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Co-occurring Symptoms of Attention Deficit Hyperactivity Disorder and Depression

Sex, Aetiology, Help-Seeking and Assessment

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Abstract

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The general aim of the thesis was to contribute to the knowledge about co-occurring symptoms of ADHD and depression in adolescence, focusing on sex differences, as well as aetiology, help-seeking and assessment.

Studies I–III used epidemiological samples of self-reports from all students in Västmanland aged 15–16 and 17–18 years. Study I investigated the prevalence of co-occurring symptoms of ADHD and depression, as well as associations between co-occurring symptoms of ADHD and depression and one environmental stress factor; experience of sexual abuse. Study II examined associations between one biological factor—a polymorphism in *TFAP-2β*—and co-occurring symptoms of ADHD with and co-occurring symptoms of depression. Study III investigated the association between the parent–adolescent relationship and seeking help from specialized mental health services in relation to symptoms of ADHD and/or depression. Study IV was a clinical study among adolescent psychiatric patients that compared self-reported ADHD symptoms via the Adult ADHD Self-Report Scale–Adolescent version (ASRS-A) and the Adult ADHD Self-Report Scale–Adolescent–Screening version (ASRS-A-S) with an ADHD diagnosis determined by the gold-standard method; the Kiddie Schedule of Affective Disorders and Schizophrenia diagnostic interview.

Studies I–III showed that the phenotype of co-occurring symptoms of ADHD and depression is frequent, with a distinct preponderance among girls. Approximately 50% of both boys and girls with co-occurring symptoms of ADHD and depression had also experienced sexual abuse, indicating that this is a group with multiple risk factors for long-term impaired mental health.

Results also support biological sex differences because girls with symptoms of ADHD and a common polymorphism of *TFAP-2β* (absence of a 9 repeat) reported more symptoms of depression, but boys did not.

Further, only 5% of the adolescents with symptoms of ADHD and/or depression sought help from specialized mental health services. The co-occurrence of symptoms of ADHD and depression was a stronger predictor of help-seeking than all other psychosocial factors investigated, including secure attachment cognitions styles to parents. Among help-seeking girls, co-occurring symptoms of ADHD and depression were more common than symptoms of ADHD without co-occurring symptoms of depression.

The ASRS-A/ASRS-A-S showed promising psychometric properties for further validation in adolescents results as a screening tool for use in adolescents.

Keywords: Attention deficit hyperactivity disorder, depression, adolescent, sex, sexual abuse, transcription factor AP-2β, help-seeking, attachment object, validation study

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To Wolfgang, Anna and Felicia

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List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. Sonnby K., Åslund C., Leppert J., Nilsson K.W. (2011) Symptoms of ADHD and depression in a large adolescent population: Co-occurring symptoms and associations to experiences of sexual abuse. *Nord J Psychiatry*, 65 (5): 315–322.
- II. Nilsson K.W., Sonnby K., Nordquist N., Comasco E., Leppert J., Orelund L., Sjöberg R.L. (2013) Transcription Factor Activating Protein-2 β (*TFAP-2 β*) genotype and symptoms of attention deficit hyperactivity disorder in relation to symptoms of depression in two independent samples. *Eur Child Adolesc Psychiatry*, Jul 4.[Epub ahead of print]
- III. Sonnby K., Nilsson K.W., Ramklint M. Influence of the parent–adolescent relationship on mental health help-seeking. (Submitted)
- IV. Sonnby K., Skordas K., Olofsdotter S., Nilsson K.W., Ramklint M. Validation of the World Health Organization Adult ADHD Self-Report Scale for use in adolescence. (Submitted)

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Abbreviations and definitions

ADHD	Attention deficit hyperactivity disorder
ASRS	Adult ADHD Self-Report Scale
ASRS-S	Adult ADHD Self-Report Scale–Screening version
ASRS-A	Adult ADHD Self-Report Scale–Adolescent version
ASRS-A-S	Adult ADHD Self-Report Scale–Adolescent–Screening version
COMT	Catechol-O-methyltransferase
CSA	Child sexual abuse
DSRS	Depression Self-Rating Scale
DSRS-A	Depression Self-Rating Scale–Adolescent version
ECR-RC9	Experiences in Close Relationships-Revised-Children-9
GLM	General linear model
GWAS	Genome-wide association study
HPA axis	Hypothalamic-pituitary-adrenal axis
OR	Odds ratio
TFAP-2 β	Transcription factor activating protein 2 β
<i>TFAP-2β</i>	Transcription factor activating protein 2 β gene
VNTR	Variable number of tandem repeats

