for internalizing and ADHD symptoms through a telephone interview with their parents. At follow-up (age 15), parents completed questionnaires regarding internalizing problems in the adolescent. In the analyses, the internalizing problems at 15 were allowed to be influenced by ADHD and internalizing problems at the earlier age 9/12. The variance in internalizing problems at 15 was divided into effects of ADHD and internalizing at 9/12 and new effects at age 15. Each source was divided into additive genetic effects, shared environmental effects and unique environmental effects.

RESULTS

We found that the data was appropriate for quantitative genetic modeling. There was a positive correlation between ADHD and internalizing problems in both boys and girls. The strength of the associations between ADHD and internalizing problems at baseline (9/12) were similar to the corresponding associations between ADHD at baseline and internalizing at 15.

Higher correlations in MZ compared to DZ twins indicated a genetic influence in the phenotype (intra-class correlations), or in the covariation between phenotypes (cross-twin-cross-trait-correlations). The greatest difference was observed within the phenotypes (i.e. adhd-9, internalizing-9, or internalizing-15). Also, MZ twins consistently displayed higher cross-twin-cross-trait correlations than DZ. Boys and girls had a slightly different pattern of intra-class and cross-twin-cross-trait correlations.

We fitted the model including A, C and E sources of covariance, as well as both quantitative and qualitative gender differences. We could exclude the C source of covariance without the model explaining the data significantly worse. But nothing else could be excluded from the model, so the model with A and E-sources of covariance and quantitative and qualitative gender differences was the model that best fitted the data.

Quantitative genetic results – explained variance in internalizing-15

The fraction of the variance explained by genetic effects for internalizing-15 (A) was 30% for girls and 35% for boys. The contribution of genetic effects from adhd-9 and internalizing-9 differed between the genders. In girls, the genetic effect from adhd-9 explained 11% of the variance in internalizing-15, whereas in boys, the genetic effect from adhd-9 only 1% of the variance in internalizing-15. In both girls and boys, internalizing-9-adhd-9 (A) explained 3%

of the variance. Also, at age 15 new non-shared environmental effects accounted for a little more than half of the variation in internalizing problems at age 15 in both genders.

6 DISCUSSION

6.1 GENERAL DISCUSSION

The findings of this thesis show that the screening interview A-TAC can be used as a tool to identify future NDPs among children also over longer time intervals. Childhood signs of ADHD and other NDPs are associated with an increased risk of psychosocial problems in adolescence. Even after adjusting for comorbidity with other NDPs, screen-positivity for ADHD doubled or tripled the odds of later psychosocial problems. However, after adjusting for parental education level, the significant effect of ADHD remained only for antisocial behavior and impaired daily functioning. We could further show that increasing levels of ADHD symptoms in childhood were associated with more hyperactivity/inattention as well as more psychosocial problems in adolescence. Girls who had been screen-positive for ADHD displayed higher problem levels than their male counterparts on several of the psychosocial outcomes, particularly for drug misuse. Girls also reported higher levels of internalizing problems than boys at all ADHD symptom levels. The screen-intermediate groups (both boys and girls), reported higher levels of psychosocial problems than the screen-negatives. Finally, we found a positive association between ADHD and internalizing problems in both genders. The longitudinal analysis, though, suggested that symptoms of ADHD and internalizing problems in childhood explained the variance in internalizing problems in adolescent girls and boys to slightly different degrees. New genetic effects contributed with around 30% to internalizing problems at age 15 in both genders, and new non-shared environmental effects accounted for the most of the variation in internalizing problems at age 15.

A-TAC is a valid screening tool

In this follow up of a screen-positive sub-sample (DOGSS) from a nation-wide, longitudinal population-based study of twins (CATSS), the A-TAC once more showed excellent screening properties for ASDs (with a sensitivity of 70%, a specificity of >90%, and AUC = 0.91). These values are comparable to previously reported numbers for the diagnostic usability of the A-TAC in clinical samples for identifying ASDs. However, the instrument showed less accuracy than in previous concurrent validation studies when screening for other NDP diagnoses than ASDs (i.e. ADHD, TDs, and LDs). As compared with findings from previous validations (Larson et al., 2010) that yielded AUCs of >0.90 for ADHD, the present study yielded an AUC of 0.77 for ADHD. Considering the current study had a time interval of three years between baseline and follow-up, this may not be surprising. The finding supports previous research that has suggested that a substantial number of children with ADHD display different symptom profiles over the course of development. Either, they may grow out of it in the sense that they no longer meet the diagnostic criteria (Shaw et al., 2007), or the ADHD symptoms may transform into other mental health problems (Biederman et al., 2010; Hofvander, Ossowski, Lundstrom, & Anckarsater, 2009).

Almost no children who screened negative at baseline met diagnostic criteria for an NDP three years later, which was shown through the negative predictive values being consistently high (≥89%). In behavioral screening, a high rate of false positives is not uncommon. This

often gives low positive predictive values. Therefore high cutoffs have been identified to be used as proxies for clinical diagnoses in epidemiological studies.

Only relying on sensitivity and specificity to assess an instrument's capacity can be misleading. There is no simple way to combine sensitivity and specificity into one measure of performance. Here, a single indicator of the performance of an instrument, such as the DOR, can be most useful. In meta-analyses of diagnostic studies that combine results from different studies into summary estimates with increased precision, the DOR is a good measurement (Deeks, Macaskill, & Irwig, 2005).

A more dimensional and continuous distribution across diagnostic NDP categories has been reported in the general population (Anckarsäter & Gillberg, 2008). The concept of 'early symptomatic syndromes eliciting neuro-developmental clinical examinations' (ESSENCE) was created to describe this interrelatedness and coexistence of NDPs across diagnostic limits (C. Gillberg, 2010). As illustrated in **Study II**, the functional impairment may still remain.

This study shows that A-TAC is a useful broadband, first-level screening instrument in a study group that is population-based. A broader screening tool like A-TAC has the advantage of assessing all NDP associated symptoms, so that common conditions such as learning disabilities or language impairment are detected.

ADHD symptoms overrule comorbidity in relation to psychosocial adolescent outcome

The findings indicate that having being screen-positive for ADHD may double or triple the odds for later psychosocial problems, despite the comorbidity of other NDP symptoms. Many studies have reported findings of negative long-term consequences of ADHD (Barbaresi et al., 2007; Currie & Stabile, 2006; Fredriksen et al., 2014; Loe & Feldman, 2007) but research is lacking on outcomes in relation to a broader spectrum of neurodevelopmental problems. The association between ADHD and other externalizing disorders, such as ODD and CD has been studied previously (Biederman, Petty, Monuteaux, et al., 2008; Kuja-Halkola, Lichtenstein, D'Onofrio, & Larsson, 2014), and it is fairly established that there is a considerable overlap between ADHD and ODD or CD. However, the causal mechanisms are complex, and the view that ADHD precedes other externalizing disorders has been challenged in previous twin studies (Kuja-Halkola et al., 2014). In our study, having symptoms of ADHD was the strongest predictor of future antisocial behavior. It is important to note however, that our findings might have been influenced by the fact that there were few individuals who were screen-positive for diagnoses like CD at age 9 or 12. This could have underestimated the impact of early externalizing behaviors in our study.

Other studies have also focused on the impact of socioeconomic factors concerning both prevalence and outcomes of ADHD (Currie & Stabile, 2006; Fried et al., 2013; Galera et al., 2013). When we added a contextual factor to our analysis (parental education level), antisocial behavior and impaired daily functioning were the only negative outcomes of ADHD that remained significant. Other studies have also found associations between ADHD and socioeconomic factors: For example, Larsson and colleagues found a dose-dependent association between lower family income and the risk of having a child diagnosed with ADHD (Larsson, Sariaslan, Langstrom, D'Onofrio, & Lichtenstein, 2014). In another follow-up of ADHD youth, Fried et al. concluded that even if ADHD was the strongest predictor for

academic underachievement, social class and IQ were also significant predictors of high school dropout or repeated grade (Fried et al., 2013).