Thesis at a glance

Study	Objective	Setting & Methods	Results	Conclusions
I	Prevalence of co-occurring symptoms of ADHD/depression and associations with sexual abuse	Epidemiologic n = 4910 ASRS-A-S DSRS-A Trauma questions	The prevalence of co-occurring symptoms of ADHD and depression in adolescence was 2 % (boys 1 %, girls 4 %). The prevalence of experience of any sexual abuse was 21 % (boys 13 %, girls 29 %). Of those with co-occurring symptoms, 48% of the boys and 47% of the girls reported a history of sexual abuse.	School-based screening for co-occurring symptoms of ADHD and depression might identify students at psychiatric and psychosocial risk.
II	Associations between symptoms of ADHD and a polymorphism of the <i>TFAP-2β</i> with symptoms of depression	Epidemiologic n = 1506 n = 175 ASRS-A-S DSRS-A Genotyping	In two independent samples of adolescents, 6 and 8% screened positively for co-occurring symptoms of ADHD and depression. Symptoms of depression were more common among girls who screened positively for ADHD and did not carry the nine-repeat allele of the <i>TFAP-2β</i> intron 1 variable number of tandem repeat (VNTR) polymorphism.	The presence of the nine-repeat variant of the <i>TFAP-2β</i> intron 1 VNTR appears to protect girls with ADHD symptoms from co-occurring symptoms of depression.
III	Help-seeking from specialized mental health services in relation to the parent-adolescent relationship	Epidemiologic n = 4506 ASRS-A-S DSRS-A ECR-RC9	Help-seeking was predicted by co-occurring symptoms of ADHD and depression (OR = 5.4), symptoms of depression (OR = 4.8) and symptoms of ADHD (OR = 2.6), as well as any experience of sexual abuse (OR = 1.7) and being female (OR = 1.6). Secure attachment to parents, assessed with the ECR-RC9, did not increase help-seeking.	Secure attachment did not increase help-seeking. Symptoms of ADHD and/or depression predicted help-seeking more than any of the investigated psychosocial factors.
IV	Validation of the World Health Organization Adult ADHD Self-Report Scale (ASRS) for use in adolescents	Clinical study; psychiatric setting n = 134 ASRS-A/ ASRS-A-S K-SADS	The diagnostic accuracy of the ASRS-A and the ASRS-A-S were sensitivity, 79% vs 74%; negative predictive value, 84% vs 81%; specificity, 60% vs 59%; and positive predictive value, 51% vs 49%. Both versions showed better properties for girls than for boys.	Both the ASRS-A and ASRS-A-S showed promising psychometric properties for further validation.

1. Introduction

In 2005, the Swedish Council on Technology Assessment in Health Care published “ADHD in girls”, which stated that girls with attention deficit hyperactivity disorder (ADHD) were under-recognized and under-treated compared with boys, despite equal impairments due to the disorder. Moreover, adolescent girls with ADHD suffered from depressive symptoms more often than girls without ADHD. At the child psychiatric clinic in Västerås at that time, boys were typically referred for symptoms of ADHD before adolescence and girls were referred for symptoms of depression during adolescence. Comorbidity was not thoroughly examined in any of the groups.

With this background, research planned with Susanne Olofsdotter and Kent W. Nilsson led to the clinical research project: *“Co-occurring symptoms and treatment response; interaction between psychosocial factors and genetic vulnerability in child and adolescent psychiatric patients”*, of which this thesis is a part. The clinical data collection became part of a new clinical routine for all referred patients, which included symptom screening for ADHD. This promptly increased the rate at which depressed adolescent girls were assessed for ADHD.

One aim of the project and focus in this thesis was to gain knowledge about co-occurring symptoms of ADHD and depression, in order to better understand aetiological aspects, help-seeking and sex differences, and to improve diagnostic assessments. It is hoped that this knowledge will be used to enhance the recognition, treatment and support for girls with ADHD to the same level as that provided for boys with ADHD.

2. Mental disorders in children and adolescents

Worldwide, 10–20% of all children and adolescents are currently affected by a mental disorder¹. After congenital disabilities and diseases during the first year of life, mental disorders are the most common cause of disease in children and adolescents in Sweden².

Childhood and adolescence are characterized by intense psychosocial, cognitive and physical development³. Suffering from serious mental health disorders during these stages might therefore have a negative impact on development^{3,4}. The consequences of early-onset mental disorders are often negative and long-lasting, and extend into adult life^{5,6}. They are also essential contributors to the global burden of disease. Depression is the third highest contributor to this burden⁷. In middle- and high-income countries, depression even is the leading cause of disease burden when years lived with disability and years lost due to preterm death are taken into account⁸.

In Sweden, 6% of the approximately 502,452 individuals aged 13–17 years are affected by depression every year (30,147 individuals). If the negative impact on psychosocial development and education was equated to the loss of income by adults in Ekman et al's study⁹, the cost of impairments caused by depression in adolescents would be 4.5 billion SEK each year.

2.1. Age of onset and sex differences of mental disorders

Mental disorders in children and adolescents have different patterns of age of onset and characteristic sex differences. More boys than girls have early-onset disorders, which often include neuropsychiatric disorders, such as ADHD¹⁰. However, more girls than boys have disorders that have their most frequent onset in adolescence, such as depression¹⁰. ADHD and depression are two of the most common reasons for seeking help at specialized child and adolescent psychiatric care facilities^{6,11}. The two preponderant groups of child psychiatric patients are boys in early grades with symptoms of ADHD and adolescent girls with symptoms of depression¹¹.

2.2. Sex, gender and mental disorders

The terms sex and gender are often used inconsistently and interchangeably in health research. However, sex refers to the biological distinction between males and females, whereas gender emphasizes the socially constructed differences between men and women¹². The sex is genetically programmed, and there are more similarities than differences between males and females.

Social constructions of gender determine attitudes about what men and women are capable of and how they should behave¹². Attributions related to gender affect many aspects of life, including needs, opportunities and access to resources¹². While sex is associated with biological functions, the genders are social constructions that differ with culture, change with history and can be displayed by both sexes¹².

The ongoing interactions of biological sex-linked variations and socio-cultural environments related to gender also shape the phenotypes of mental disorders¹². The distinction between sex and gender is therefore of importance in health research and needs to be considered in a systematic way, with gender regarded as a kind of environment¹².

2.3. ADHD

ADHD is a disorder characterized by attention deficits, impulsivity and hyperactivity^{13,14}. The onset must be before the age of 12 years and symptoms must cause impairment in at least two areas of everyday life such as at home and in school¹³. ADHD can be divided into separate subtypes according to the predominant type of symptoms; inattentive type, hyperactive type or combined type^{13,15}. Further, ADHD is associated with suicidal attempts and completed suicide^{16,17}. Symptoms of ADHD have negative effect on school performance^{18,19}, social relationships²⁰, physical health²¹, and increase suicidal risk¹⁷. Early recognition and treatment improves prognosis, including occupational outcome^{22,23}.

Sex differences concerning the prevalence of ADHD are affected by many sources of uncertainties. For example, teachers are more reliable in reporting ADHD symptoms in boys than in girls^{19,24}, and many studies that rely on clinical populations have overestimated ADHD in boys because of referral bias²⁵. Further, the symptom criteria seem to be more appropriate for boys than girls; girls have been found to be equally as impaired as boys, despite not fulfilling all the symptom criteria²⁶.

ADHD is estimated to affect about 5–9% of the population; the prevalence rates in the literature range from 2% to 18%, depending on the study population, the methodology of the study—particularly the definition of ADHD—and the diagnostic methods used^{14, 26, 27}. Parent reports yield higher prevalence rates than teacher reports, especially for girls^{14, 28}. Semi-structured diagnostic interviews that also assess impairment produce lower prevalence rates¹⁴.

Girls and boys with ADHD are characterized by different impairment profiles. Boys with ADHD are more impaired in motor skills than girls with ADHD, and have persistent delayed development compared with male controls without ADHD, whereas girls with ADHD do not differ from female controls without ADHD. However, girls with ADHD are more impaired than boys on oculomotor control and visuo-spatial functions²⁹. Moreover, when boys and girls with ADHD were followed up according to their impairment profiles, children with the ADHD subtype least common for their sex (inattentive subtype in boys and combined subtype in girls) improved less with age³⁰.

2.4. Depression

Depression is a disorder with life-threatening potential through its association with suicide and is characterized by sadness, irritability and/or loss of interest^{13, 31}. Depressed children and adolescents can present with irritability as the only mandatory symptom of depression¹³. Adolescent depression is associated with negative impact on academic, social and health outcomes, as well as with other psychiatric problems including depression in adulthood^{31, 32}. The most common duration of a depressive episode in adolescence is at least one year³³. Depression of such long duration has a poor long-term mental health prognosis³⁴. The prevalence of depression before adolescence is 1–3%, with a ratio between sexes of approximately 1:1^{35, 36}. Around puberty, there is an increase to a sex ratio of at least twice as many girls as boys with a one-year-prevalence of 6%, and a life time prevalence of 12%^{27, 33, 37}.