Different gender profiles in adolescent outcome

In **Study III**, higher levels of ADHD symptoms during childhood were associated with more ADHD symptoms during adolescence. Given that the A-TAC interview showed good predictive validity for ADHD, this was not surprising (Hallerod et al., 2010; Hansson et al., 2005; Larson et al., 2010; Larson et al., 2013). Our finding that girls and boys reported somewhat different problem profiles also replicates results from previous longitudinal follow-ups. Girls displayed higher levels of internalizing problems than boys on all ADHD symptom levels, similar to findings from another study using a Swedish population-based sample (Bremberg & Dalman, 2015). Higher rates of internalizing problems in girls with ADHD have been reported earlier in a number of studies, both clinical and population-based studies (Bauermeister et al., 2007; Biederman, Ball, et al., 2008; Cho et al., 2009; Chronis-Tuscano et al., 2010; Hinshaw et al., 2012; Jensen & Steinhausen, 2015; Novik et al., 2006; Yoshimasu et al., 2012). ADHD symptoms seem to contribute in a gender-specific way to the total internalizing problem load (Baldwin & Dadds, 2008). The results in our Study IV further support this, given that the association between ADHD and internalizing symptoms remained significant for girls, however not for boys, once comorbidity was considered.

Two meta-analyses (Charach, Yeung, Climans, & Lillie, 2011; Lee, Humphreys, Flory, Liu, & Glass, 2011) have shown that children diagnosed with ADHD have a higher risk for developing substance use disorder compared to children without ADHD. The Lee study adjusted for gender, but could not find any significant gender interaction effects. In contrast to our study, both of these studies used study groups with samples of clinically confirmed ADHD.

Cultural differences may explain part of this difference; in Sweden, alcohol use may be more prevalent among girls than boys (CAN, 2014), which may explain the lack of a particular association between ADHD and alcohol misuse in girls. In a population-based Swedish study though, Lövenhag et al. found that symptoms of inattention were independently associated with alcohol use among girls, even when antisocial behavior was adjusted for (Lovenhag, Larm, Aslund, & Nilsson, 2015). Since we did not analyze the associations of the subdimensions of ADHD symptoms (inattention, hyperactivity, and impulsivity) in relation to outcomes in our studies, we cannot exclude the possibility of similar associations in our cohorts. In contrast, the results demonstrated a positive association between a high degree of ADHD symptoms and drug misuse in girls, which was significantly stronger than the corresponding association in boys. A higher risk of drug misuse among ADHD girls than among ADHD boys is in line with findings from previous follow-up studies of clinical samples (Biederman, Monuteaux, et al., 2006; Dalsgaard et al., 2014), as well as in population-based ADHD samples (Disney et al., 1999). Thus, there are numerous studies indicating a higher risk for substance abuse and dependence in girls with ADHD as compared with boys with ADHD, as well in comparison with girls without ADHD.

Previous research has also found associations between subthreshold levels of ADHD and negative outcomes (Balazs & Kereszteny, 2014; Bussing et al., 2010; Faraone, Kunwar, Adamson, & Biederman, 2009; Hong et al., 2014; Malmberg, Edbom, Wargelius, & Larsson, 2011; Mick et al., 2011; Shankman et al., 2009). In our study, both boys and girls in the screen-intermediate group displayed a higher degree of problems compared to participants in the screen-negative group. Interestingly, for some outcomes, participants in the screen-intermediate group demonstrated almost as high degree of psychosocial problems as their screen-positive peers. Some earlier studies have suggested that a subthreshold level of ADHD symptoms is a potential risk factor for maladjustment (Balazs & Kereszteny, 2014). It has been pointed out that despite this risk, children with subthreshold symptom levels are not likely to get support to the degree they need (Bussing et al., 2010). A strong argument for also taking subthreshold ADHD levels into account are the findings that a majority of children with psychiatric conditions are at risk of developing the equivalent full psychiatric syndrome in adulthood (Shankman et al., 2009).

ADHD and internalizing problems

Our finding of a positive correlation between ADHD and internalizing problems in both genders in **Study IV**, is in line with an earlier study of adolescents showing co-occurrence of internalizing and externalizing (such as ADHD) psychopathology (Cosgrove et al., 2011).

When we analyzed how genetic and environmental risk factors associated with baseline symptoms of ADHD and internalizing problems contributed to the variation in internalizing problems at age 15, we found that genetic innovation at age 15 explained a substantial part of the variation in internalizing problems in adolescence in both genders. Our findings of genetic innovation suggest that parts of the influences are specific to developmental phases. New non-shared environmental effects accounted for a little more than half of the variation in internalizing problems at age 15 in both boys and girls. This is in line with results by Cosgrove et al. (2011), who found both genetic and environmental influences on the co-occurrence of internalizing and externalizing disorders.

The results demonstrated some gender differences. In particular, genes explained more of the variance in internalizing problems in adolescence in girls, as compared to boys. In line with our findings, previous research has demonstrated gender-specific differences in relation to the genetic contribution to separation anxiety (Eaves et al., 1997). Moreover, a positive association between ADHD and anxiety symptoms specifically in girls has previously been demonstrated (Baldwin & Dadds, 2008). In contrast to our study, however, the results in their study failed to support that ADHD symptoms predict the development of anxiety symptoms over time (Baldwin & Dadds, 2008). This discrepancy in findings could stem from differences in the methodology and the measurement used, given that the outcome variable in our study also encompassed depressive symptoms.

Unique environmental influences have been shown to be of importance in a smaller cross-sectional twin study which found higher levels of depressive symptomatology in MZ twins with ADHD than their non-affected MZ co-twin (Piek et al., 2010). This is in line with results in our **Study IV** where unique environmental influences, emerging in adolescence, explained

about half of the variance in internalizing at age 15 in both genders. Shared environmental factors, on the other hand, did not contribute significantly to the variance. In contrast to this, others have found that shared environmental factors can be of importance in explaining the variance within broad internalizing and externalizing disorders (Burt, 2009), and that associations between parental depressive symptoms and offspring behavioral and emotional problems have been significant (McAdams et al., 2015).

6.2 LIMITATIONS

Observational studies such as the ones included in this thesis, are limited in the sense that they cannot assess causality. There may be several competing explanations that might explain the observed associations between variables. A specific limitation of this thesis is that we did not have access to information on what type of interventions that had been offered between baseline and follow-up; e.g. if the child had been given stimulant medication.

In **Study I**, there was a three-year gap between the parental assessment of the adolescents using A-TAC and the actual clinical assessment. This could have led to an impaired ability of the A-TAC in differentiating between NDPs (apart from ASD). The complex psychosocial problems associated with puberty and emerging around the time of the clinical examination may also have interfered with interpreting the results. The A-TAC showed lower DOR/AUC for disorders other than ASDs (especially ADHD). This may be due to the time lag between parental assessment and clinical examination, but maybe also to a "twin sample bias" when using screen-negative co-twins consisting of genetically at-risk siblings. Despite this, numerous studies have reported that twins differ only marginally from singletons (Deary, 2006; Johnson, Krueger, Bouchard, & McGue, 2002).

The outcome measures in **Study II** were based mainly on self and parent report. The time lag between baseline and follow-up was three to six years. In some twin-pairs, both twins were screen-positive, and also shared the same environment. This could have affected our results. However, it was adjusted for statistically by using a robust sandwich estimator adjusting correlated data when calculating confidence intervals. An analysis of the attrition group showed that the attrition group had fewer girls, more boys, more ADHD screen-positive cases and parental education levels were more concentrated to secondary school level. These differences suggest that the attrition group might have had a heavier problem load than the study cohort.

A limitation in **Study III** is also the lack of information on previous/ongoing health care contacts or diagnostic status. In both **Study III** and **IV**, we only included children whose parents participated in the baseline A-TAC interview, and those families where both children and parents participated at follow-up. The response rate at baseline was 77% and at follow-up 44% (since we were using both parent and child report). If we had included only parent report at follow-up, the response rate would have been 49%. Including only child report at follow-up would have yielded a response rate of 50%. However, the added information from both sources was considered to be too valuable to omit. Some of the attrition could probably be explained by more troubled families not participating, which has previously been

demonstrated in analyses of the attrition in CATSS (Anckarsater et al., 2011). Thus, the findings from both **Study III** and **IV** must be interpreted with these limitations kept in mind.