There is some evidence that depression in adult males has specific features with increased symptoms of aggression, impulsiveness and alcohol over-consumption^{38, 39}. However, these “male” symptoms have also been found to be highly prevalent in females⁴⁰. Further, none of the “male” depression studies investigated the coexistence of symptoms of ADHD. The perceptions of “male” and “female” symptoms may also be filtered through the sex-specific socio-cultural expectations of the observer in addition to different comorbidity profiles in men and women with depression⁴¹⁻⁴³.

3. Comorbidity

Comorbidity in child and adolescent psychiatric disorders is very common^{10, 44}. Population-based studies demonstrate comorbidity rates far exceeding those expected from the relatively low prevalence of each separate condition^{35, 36}. In clinical settings, comorbidity rates of 45–65% have been found, with higher rates occurring when semi-structured diagnostic interviews have been used for assessment^{11, 45}. Comorbidity is associated with greater severity of illness, greater impairment, lower treatment response and worse prognosis⁴⁵⁻⁴⁷. It is therefore important that comorbidity is evaluated^{45, 48}. Further, comorbidity indicates a need for interventions beyond those effective in individuals with single diagnoses⁴⁹.

3.1. Comorbid ADHD and depression/co-occurring symptoms

The prevalence of ADHD and comorbid depression varies between 15% and 75%, with lower prevalence rates in population-based studies than in clinical populations^{35, 50-52}, and show a preponderance of adolescent girls^{26, 53}. Moreover, girls with ADHD have more than double the risk for depression than girls without ADHD. In girls with ADHD, depression is associated with an earlier age of onset, more than double the duration, more severe depression-associated impairment and a greater likelihood of requiring psychiatric hospitalization than in girls with depression but without ADHD⁵⁴. In fact, several studies on patterns of familial aggregation of ADHD and depression suggest the possible existence of a subtype of comorbid ADHD and depression in females⁵⁵⁻⁵⁷.

In boys, ADHD confers an increased risk for suicide through comorbid depression and conduct disorder, compared with girls with ADHD and boys without ADHD^{16, 58}.

4. Etiological models of mental disorders - emphasis on ADHD and depression

Historically, *biological* and *environmental* models competed as free-standing explanations of mental disorders and the nature vs nurture debate has been going on for centuries⁵⁹. In the 1950s the biopsychosocial model was proposed by the neurologist and psychiatrist Roy Grinker⁶⁰, and later followed by Engel in the 1970s⁶¹. It integrates influences from biology and environment in an eclectic manner⁶¹. Inherited genetic vulnerability is thought to sensitize the individual to stress and prompt the development of mental disorders. According to the model, an individual without this vulnerability would be better prepared to handle stress in life. This theory was tested in 2002 when Caspi et al presented a study of gene–environment interactions in the development of depression, which has been replicated in other studies⁶²⁻⁶⁴. In the last decades of the 20th century, the new knowledge of *epigenetics*—continuing genetic alterations in living organisms—was integrated into the models explaining mental disorders⁵⁹. For example, both prenatal and post-natal stress of infants has an impact through epigenetic alterations on stress regulation, causing sensitization to the stress response⁶⁵.⁶⁶ From an evolutionary aspect, this is an adaption to adversities of the environment, which increases the chances of survival and early reproduction in the offspring⁶⁵.

4.1. Biology in mental disorders

Childhood and adolescence are periods of intensive physical, cognitive and psychosocial development. However, typically developed boys and girls show sex differences in maturation speed, with boys up to a year and a half behind girls²⁹. There are differences in brain morphology and development as well as motor skills, eye-hand coordination and executive functions. These skills improve with age in typically developed children and adolescents, and improve faster among girls than boys. Boys and girls of the same biological age are therefore in different phases of their development. Further, individuals with ADHD are impaired according to the skills mentioned above, when compared with typically developed children and

adolescents. However, compared with boys of the same age, girls with ADHD may be protected by their earlier maturation²⁹.

On the other hand, the pubertal increase of sex hormones in females and the associated changes in the central nervous system may increase their ADHD symptoms in adolescence^{29, 68}. Adolescent boys experience a decrease in their ADHD symptoms at this stage of development, mainly in hyperactivity/impulsivity^{67, 68}.

Physiological changes associated with female sex hormone levels in puberty are also involved in the development of the gender gap in depression prevalence, with at least twice as many affected adolescent girls as boys. However, before puberty and after menopause, the prevalence of depression is approximately equal among males and females⁶⁶.

In conclusion, there are physiological differences between boys and girls that influence both ADHD and depression symptoms.

Genetics and mental disorders

Genes are universal to living organisms and constitute a growing research field regarding mental disorders in humans. Each cell nucleus includes chromosomes with DNA, which contain all the hereditary material of the organism. The DNA consists of chemical base pairs; combinations of the bases adenine (A), guanine (G), cytosine (C) and thymine (T)⁶⁹. The expression of the DNA varies with tissue type, and this affects which parts of the DNA are active for transcription⁶⁹. Genetic characteristics are contributors to complex traits, such as psychiatric disorders, which are associated with alterations of neural transmission of the central nervous system in the brain⁷⁰. The human brain consists of more than 100 billion neurons that are in touch with each other through synapses, where they receive, process and send signals. Most signals of the central nervous system are transmitted by approximately ten different transmitter substances⁷⁰.

Several mental disorders, such as depression, anxiety disorders and eating disorders, have been related to the dysregulation of the monoaminergic neurotransmission system⁷¹. Examples of monoamine neurotransmitters are the catecholamines (dopamine, noradrenaline and adrenaline) and the tryptamines (serotonin and histamine)⁷⁰. Monoaminergic transmission and groups of monoaminergic genes are implicated to be of importance for both ADHD and depression⁷²⁻⁷⁴.

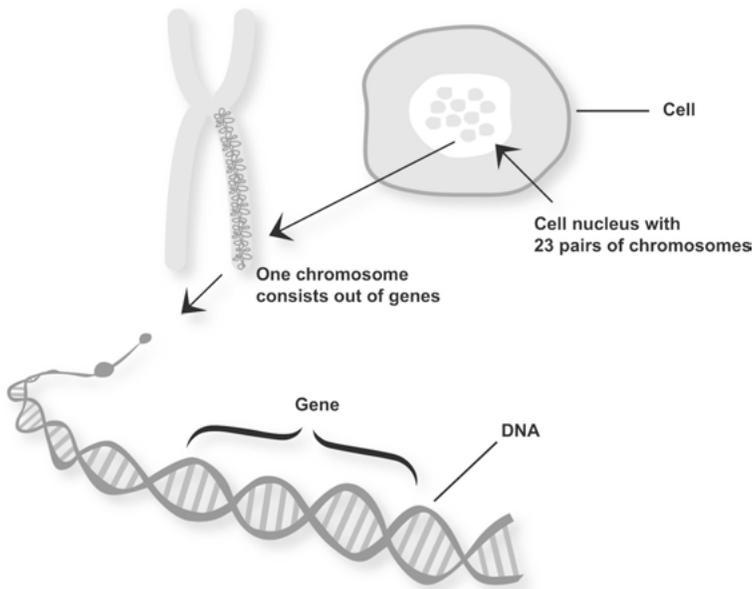


Figure 1. A cell with 23 pairs of chromosomes, containing genes and the DNA.

The heritability of psychiatric disorders is considerable. Genetic vulnerability explains 30–40% of depression and 70–80% of ADHD cases^{75, 76}. Candidate gene studies and whole-genome studies have failed to identify specific genetic associations conferring depression or ADHD^{77, 78}. It is therefore assumed that the phenotypes of depression and ADHD may result from several different genotypes^{79, 80}.

Studies on patterns of familial aggregation of ADHD and depression suggest that a subtype of comorbid ADHD and depression may exist preferentially in females^{55, 56, 81}. Previous studies have failed to identify genetic loci with significant genome-wide associations with ADHD and depression when considered separately^{82, 83}. However, a recent genome-wide-association study (GWAS) on shared genetic risk of psychiatric disorders, including ADHD and depression, supported the role of calcium channels signalling genes and specific single-nucleotide polymorphisms for both disorders⁸⁴. In addition, monoaminergic transmission and groups of monoaminergic genes have been studied for both disorders in a considerable number of studies^{72, 73}.