6.3 STRENGTHS

Study I has several strengths: we used a substantial population-based cohort of screen-positive children with their screen-negative siblings, also including controls, and both boys and girls. Moreover, participants underwent rigorous neuropsychological assessment. Psychiatric interviews were conducted using K-SADS-PL schedule, with several trained clinicians (i.e., psychologists and one experienced child psychiatrist), arriving at a consensus diagnosis.

A special strength of **Study II** lies in the fact that we have assessed a broad spectrum of NDPs simultaneously at baseline, and assessed a wide range of psychosocial outcomes at follow-up. These outcomes were chosen to reflect key aspects of an adolescent development and considered to be crucial for the further development into adulthood.

In **Study III**, in contrast to many longitudinal follow-ups of ADHD, we were able to make direct comparisons of boys and girls from the same cohort using the same methodology. The sample of twins (4635) was large, not restricted to any ADHD subtype, and included a large number of girls (2383 or 51%). To our knowledge, the investigation of degree of ADHD symptoms in relation to gender is novel and has not been examined in previous research. Through stratifying both baseline and follow-up problem levels we could identify what may be interpreted a dose-dependent relationship between ADHD-symptoms levels and other problems. This finding is in line with those from other studies assessing both subthreshold and threshold and their associated outcomes.

A twin study design makes it possible to decompose co-variation between internalizing problems and ADHD at baseline and their effects on internalizing problems at age 15 into components of stability and innovation, as well as decomposing these sources into their genetic and environmental etiologies. The longitudinal design of **Study IV** enabled us to explore genetic and environmental factors both in childhood and adolescence, as well as developmental aspects over time.

7   CLINICAL IMPLICATIONS

Many screening tools available at present are designed to assess one specific diagnosis or disorder, and may then miss overlapping conditions and coexisting disorders. In this dissertation project, the A-TAC was used throughout the studies. It was designed to simultaneously assess for multiple diagnoses, and the results in **Study I** demonstrated that it can be useful as a screening-instrument in a population-based study group. In order to extend this line of research and conduct population-studies on larger groups from the STR, the A-TAC can contribute considerably to our knowledge of the development of ADHD and other NDPs and associated disorders. In addition to its usefulness in research the A-TAC might be of value in a clinical situation as a quick screening tool, instead of other more time consuming diagnostic screening tools.

We found an increased psychosocial problem load in adolescence in individuals who were screen-positive for NDPs in childhood. Therefore early detection of NDPs and also assessing coexisting problems and disorders is of paramount importance for the ability to design individualized prevention and treatment strategies. Our results underscore the risk for children with ADHD to become marginalized in society and that they may suffer serious consequences in education, psychosocial health, and future occupational life. A wider risk assessment perspective during adolescence is important, given the higher levels of various negative outcomes for the 15-year olds in **Study II**.

Study III has highlighted that individuals with subthreshold ADHD also might have a substantial problem load in daily life, without getting adequate understanding, help, and support. Girls and boys might display different risk profiles, and support and interventions could thus benefit from being individualized. Our results underline the importance of assessing psychosocial problem areas, such as drug misuse. In general, this supports the value of assessing dimensional traits of psychopathology, which was extensively discussed preceding the publication of DSM-5.

Clinicians and researchers need to consider complex etiologic and developmental models for the comorbidity between internalizing problems and ADHD, and clinicians could be aware of the risk for girls with ADHD to develop internalizing problems.

Our findings clearly point to ADHD as the single most important neurodevelopmental condition associated with antisocial development during adolescence. Even though screening for ADHD may seem as the most important risk strategy, there may be an advantage in applying a comprehensive assessment of the entire neurodevelopmental spectrum, in that the individual child may have specific needs that warrant interventions. Perhaps even more important is to consider the family's social situation, since there may be a need to compensate a child with more active, external support.

8 FUTURE RESEARCH

This thesis is focusing on the negative outcomes of NDPs and especially of ADHD. In the future it would be interesting to learn more about the protective factors that could help someone with ADHD to manage better. It is important to develop other treatment options than medication, especially for those who do not tolerate the medication very well, or who would prefer other ways to influence the brain and body.

Further studies could be done on twin-data to explore other aspects of an adolescent's life, seeing how different lifestyles influence psychosocial outcomes.

In this thesis, the three subdimensions of ADHD (inattention, hyperactivity, and impulsivity) have not been addressed separately. To investigate whether different subdimensions of ADHD are associated with psychosocial outcomes in unique ways, is thus an interesting issue to explore further.

9 CONCLUSIONS

The results in this thesis suggest that A-TAC is an effective screening tool for NDPs, and that it can be used for the purpose of predictive assessment in the general population. Overall, it demonstrated satisfactory psychometric properties as a screening instrument.

Symptoms of NDPs or other mental health problems at the age of 9 or 12 were associated with more psychosocial problems during adolescence. Despite the presence of comorbidity, childhood ADHD symptoms stand out as the most important risk factor for later antisocial development and impaired daily functioning.

ADHD symptoms as well as their associated negative outcomes are dimensionally distributed in the population, and girls and boys display somewhat different risk profiles, even after controlling for other neuropsychiatric symptoms. The finding that ADHD symptoms are associated with higher drug misuse in girls motivates particular attention and active screening routines.

ADHD and internalizing problems were associated. There was a gender difference in the genetic explanation of internalizing problems at 15. In both genders, both new genetic and environmental factors emerged in adolescence. The findings point to the need for increased awareness of the complex etiologic and developmental models for the comorbidity between internalizing symptoms and ADHD.

10 ACKNOWLEDGEMENTS

Then, I would like to express my sincere gratitude to all the people who have inspired, supported and encouraged me during these years. This thesis would not have been possible to finish without their help. I would especially like to thank:

Clara Hellner Gumpert, my main supervisor, for so many things along the way! First of all for giving me the opportunity to become a doctoral student at KI, and for giving me necessary financial support. Without you I could neither have started, nor finished this doctoral journey! I am very grateful for co-working with you during these years of learning more about all the aspects of the scientific world. Thank you for sharing your competence and experience with me and for supporting and helping me throughout these years so that I could reach my goal!

Co-supervisor **Henrik Anckarsäter**, for giving me the courage to aim for a PhD and for never doubting my capacity, even when I did so myself. The times I spent in the Gothenburg forensic research group during the data collection in DOGSS, were always joyful and enjoyable.

Co-supervisor **Paul Lichtenstein**, for sharing your enthusiasm for research and your great knowledge of twin studies and their possibilities. Towards the end of my PhD studies, I have understood more and more of the topics we have discussed, which has made me feel that I have learned a lot.

Co-supervisor **Yasmina Molero**, for giving me endless support and guidance in the daily, smaller details, helping me to structure my work so that I could move forward in my PhD project. You have been easy to reach and have a chat with, sitting in the same building as me at MEB.

Former co-supervisor **Eva Serlachius**, for helping me to find this PhD project and providing me with the right co-supervisors to give me the support I needed.

Matteo Bottai and **Ralf Kuja-Halkola**, experts in biostatistics as well as co-authors. For

11 REFERENCES

Anckarsater, H., Lundstrom, S., Kollberg, L., Kerekes, N., Palm, C., Carlstrom, E., . . . Lichtenstein, P. (2011). The Child and Adolescent Twin Study in Sweden (CATSS). *Twin Res Hum Genet, 14*(6), 495-508.

Anckarsäter, H., Larson, T., Hansson, S.L., Carlström, E., Ståhlberg, O.,, & Gillberg, C., Råstam, M., Gillberg, C., Lichtenstein, P. (2008). Child Neurodevelopmental and Behavioural Problems are Intercorrelated

and Dimensionally Distributed in the General Population. *The Open Psychiatry Journal,* (2), 5-11.

Antshel, K. M., Zhang-James, Y., & Faraone, S. V. (2013). The comorbidity of ADHD and autism spectrum disorder. *Expert Rev Neurother, 13*(10), 1117-1128. doi: 10.1586/14737175.2013.840417

APA. (2000). *DSM-IV-TR*. Washington, D.C.: American Psychiatric Association.

APA. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.)*. Washington DC: American Psychiatric Association.

Arseneault, L., Milne, B. J., Taylor, A., Adams, F., Delgado, K., Caspi, A., & Moffitt, T. E. (2008). Being bullied as an environmentally mediated contributing factor to children's internalizing problems: a study of twins discordant for victimization. *Arch Pediatr Adolesc Med, 162*(2), 145-150. doi: 10.1001/archpediatrics.2007.53

Ask, H., Waaktaar, T., Seglem, K. B., & Torgersen, S. (2015). Common Etiological Sources of Anxiety, Depression, and Somatic Complaints in Adolescents: A Multiple Rater twin Study. *J Abnorm Child Psychol*. doi: 10.1007/s10802-015-9977-y

Baird, G., Simonoff, E., Pickles, A., Chandler, S., Loucas, T., Meldrum, D., & Charman, T. (2006). Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet, 368*(9531), 210-215. doi: 10.1016/S0140-6736(06)69041-7

Balazs, J., & Kereszteny, A. (2014). Subthreshold attention deficit hyperactivity in children and adolescents: a systematic review. *Eur Child Adolesc Psychiatry, 23*(6), 393-408. doi: 10.1007/s00787-013-0514-7

Baldwin, J. S., & Dadds, M. R. (2008). Examining alternative explanations of the covariation of ADHD and anxiety symptoms in children: a community study. *J Abnorm Child Psychol, 36*(1), 67-79. doi: 10.1007/s10802-007-9160-1

Barbaresi, W. J., Katusic, S. K., Colligan, R. C., Weaver, A. L., & Jacobsen, S. J. (2007). Long-term school outcomes for children with attention-deficit/hyperactivity disorder: a population-based perspective. *J Dev Behav Pediatr, 28*(4), 265-273. doi: 10.1097/DBP.0b013e31811ff87d

Barkley, R. A. (2002). Major life activity and health outcomes associated with attention-deficit/hyperactivity disorder. *J Clin Psychiatry, 63 Suppl 12*, 10-15.

Bauermeister, J. J., Shrout, P. E., Chavez, L., Rubio-Stipec, M., Ramirez, R., Padilla, L., . . . Canino, G. (2007). ADHD and gender: are risks and sequela of ADHD the same for

boys and girls? *J Child Psychol Psychiatry, 48*(8), 831-839. doi: 10.1111/j.1469-7610.2007.01750.x

Bergfalk, H. (2006). Qb Test User Manual. Gothenburg: Qb Tech AB.

Biederman, J., Ball, S. W., Monuteaux, M. C., Mick, E., Spencer, T. J., McCreary, M., . . . Faraone, S. V. (2008). New insights into the comorbidity between ADHD and major depression in adolescent and young adult females. *J Am Acad Child Adolesc Psychiatry, 47*(4), 426-434. doi: 10.1097/CHI.0b013e31816429d3

Biederman, J., & Faraone, S. V. (2006). The effects of attention-deficit/hyperactivity disorder on employment and household income. *MedGenMed, 8*(3), 12.

Biederman, J., Faraone, S. V., Spencer, T., Wilens, T., Mick, E., & Lapey, K. A. (1994). Gender differences in a sample of adults with attention deficit hyperactivity disorder. *Psychiatry Res, 53*(1), 13-29.

Biederman, J., Faraone, S. V., Spencer, T. J., Mick, E., Monuteaux, M. C., & Aleardi, M. (2006). Functional impairments in adults with self-reports of diagnosed ADHD: A controlled study of 1001 adults in the community. *J Clin Psychiatry, 67*(4), 524-540.

Biederman, J., Mick, E., Faraone, S. V., Braaten, E., Doyle, A., Spencer, T., . . . Johnson, M. A. (2002). Influence of gender on attention deficit hyperactivity disorder in children referred to a psychiatric clinic. *Am J Psychiatry, 159*(1), 36-42.

Biederman, J., Monuteaux, M. C., Mick, E., Spencer, T., Wilens, T. E., Klein, K. L., . . . Faraone, S. V. (2006). Psychopathology in females with attention-deficit/hyperactivity disorder: a controlled, five-year prospective study. *Biol Psychiatry, 60*(10), 1098-1105. doi: 10.1016/j.biopsych.2006.02.031

Biederman, J., Petty, C. R., Dolan, C., Hughes, S., Mick, E., Monuteaux, M. C., & Faraone, S. V. (2008). The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study. *Psychol Med, 38*(7), 1027-1036. doi: 10.1017/S0033291707002668

Biederman, J., Petty, C. R., Evans, M., Small, J., & Faraone, S. V. (2010). How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD. *Psychiatry Res, 177*(3), 299-304. doi: 10.1016/j.psychres.2009.12.010

Biederman, J., Petty, C. R., Monuteaux, M. C., Mick, E., Parcell, T., Westerberg, D., & Faraone, S. V. (2008). The longitudinal course of comorbid oppositional defiant disorder in girls with attention-deficit/hyperactivity disorder: findings from a controlled 5-year prospective longitudinal follow-up study. *J Dev Behav Pediatr, 29*(6), 501-507. doi: 10.1097/DBP.0b013e318190b290

Biederman, J., Petty, C. R., O'Connor, K. B., Hyder, L. L., & Faraone, S. V. (2012). Predictors of persistence in girls with attention deficit hyperactivity disorder: results from an 11-year controlled follow-up study. *Acta Psychiatr Scand, 125*(2), 147-156. doi: 10.1111/j.1600-0447.2011.01797.x

Bitsko, R. H., Danielson, M., King, M., Visser, S. N., Scahill, L., & Perou, R. (2013). Health care needs of children with Tourette syndrome. *J Child Neurol, 28*(12), 1626-1636. doi: 10.1177/0883073812465121

Bremberg, S., & Dalman, C. (2015). Begrepp, mätmetoder och förekomst av psykisk hälsa, psykisk ohälsa och psykiatriska tillstånd hos barn och unga - EN KUNSKAPSÖVERSIKT.

Burt, S. A. (2009). Rethinking environmental contributions to child and adolescent psychopathology: a meta-analysis of shared environmental influences. *Psychol Bull, 135*(4), 608-637. doi: 10.1037/a0015702

Buschgens, C. J., van Aken, M. A., Swinkels, S. H., Altink, M. E., Fliers, E. A., Rommelse, N. N., . . . Buitelaar, J. K. (2008). Differential family and peer environmental factors are related to severity and comorbidity in children with ADHD. *J Neural Transm, 115*(2), 177-186. doi: 10.1007/s00702-007-0838-x

Bussing, R., Mason, D. M., Bell, L., Porter, P., & Garvan, C. (2010). Adolescent outcomes of childhood attention-deficit/hyperactivity disorder in a diverse community sample. *J Am Acad Child Adolesc Psychiatry, 49*(6), 595-605. doi: 10.1016/j.jaac.2010.03.006

CAN. (2014). *Skolelevers drogvanor 2014*. Centralförbundet för Alkohol- och Narkotikaupplysning.