Even though candidate genes for the disorders do not overlap to any considerable extent, the fact that they belong to closely interrelated systems makes it realistic to assume that comorbid ADHD and depression may share genetic risk via candidate genes. This is the case with ADHD and severe conduct disorder, which share genetic risk via the high-activity catechol-O-methyltransferase (COMT) genotype⁸⁵. Recently, in GWAS

analyses, ADHD has been associated with both common and rare copy number genetic variants, suggesting the existence of several pathways to the disorder^{86, 87}. Functional polymorphisms of transcription factors with binding sites on candidate genes relevant to monoaminergic functions for several psychiatric disorders could be involved in the distinct subtype of ADHD with co-occurring depression.

Among several other genes of monoaminergic transmission believed to be related to ADHD and depression, the transcription factor activating protein 2-family, including the transcription factor activating protein-2 β gene (*TFAP-2 β*), is suggested to be involved in the neurophysiology of both disorders^{71, 88}.

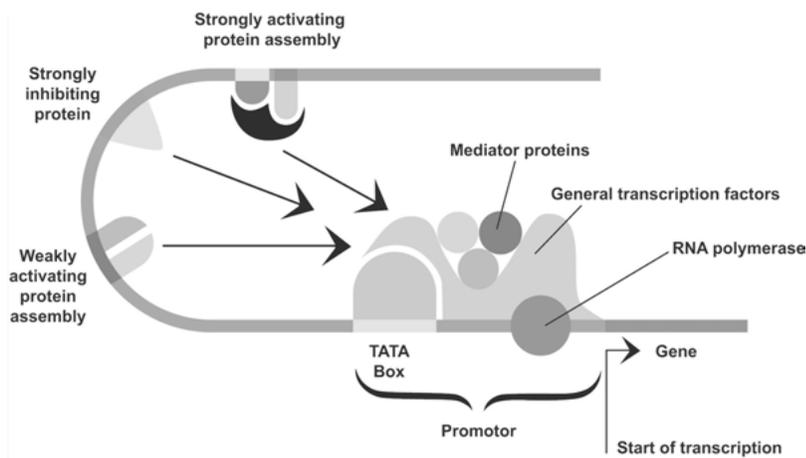


Figure 2. Schematic picture of a regulatory region of a gene, including transcription factors.

Transcription factors are proteins that regulate genetic transcription. They bind to promoter regions—specific DNA sequences, where transcription starts—and thereby control the transfer (or transcription) of genetic information from DNA to RNA, thus regulating the production of new proteins⁶⁹. The TFAP-2 β -family is extensively involved in the production of proteins in the brain, of which several are part of the monoaminergic system⁸⁹. More specifically, high brain stem levels of the TFAP-2 family has been associated with both dopamine and serotonin turnover. The TFAP-2-family is therefore suggested to play a regulatory role in monoaminergic gene expression in the brainstem nuclei, which can affect release and metabolism of serotonin and dopamin^{90, 91}.

Several genes involved in brainstem CNS transmitter systems, which are of fundamental importance for personality and behaviour, display multiple binding sites for the TFAP-2-family (including the TFAP-2 β -family) in their

regulatory regions (e.g., 5HTTLPR, DBH, DAT, D1ADR, AADC, 5-HT2A, TPH and CHAT)⁷¹.

In the *TFAP-2β* gene there is a common variable number of tandem repeat (VNTR) polymorphisms consisting of 8, 9 or 10 repeats⁹², located at the first intron. It has been shown to be of functional importance⁹³, so that a 9-repeat variant of this polymorphism has been associated with increased gene expression (higher levels of the intracellular cytokines TNF-α and high-sensitivity C-reactive peptide) compared with the 10-repeat variant⁹².

4.2. Biological–environmental interplay and mental disorders

Epigenetics is the ongoing gene–environment interaction with genetic alterations, without changes in the DNA sequence^{94,95-97}. The genetic alterations influence gene expression, which in turn modulates the production of proteins that mediate physical changes. Epigenetics provides a wider understanding of how positive and negative environments contribute to health and sickness⁹⁸. It also challenges former knowledge, by showing that complex interactions between biological, psychological and socio-cultural factors exist⁹⁸. For instance, there are numerous studies on the prevalence of depression, which consistently show at least a doubling in prevalence in women between puberty and menopause^{27, 33}. However, the potent environmental/socio-cultural stress factor of sexual abuse is 3–12 times more common among females than among males^{99, 100}. Stress leads to epigenetic changes in the stress response conveyed by the HPA axis (e.g. release of glucocorticoid hormones), which can at least partly explain the increased prevalence of depression among women⁹⁷.