Canitano, R., & Vivanti, G. (2007). Tics and Tourette syndrome in autism spectrum disorders. *Autism, 11*(1), 19-28. doi: 10.1177/1362361307070992

Chang, Z., Lichtenstein, P., Asherson, P. J., & Larsson, H. (2013). Developmental twin study of attention problems: high heritabilities throughout development. *JAMA Psychiatry, 70*(3), 311-318. doi: 10.1001/jamapsychiatry.2013.287

Charach, A., Yeung, E., Climans, T., & Lillie, E. (2011). Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. *J Am Acad Child Adolesc Psychiatry, 50*(1), 9-21. doi: 10.1016/j.jaac.2010.09.019

Cho, S. C., Kim, B. N., Kim, J. W., Rohde, L. A., Hwang, J. W., Chungh, D. S., . . . Kim, H. W. (2009). Full syndrome and subthreshold attention-deficit/hyperactivity disorder in a Korean community sample: comorbidity and temperament findings. *Eur Child Adolesc Psychiatry, 18*(7), 447-457. doi: 10.1007/s00787-009-0755-7

Chronis-Tuscano, A., Molina, B. S., Pelham, W. E., Applegate, B., Dahlke, A., Overmyer, M., & Lahey, B. B. (2010). Very early predictors of adolescent depression and suicide attempts in children with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry, 67*(10), 1044-1051. doi: 10.1001/archgenpsychiatry.2010.127

Compton, W. M., Thomas, Y. F., Stinson, F. S., & Grant, B. F. (2007). Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry, 64*(5), 566-576. doi: 10.1001/archpsyc.64.5.566

Cosgrove, V. E., Rhee, S. H., Gelhorn, H. L., Boeldt, D., Corley, R. C., Ehringer, M. A., . . . Hewitt, J. K. (2011). Structure and etiology of co-occurring internalizing and externalizing disorders in adolescents. *J Abnorm Child Psychol, 39*(1), 109-123. doi: 10.1007/s10802-010-9444-8

Cubo, E. (2012). Review of prevalence studies of tic disorders: methodological caveats. *Tremor Other Hyperkinet Mov (N Y), 2*.

Currie, J., & Stabile, M. (2006). Child mental health and human capital accumulation: the case of ADHD. *J Health Econ, 25*(6), 1094-1118. doi: 10.1016/j.jhealeco.2006.03.001

Dalsgaard, S., Mortensen, P. B., Frydenberg, M., & Thomsen, P. H. (2014). ADHD, stimulant treatment in childhood and subsequent substance abuse in adulthood - a

naturalistic long-term follow-up study. *Addict Behav, 39*(1), 325-328. doi: 10.1016/j.addbeh.2013.09.002

De Alwis, D., Agrawal, A., Reiersen, A. M., Constantino, J. N., Henders, A., Martin, N. G., & Lynskey, M. T. (2014). ADHD symptoms, autistic traits, and substance use and misuse in adult Australian twins. *J Stud Alcohol Drugs, 75*(2), 211-221.

Deary, I. J. (2006). Educational performance in twins. *BMJ, 333*(7578), 1080-1081. doi: 10.1136/bmj.39037.543148.80

Deeks, J. J., Macaskill, P., & Irwig, L. (2005). The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol, 58*(9), 882-893. doi: 10.1016/j.jclinepi.2005.01.016

Disney, E. R., Elkins, I. J., McGue, M., & Iacono, W. G. (1999). Effects of ADHD, conduct disorder, and gender on substance use and abuse in adolescence. *Am J Psychiatry, 156*(10), 1515-1521.

Eaves, L. J., Silberg, J. L., Meyer, J. M., Maes, H. H., Simonoff, E., Pickles, A., . . . Hewitt, J. K. (1997). Genetics and developmental psychopathology .2. The main effects of genes and environment on behavioral problems in the Virginia twin study of adolescent behavioral development. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 38*(8), 965-980. doi: DOI 10.1111/j.1469-7610.1997.tb01614.x

Einarsson, E., Sigurdsson, J. F., Gudjonsson, G. H., Newton, A. K., & Bragason, O. O. (2009). Screening for attention-deficit hyperactivity disorder and co-morbid mental disorders among prison inmates. *Nord J Psychiatry, 63*(5), 361-367. doi: 10.1080/08039480902759184

Elkins, I. J., McGue, M., & Iacono, W. G. (2007). Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. *Arch Gen Psychiatry, 64*(10), 1145-1152. doi: 10.1001/archpsyc.64.10.1145

Elliot, D. S., Huizinga, D., & Ageton, S. S. E. (1985). *Explaining delinquency and drug use.*: Beverly Hills: Sage.

Faraone, S. V., Kunwar, A., Adamson, J., & Biederman, J. (2009). Personality traits among ADHD adults: implications of late-onset and subthreshold diagnoses. *Psychol Med, 39*(4), 685-693. doi: 10.1017/S0033291708003917

Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A., & Sklar, P. (2005). Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry, 57*(11), 1313-1323. doi: 10.1016/j.biopsych.2004.11.024

Faraone, S. V., Sergeant, J., Gillberg, C., & Biederman, J. (2003). The worldwide prevalence of ADHD: is it an American condition? *World Psychiatry, 2*(2), 104-113.

Fredriksen, M., Dahl, A. A., Martinsen, E. W., Klungsoyr, O., Faraone, S. V., & Peleikis, D. E. (2014). Childhood and persistent ADHD symptoms associated with educational failure and long-term occupational disability in adult ADHD. *Atten Defic Hyperact Disord, 6*(2), 87-99. doi: 10.1007/s12402-014-0126-1

Fried, R., Petty, C., Faraone, S. V., Hyder, L. L., Day, H., & Biederman, J. (2013). Is ADHD a Risk Factor for High School Dropout? A Controlled Study. *J Atten Disord.* doi: 10.1177/1087054712473180

Galera, C., Pingault, J. B., Fombonne, E., Michel, G., Lagarde, E., Bouvard, M. P., & Melchior, M. (2013). Attention problems in childhood and adult substance use. *J Pediatr, 163*(6), 1677-1683 e1671. doi: 10.1016/j.jpeds.2013.07.008

Garcia, S. E., Tully, E. C., Tarantino, N., South, S., Iacono, W. G., & McGue, M. (2013). Changes in genetic and environmental influences on trait anxiety cfrom middle adolescence to early adulthood. *J Affect Disord, 151*(1), 46-53. doi: 10.1016/j.jad.2013.05.046

Gaub, M., & Carlson, C. L. (1997). Gender differences in ADHD: a meta-analysis and critical review. *J Am Acad Child Adolesc Psychiatry, 36*(8), 1036-1045. doi: 10.1097/00004583-199708000-00011

Geluk, C. A., Jansen, L. M., Vermeiren, R., Doreleijers, T. A., van Domburgh, L., de Bildt, A., . . . Hartman, C. A. (2012). Autistic symptoms in childhood arrestees: longitudinal association with delinquent behavior. *J Child Psychol Psychiatry, 53*(2), 160-167. doi: 10.1111/j.1469-7610.2011.02456.x

Gillberg, C. (2010). The ESSENCE in child psychiatry: Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations. *Res Dev Disabil, 31*(6), 1543-1551. doi: 10.1016/j.ridd.2010.06.002

Gillberg, C., Coleman, M. (2000). *The Biology of the Autistic Syndromes*. Cambridge: Cambridge University Press.

Gillberg, C., Gillberg, C., Rastam, M., & Wentz, E. (2001). The Asperger Syndrome (and high-functioning autism) - Diagnostic Interview (ASDI): a preliminary study of a new structured clinical interview. *Autism, 5*(1), 57-66. doi: Doi 10.1177/1362361301005001006

Gillberg, C., & Soderstrom, H. (2003). Learning disability. *Lancet, 362*(9386), 811-821. doi: 10.1016/S0140-6736(03)14275-4

Gilmour, J., Hill, B., Place, M., & Skuse, D. H. (2004). Social communication deficits in conduct disorder: a clinical and community survey. *J Child Psychol Psychiatry, 45*(5), 967-978. doi: 10.1111/j.1469-7610.2004.t01-1-00289.x

Glas, A. S., Lijmer, J. G., Prins, M. H., Bonsel, G. J., & Bossuyt, P. M. (2003). The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol, 56*(11), 1129-1135.

Goodman, R. (2001). Psychometric properties of the strengths and difficulties questionnaire. *J Am Acad Child Adolesc Psychiatry, 40*(11), 1337-1345. doi: 10.1097/00004583-200111000-00015

Gross-Tsur, V., Goldzweig, G., Landau, Y. E., Berger, I., Shmueli, D., & Shalev, R. S. (2006). The impact of sex and subtypes on cognitive and psychosocial aspects of ADHD. *Dev Med Child Neurol, 48*(11), 901-905. doi: 10.1017/S0012162206001976

Hallerod, S. L., Larson, T., Stahlberg, O., Carlstrom, E., Gillberg, C., Anckarsater, H., . . . Gillberg, C. (2010). The Autism--Tics, AD/HD and other Comorbidities (A-TAC) telephone interview: convergence with the Child Behavior Checklist (CBCL). *Nord J Psychiatry, 64*(3), 218-224. doi: 10.3109/08039480903514443

Hansson, S. L., Svanstrom Rojvall, A., Rastam, M., Gillberg, C., Gillberg, C., & Anckarsater, H. (2005). Psychiatric telephone interview with parents for screening of childhood autism - tics, attention-deficit hyperactivity disorder and other comorbidities (A-

TAC): preliminary reliability and validity. *Br J Psychiatry, 187*, 262-267. doi: 10.1192/bjp.187.3.262

Hicks, B. M., DiRago, A. C., Iacono, W. G., & McGue, M. (2009). Gene-environment interplay in internalizing disorders: consistent findings across six environmental risk factors. *J Child Psychol Psychiatry, 50*(10), 1309-1317. doi: 10.1111/j.1469-7610.2009.02100.x

Hinshaw, S. P., Owens, E. B., Sami, N., & Fargeon, S. (2006). Prospective follow-up of girls with attention-deficit/hyperactivity disorder into adolescence: Evidence for continuing cross-domain impairment. *J Consult Clin Psychol, 74*(3), 489-499. doi: 10.1037/0022-006X.74.3.489

Hinshaw, S. P., Owens, E. B., Zalecki, C., Huggins, S. P., Montenegro-Nevado, A. J., Schrodek, E., & Swanson, E. N. (2012). Prospective follow-up of girls with attention-deficit/hyperactivity disorder into early adulthood: continuing impairment includes elevated risk for suicide attempts and self-injury. *J Consult Clin Psychol, 80*(6), 1041-1051. doi: 10.1037/a0029451

Hofvander, B., Ossowski, D., Lundstrom, S., & Anckarsater, H. (2009). Continuity of aggressive antisocial behavior from childhood to adulthood: The question of phenotype definition. *Int J Law Psychiatry, 32*(4), 224-234. doi: 10.1016/j.ijlp.2009.04.004

Hong, S. B., Dwyer, D., Kim, J. W., Park, E. J., Shin, M. S., Kim, B. N., . . . Cho, S. C. (2014). Subthreshold attention-deficit/hyperactivity disorder is associated with functional impairments across domains: a comprehensive analysis in a large-scale community study. *Eur Child Adolesc Psychiatry, 23*(8), 627-636. doi: 10.1007/s00787-013-0501-z

Hurtig, T., Ebeling, H., Taanila, A., Miettunen, J., Smalley, S., McGough, J., . . . Moilanen, I. (2007). ADHD and comorbid disorders in relation to family environment and symptom severity. *Eur Child Adolesc Psychiatry, 16*(6), 362-369. doi: 10.1007/s00787-007-0607-2

Idring, S., Rai, D., Dal, H., Dalman, C., Sturm, H., Zander, E., . . . Magnusson, C. (2012). Autism spectrum disorders in the Stockholm Youth Cohort: design, prevalence and validity. *PLoS One, 7*(7), e41280. doi: 10.1371/journal.pone.0041280

Jensen, C. M., & Steinhausen, H. C. (2015). Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study. *Atten Defic Hyperact Disord, 7*(1), 27-38. doi: 10.1007/s12402-014-0142-1

Johnson, W., Krueger, R. F., Bouchard, T. J., & McGue, M. (2002). The personalities of twins: Just ordinary folks. *Twin Research, 5*(2), 125-131. doi: Doi 10.1375/1369052022992

Junger-Tas, J., & Marshall, I. H. (1999). The Self-Report Methodology in Crime Research. *The University of Chicago*.

Junger-Tas, J., Terlouw, G.-J., & W., K. M. (1994). *Delinquent behavior among young people in the western world: first results of the international self-report delinquency study*: Kugler Publications - Amsterdam / New York.

Kadesjo, B., & Gillberg, C. (1999). Developmental coordination disorder in Swedish 7-year-old children. *J Am Acad Child Adolesc Psychiatry, 38*(7), 820-828. doi: 10.1097/00004583-199907000-00011

Kanne, S. M., Christ, S. E., & Reiersen, A. M. (2009). Psychiatric symptoms and psychosocial difficulties in young adults with autistic traits. *J Autism Dev Disord, 39*(6), 827-833. doi: 10.1007/s10803-008-0688-x

Kaufman, J., Birmaher, B., Brent, D. A., Ryan, N. D., & Rao, U. (2000). K-Sads-PL. *J Am Acad Child Adolesc Psychiatry, 39*(10), 1208. doi: 10.1097/00004583-200010000-00002

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., . . . Zaslavsky, A. M. (2006). The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *Am J Psychiatry, 163*(4), 716-723. doi: 10.1176/ajp.2006.163.4.716

Khalifa, N., & von Knorring, A. L. (2003). Prevalence of tic disorders and Tourette syndrome in a Swedish school population. *Dev Med Child Neurol, 45*(5), 315-319.

Kim, Y. S., Leventhal, B. L., Koh, Y. J., Fombonne, E., Laska, E., Lim, E. C., . . . Grinker, R. R. (2011). Prevalence of autism spectrum disorders in a total population sample. *Am J Psychiatry, 168*(9), 904-912. doi: 10.1176/appi.ajp.2011.10101532

Kirby, A., Sugden, D., & Purcell, C. (2014). Diagnosing developmental coordination disorders. *Arch Dis Child, 99*(3), 292-296. doi: 10.1136/archdischild-2012-303569

Kotte, A., Joshi, G., Fried, R., Uchida, M., Spencer, A., Woodworth, K. Y., . . . Biederman, J. (2013). Autistic traits in children with and without ADHD. *Pediatrics, 132*(3), e612-622. doi: 10.1542/peds.2012-3947

Kuja-Halkola, R., Lichtenstein, P., D'Onofrio, B. M., & Larsson, H. (2014). Codevelopment of ADHD and externalizing behavior from childhood to adulthood. *J Child Psychol Psychiatry*. doi: 10.1111/jcpp.12340

Lahey, B. B., Hartung, C. M., Loney, J., Pelham, W. E., Chronis, A. M., & Lee, S. S. (2007). Are there sex differences in the predictive validity of DSM-IV ADHD among younger children? *J Clin Child Adolesc Psychol, 36*(2), 113-126. doi: 10.1080/15374410701274066

Landerl, K., & Moll, K. (2010). Comorbidity of learning disorders: prevalence and familial transmission. *J Child Psychol Psychiatry, 51*(3), 287-294. doi: 10.1111/j.1469-7610.2009.02164.x

Larson, T., Anckarsater, H., Gillberg, C., Stahlberg, O., Carlstrom, E., Kadesjo, B., . . . Gillberg, C. (2010). The autism--tics, AD/HD and other comorbidities inventory (A-TAC): further validation of a telephone interview for epidemiological research. *BMC Psychiatry, 10*, 1. doi: 10.1186/1471-244X-10-1

Larson, T., Kerekes, N., Selinus, E. N., Lichtenstein, P., Gumpert, C. H., Anckarsater, H., . . . Lundstrom, S. (2014). Reliability of Autism-Tics, AD/HD, and other Comorbidities (A-TAC) inventory in a test-retest design. *Psychol Rep, 114*(1), 93-103. doi: 10.2466/03.15.PR0.114k10w1

Larson, T., Lundstrom, S., Nilsson, T., Selinus, E. N., Rastam, M., Lichtenstein, P., . . . Kerekes, N. (2013). Predictive properties of the A-TAC inventory when screening for childhood-onset neurodevelopmental problems in a population-based sample. *BMC Psychiatry, 13*, 233. doi: 10.1186/1471-244X-13-233

Larsson, H., Anckarsater, H., Rastam, M., Chang, Z., & Lichtenstein, P. (2012). Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: a

quantitative genetic study of 8,500 twin pairs. *J Child Psychol Psychiatry, 53*(1), 73-80. doi: 10.1111/j.1469-7610.2011.02467.x

Larsson, H., Sariaslan, A., Langstrom, N., D'Onofrio, B., & Lichtenstein, P. (2014). Family income in early childhood and subsequent attention deficit/hyperactivity disorder: a quasi-experimental study. *J Child Psychol Psychiatry, 55*(5), 428-435. doi: 10.1111/jcpp.12140

Lee, S. S., Humphreys, K. L., Flory, K., Liu, R., & Glass, K. (2011). Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. *Clin Psychol Rev, 31*(3), 328-341.