In a study of interpersonal vulnerability factors for depression among adolescents, few differences were found between boys and girls, although the factors were more frequent among girls. As the frequency of exposure to stressful events or sexual abuse was not investigated, the increased frequency of the vulnerability factors found (negative self-perceptions in the domains of achievement, global self-worth and physical appearance) might be consequences of sexual abuse¹⁰¹.

However, there are also studies indicating that both prenatal stress and postnatal stress are associated with sex differences in the stress response^{97, 98, 102, 103}.

Stress and mental disorders

In the 1930s, endocrinologist Hans Selye identified a reaction that he later called “stress”; an unspecific response of an organism to stressors. Further, he proposed glucocorticoid hormones to be associated with the physiological stress response^{104, 105}. The function of the stress response is to adapt the organism to surrounding stimuli¹⁰⁵. Different kinds of stress have been identified, such as “positive stress” and “negative stress”, that are related to the triggering stimuli (e.g., triggering stimuli of attempting an interesting and demanding task versus escaping a physical attack)¹⁰⁵. Moreover, there are differences according to the duration of stress stimuli; short duration of intensive stress causes “acute stress”, and long-lasting stress causes “chronic stress”. The duration and also the severity of the stress stimuli is associated with different physiological stress response patterns as well as different associations with negative health effects^{105, 106}.

Historically, research on the fight and flight stress response has been performed mainly in male animals and humans, as females have greater cyclical variation in neuroendocrine patterns than males and their results are often confusing and uninterpretable. As a consequence, evidence concerning the fight or flight response in females has been inconsistent¹⁰⁷. A complementary stress response model, more prominent among females than males, is the “tend and befriend” model proposed by Taylor in 2000¹⁰⁷. The model suggests that the female response to stress has evolved selectively to maximize the survival of the individual and her offspring¹⁰⁷. During situations of stress, the female responds by “tending”: nurturing her offspring using behaviours that protect them from harm and reduce the neuroendocrine responses that might otherwise have a negative effect on their health¹⁰⁷. Through “befriending”—affiliating with social groups—females also reduce the risk for themselves and their offspring¹⁰⁷. Further, Taylor hypothesized that females create, maintain and utilize social groups, especially relations with other females, to manage stressful conditions, and that female responses to stress build on attachment and caregiving processes that downregulate sympathetic and HPA axis responses to stress¹⁰⁷.

Research on acute stress responses supports sex differences in information processing and social behaviour in humans^{102, 103, 108}, which is consistent with animal studies^{109, 110}. Proneness to sex-related stress responses (fight or flight in males and tend and befriend in females), may influence phenotypic patterns of mental disorders at the group level, including ADHD and depression¹¹¹. In fact, stress has been shown to cause elevated levels of externalizing behaviour in males compared with females¹¹², and separation of mothers from their offspring causes increased levels of internalizing symptoms¹¹³.

Sexual abuse: a common environmental stress factor

The prevalence of sexual abuse in international population-based studies is estimated to be 20%, with a consistent preponderance of female victims¹¹⁴⁻¹¹⁶. Hornor et al define sexual abuse as “any sexual conduct or contact of an adult or significant older child with or upon a child for the purposes of the sexual gratification of the perpetrator”, page 359¹¹⁷. Sexual abuse constitutes a common type of trauma or environmental stress and is a complex life experience with often long-lasting negative consequences for the victim¹¹⁸. Children and adolescents who experience sexual abuse often feel powerless and unable to control what happens, which is a stressor with neurodevelopmental effects¹¹⁷. The experience of sexual abuse, and the individual responses to it, have the potential to disrupt normal development and may influence a child’s adaptation and subsequent development of cognition and attention, social skills, personality style, self-concept, self-esteem and impulse control⁵. The risk of developing psychopathology as a consequence of sexual abuse is influenced by the accumulative effect of the severity of the traumatizing events and the number of events^{119, 120}. Sexual abuse has been associated, throughout the whole life continuum, with reduced quality of life and impaired physical and mental health, including major depression and suicidal behaviour^{66, 119, 121-126}.

Furthermore, sexually abused individuals have an unexpectedly high prevalence of ADHD, and adults with ADHD retrospectively report a higher prevalence of childhood sexual abuse^{127, 128}. It is unknown whether ADHD confers vulnerability to the development of depression, anxiety or PTSD in those who have experienced sexual abuse, or if ADHD symptoms confer behaviours that increase the risk of experiencing sexual abuse. Moreover, depression is characterized by indifference to one’s own security and one’s own problem behaviours, such as increased alcohol consumption, which may lead to situations with an increased risk of sexual abuse¹²⁹. Figure 3 presents possible aetiological models.