Levy, F., Hay, D. A., Bennett, K. S., & McStephen, M. (2005). Gender differences in ADHD subtype comorbidity. *J Am Acad Child Adolesc Psychiatry, 44*(4), 368-376. doi: 10.1097/01.chi.0000153232.64968.c1

Lichtenstein, P., De Faire, U., Floderus, B., Svartengren, M., Svedberg, P., & Pedersen, N. L. (2002). The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. *J Intern Med, 252*(3), 184-205. doi: DOI 10.1046/j.1365-2796.2002.01032.x

Loe, I. M., & Feldman, H. M. (2007). Academic and educational outcomes of children with ADHD. *J Pediatr Psychol, 32*(6), 643-654. doi: 10.1093/jpepsy/jsl054

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord, 24*(5), 659-685.

Lovenhag, S., Larm, P., Aslund, C., & Nilsson, K. W. (2015). Antisocial behavior reduces the association between subdimensions of ADHD symptoms and alcohol use in a large population-based sample of adolescents. *Scand J Psychol, 56*(5), 489-497. doi: 10.1111/sjop.12234

Lundh, A. (2012). *On the Children's Global Assessment Scale (CGAS)*: Karolinska Institutet, Stockholm.

Lundstrom, S., Forsman, M., Larsson, H., Kerekes, N., Serlachius, E., Langstrom, N., & Lichtenstein, P. (2014). Childhood neurodevelopmental disorders and violent criminality: a sibling control study. *J Autism Dev Disord, 44*(11), 2707-2716. doi: 10.1007/s10803-013-1873-0

Magnusson, P. K., Almqvist, C., Rahman, I., Ganna, A., Viktorin, A., Walum, H., . . . Lichtenstein, P. (2013). The Swedish Twin Registry: establishment of a biobank and other recent developments. *Twin Res Hum Genet, 16*(1), 317-329. doi: 10.1017/thg.2012.104

Malmberg, K., Edbom, T., Wargelius, H. L., & Larsson, J. O. (2011). Psychiatric problems associated with subthreshold ADHD and disruptive behaviour diagnoses in teenagers. *Acta Paediatr, 100*(11), 1468-1475. doi: 10.1111/j.1651-2227.2011.02363.x

Martikainen, P., Bartley, M., & Lahelma, E. (2002). Psychosocial determinants of health in social epidemiology. *Int J Epidemiol, 31*(6), 1091-1093. doi: DOI 10.1093/ije/31.6.1091

Matson, J. L., & Cervantes, P. E. (2014). Commonly studied comorbid psychopathologies among persons with autism spectrum disorder. *Res Dev Disabil, 35*(5), 952-962. doi: 10.1016/j.ridd.2014.02.012

McAdams, T. A., Rijsdijk, F. V., Neiderhiser, J. M., Narusyte, J., Shaw, D. S., Natsuaki, M. N., . . . Eley, T. C. (2015). The relationship between parental depressive symptoms and offspring psychopathology: evidence from a children-of-twins study and an adoption study. *Psychol Med*, 1-12. doi: 10.1017/S0033291715000501

Mick, E., Byrne, D., Fried, R., Monuteaux, M., Faraone, S. V., & Biederman, J. (2011). Predictors of ADHD persistence in girls at 5-year follow-up. *J Atten Disord, 15*(3), 183-192. doi: 10.1177/1087054710362217

Missiuna, C., Cairney, J., Pollock, N., Campbell, W., Russell, D. J., Macdonald, K., . . . Cousins, M. (2014). Psychological distress in children with developmental coordination disorder and attention-deficit hyperactivity disorder. *Res Dev Disabil, 35*(5), 1198-1207. doi: 10.1016/j.ridd.2014.01.007

Molina, B. S. G., & Pelham, W. E. (2003). Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. *Journal of Abnormal Psychology, 112*(3), 497-507. doi: Doi 10.1037/0021-843x.112.3.497

Moruzzi, S., Ogliari, A., Ronald, A., Happe, F., & Battaglia, M. (2011). The nature of covariation between autistic traits and clumsiness: a twin study in a general population sample. *J Autism Dev Disord, 41*(12), 1665-1674. doi: 10.1007/s10803-011-1199-8

Mrug, S., Molina, B. S., Hoza, B., Gerdes, A. C., Hinshaw, S. P., Hechtman, L., & Arnold, L. E. (2012). Peer rejection and friendships in children with Attention-Deficit/Hyperactivity Disorder: contributions to long-term outcomes. *J Abnorm Child Psychol, 40*(6), 1013-1026. doi: 10.1007/s10802-012-9610-2

Neale, M. (2006). *Methodology for Genetic Studies of Twins and Families*. The Netherlands.: Kluwer Academic Publishers B.V. Dordrecht.

Neale M., e. a., eds. (2003). *Mx: statistical modeling.* (Vol. 6th ed.). Richmond: VA: Department of Psychiatry.

Novik, T. S., Hervas, A., Ralston, S. J., Dalsgaard, S., Rodrigues Pereira, R., Lorenzo, M. J., & Group, A. S. (2006). Influence of gender on attention-deficit/hyperactivity disorder in Europe--ADORE. *Eur Child Adolesc Psychiatry, 15 Suppl 1*, I15-24. doi: 10.1007/s00787-006-1003-z

Nussbaum, N. L. (2012). ADHD and female specific concerns: a review of the literature and clinical implications. *J Atten Disord, 16*(2), 87-100. doi: 10.1177/1087054711416909

Odgers, C. L., Moffitt, T. E., Broadbent, J. M., Dickson, N., Hancox, R. J., Harrington, H., . . . Caspi, A. (2008). Female and male antisocial trajectories: from childhood origins to adult outcomes. *Dev Psychopathol, 20*(2), 673-716. doi: 10.1017/S0954579408000333

Piek, J. P., Barrett, N. C., Smith, L. M., Rigoli, D., & Gasson, N. (2010). Do motor skills in infancy and early childhood predict anxious and depressive symptomatology at school age? *Human Movement Science, 29*(5), 777-786.

Plomin, R., Knopik VS, Neiderhiser JM. (2013). *Behavioral genetics* (Sixth Edition ed.). New York: Worth.

Polanczyk, G., de Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry, 164*(6), 942-948. doi: 10.1176/ajp.2007.164.6.942

Polatajko, H. J., & Cantin, N. (2005). Developmental coordination disorder (dyspraxia): an overview of the state of the art. *Semin Pediatr Neurol, 12*(4), 250-258. doi: 10.1016/j.spen.2005.12.007

Pulay, A. J., Dawson, D. A., Hasin, D. S., Goldstein, R. B., Ruan, W. J., Pickering, R. P., . . . Grant, B. F. (2008). Violent behavior and DSM-IV psychiatric disorders: results from the national epidemiologic survey on alcohol and related conditions. *J Clin Psychiatry, 69*(1), 12-22.

Rabe-Hesketh, S., & Everitt, B. (2007). *A handbook of statistical analyses using Stata* (4th ed.). Boca Raton: Chapman & Hall/CRC.

Reiersen, A. M. (2011). Links between autism spectrum disorder and ADHD symptom trajectories: important findings and unanswered questions. *J Am Acad Child Adolesc Psychiatry, 50*(9), 857-859. doi: 10.1016/j.jaac.2011.06.012

Reiersen, A. M., Constantino, J. N., & Todd, R. D. (2008). Co-occurrence of motor problems and autistic symptoms in attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry, 47*(6), 662-672. doi: 10.1097/CHI.0b013e31816bff88

Reiersen, A. M., Constantino, J. N., Volk, H. E., & Todd, R. D. (2007). Autistic traits in a population-based ADHD twin sample. *J Child Psychol Psychiatry, 48*(5), 464-472. doi: 10.1111/j.1469-7610.2006.01720.x

Ring. (2000). *Stöld, våld och droger bland pojkar och flickor i årskurs nio - Resultat från tre självdeklarationsundersökningar*. (1100-6676).

Ringman, J. M., & Jankovic, J. (2000). Occurrence of tics in Asperger's syndrome and autistic disorder. *J Child Neurol, 15*(6), 394-400.

Rizzo, R., Gulisano, M., Pellico, A., Cali, P. V., & Curatolo, P. (2014). Tourette syndrome and comorbid conditions: a spectrum of different severities and complexities. *J Child Neurol, 29*(10), 1383-1389. doi: 10.1177/0883073814534317

Ronald, A., Edelson, L. R., Asherson, P., & Saudino, K. J. (2010). Exploring the relationship between autistic-like traits and ADHD behaviors in early childhood: findings from a community twin study of 2-year-olds. *J Abnorm Child Psychol, 38*(2), 185-196. doi: 10.1007/s10802-009-9366-5

Ruchkin, V., & Schwab-Stone, M. (2003). What can we learn from developmental studies of psychiatric disorders? *Lancet, 362*(9400), 1951-1952. doi: 10.1016/S0140-6736(03)15084-2

Rucklidge, J. J. (2010). Gender differences in attention-deficit/hyperactivity disorder. *Psychiatr Clin North Am, 33*(2), 357-373. doi: 10.1016/j.psc.2010.01.006

Scott, I. A., Greenberg, P. B., & Poole, P. J. (2008). Cautionary tales in the clinical interpretation of studies of diagnostic tests. *Intern Med J, 38*(2), 120-129. doi: 10.1111/j.1445-5994.2007.01436.x

Shaffer, D., Gould, M. S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., & Aluwahlia, S. (1983). A children's global assessment scale (CGAS). *Arch Gen Psychiatry, 40*(11), 1228-1231.

Shankman, S. A., Lewinsohn, P. M., Klein, D. N., Small, J. W., Seeley, J. R., & Altman, S. E. (2009). Subthreshold conditions as precursors for full syndrome disorders: a 15-year longitudinal study of multiple diagnostic classes. *J Child Psychol Psychiatry, 50*(12), 1485-1494. doi: 10.1111/j.1469-7610.2009.02117.x

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D., . . . Rapoport, J. L. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proc Natl Acad Sci U S A, 104*(49), 19649-19654. doi: 10.1073/pnas.0707741104

Simonoff, E., Jones, C. R., Baird, G., Pickles, A., Happe, F., & Charman, T. (2013). The persistence and stability of psychiatric problems in adolescents with autism spectrum disorders. *J Child Psychol Psychiatry, 54*(2), 186-194. doi: 10.1111/j.1469-7610.2012.02606.x

Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., & Baird, G. (2008). Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *J Am Acad Child Adolesc Psychiatry, 47*(8), 921-929. doi: 10.1097/CHI.0b013e318179964f

Siponmaa, L., Kristiansson, M., Jonson, C., Nyden, A., & Gillberg, C. (2001). Juvenile and young adult mentally disordered offenders: the role of child neuropsychiatric disorders. *J Am Acad Psychiatry Law, 29*(4), 420-426.

Smalley, S. L., McGough, J. J., Moilanen, I. K., Loo, S. K., Taanila, A., Ebeling, H., . . . Jarvelin, M. R. (2007). Prevalence and psychiatric comorbidity of attention-deficit/hyperactivity disorder in an adolescent Finnish population. *J Am Acad Child Adolesc Psychiatry, 46*(12), 1575-1583. doi: 10.1097/chi.0b013e3181573137

Solberg, M. E., & Olweus, D. (2003). Prevalence estimation of school bullying with the Olweus Bully Victim Questionnaire. *Aggress Behav, 29*(3), 239-268. doi: Doi 10.1002/Ab.10047

St Clair, M. C., Pickles, A., Durkin, K., & Conti-Ramsden, G. (2011). A longitudinal study of behavioral, emotional and social difficulties in individuals with a history of specific language impairment (SLI). *J Commun Disord, 44*(2), 186-199. doi: 10.1016/j.jcomdis.2010.09.004

Staller, J., & Faraone, S. V. (2006). Attention-deficit hyperactivity disorder in girls: epidemiology and management. *CNS Drugs, 20*(2), 107-123.

Sturm, H., Fernell, E., & Gillberg, C. (2004). Autism spectrum disorders in children with normal intellectual levels: associated impairments and subgroups. *Dev Med Child Neurol, 46*(7), 444-447.

Tape, T. (2004). *Interpreting Diagnostic Tests*: University of Nebraska Medical Center.

Tseng, M. H., Howe, T. H., Chuang, I. C., & Hsieh, C. L. (2007). Cooccurrence of problems in activity level, attention, psychosocial adjustment, reading and writing in children with developmental coordination disorder. *International Journal of Rehabilitation Research, 30*(4), 327-332.

Twyman, K. A., Saylor, C. F., Saia, D., Macias, M. M., Taylor, L. A., & Spratt, E. (2010). Bullying and ostracism experiences in children with special health care needs. *Journal of Developmental & Behavioral Pediatrics, 31*(1), 1-8.

Walkup, J. T., Ferrao, Y., Leckman, J. F., Stein, D. J., & Singer, H. (2010). Tic disorders: some key issues for DSM-V. *Depress Anxiety, 27*(6), 600-610. doi: 10.1002/da.20711

Washbrook, E., Propper, C., & Sayal, K. (2013). Pre-school hyperactivity/attention problems and educational outcomes in adolescence: prospective longitudinal study. *Br J Psychiatry, 203*(3), 265-271. doi: 10.1192/bjp.bp.112.123562

Waszczuk, M. A., Zavos, H. M., Gregory, A. M., & Eley, T. C. (2014). The phenotypic and genetic structure of depression and anxiety disorder symptoms in childhood, adolescence, and young adulthood. *JAMA Psychiatry, 71*(8), 905-916. doi: 10.1001/jamapsychiatry.2014.655

Wechsler, D. (2003). *Wechsler Intelligence Scale for children* (4th ed.). San Antonio: Harcourt Assessment.

Westendorp, M., Hartman, E., Houwen, S., Smith, J., & Visscher, C. (2011). The relationship between gross motor skills and academic achievement in children with learning disabilities. *Res Dev Disabil, 32*(6), 2773-2779. doi: 10.1016/j.ridd.2011.05.032

WHO. (1992). *International Classification of Diseases (10th Revision)*. Geneva.

Viner, R. M., & Taylor, B. (2007). Adult outcomes of binge drinking in adolescence: findings from a UK national birth cohort. *J Epidemiol Community Health, 61*(10), 902-907. doi: 10.1136/jech.2005.038117

Yoshimasu, K., Barbaresi, W. J., Colligan, R. C., Voigt, R. G., Killian, J. M., Weaver, A. L., & Katusic, S. K. (2012). Childhood ADHD is strongly associated with a broad range of psychiatric disorders during adolescence: a population-based birth cohort study. *J Child Psychol Psychiatry, 53*(10), 1036-1043. doi: 10.1111/j.1469-7610.2012.02567.x

Zulauf, C. A., Sprich, S. E., Safren, S. A., & Wilens, T. E. (2014). The complicated relationship between attention deficit/hyperactivity disorder and substance use disorders. *Curr Psychiatry Rep, 16*(3), 436. doi: 10.1007/s11920-013-0436-6