1. →	2. →	3. →	Phenotype with co-occurring symptoms of ADHD and depression
CSA	ADHD	DEP	The stress of sexual abuse may increase the risk for ADHD and depression. ADHD increases the risk for depression, because it elevates stress levels.
CSA	DEP	ADHD	The stress of sexual abuse may increase the risk for depression and ADHD. Depression may contribute to ADHD through overlapping symptoms.
ADHD	CSA	DEP	ADHD may confer increased risk for sexual abuse because the symptoms of impulsivity and impaired executive functions may reduce the ability to foresee or avoid risk. Both ADHD and exposure to sexual abuse increase the risk for the development of depression.
ADHD	DEP	CSA	ADHD may confer increased risk for sexual abuse because the symptoms of impulsivity and impaired executive functions may reduce the ability to foresee or avoid risk. ADHD increases the risk for depression, because it elevates stress levels. Depression may confer the risk for sexual abuse because it is associated with indifference to one's own security and increased alcohol consumption. The stress of sexual abuse may increase the expression of symptoms of both ADHD and depression.
DEP	CSA	ADHD	Depression may confer the risk for sexual abuse because it is associated with indifference to one's own security and increased alcohol consumption. Depression and the stress of sexual abuse may contribute to ADHD symptom development.
DEP	ADHD	CSA	Depression may confer the risk for sexual abuse because it is associated with indifference to one's own security and increased alcohol consumption. Depression may contribute to ADHD through overlapping symptoms. ADHD may confer increased risk for sexual abuse because the symptoms of impulsivity and impaired executive functions may reduce the ability to foresee or avoid risk. The stress of sexual abuse may increase the expression of symptoms of both ADHD and depression.

Figure 3. Conceivable stepwise aetiological models of the phenotype with co-occurring symptoms of ADHD and depression (DEP) in relation to child/adolescent sexual abuse (CSA).

Attachment theory and mental disorders

The attachment theory conceptualizes humans as being biologically prepared to form affectionate bonds with a caregiver¹³⁰. The development of such an attachment to a caregiver protects the infant from dangers and stress, which thereby increases the likelihood of survival and reproductive success¹³⁰. Both the prerequisite genetics of the child and environmental factors, such as the ability and willingness of the caregiver to respond to the attachment needs of the infant, influence the attachment process¹³¹⁻¹³⁴.

Based on Bowlby's attachment theory, Mary Ainsworth made observations of children and their caregivers in a laboratory setting. Her "strange situation procedure" included the child's separation from and reunion with the caregiver¹³⁵, and formed the basis for the identification of different attachment patterns: secure attachment, insecure avoidant attachment and insecure anxious/resistant (preoccupied) attachment. Later research added a fourth attachment pattern, called insecure disorganized (fearful) attachment¹³⁶.

The attachment patterns, also called attachment styles¹³⁷, can be measured along two dimensions, attachment anxiety and attachment avoidance. Attachment styles continue to be important for interpersonal behaviour and development throughout the lifespan¹³⁸⁻¹⁴⁰. The internal working models of the self and others, which are created in infancy, are supposed to constitute the foundation for the development of corresponding models used in adult life^{138, 140}.

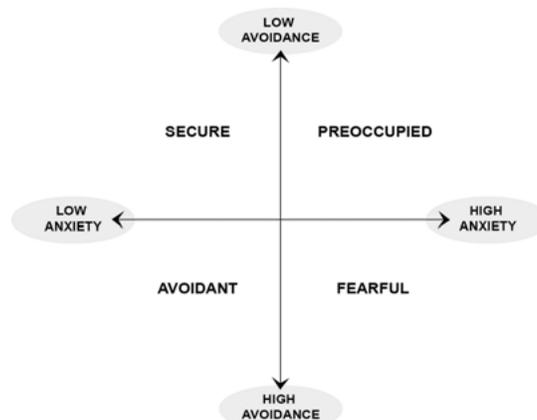


Figure 4. The dimensions of attachment anxiety and attachment avoidance in relation to characteristics of secure, preoccupied, avoidant and fearful attachment style.

The secure attachment style is characterized by low scores on both the dimensions of attachment anxiety and attachment avoidance. Further characteristics are a relative resilience to problems with interpersonal functioning, emotion regulation and mental health, in comparison to the insecure attachment styles¹⁴¹. The attachment styles with higher attachment anxiety or attachment avoidance both rely on secondary attachment strategies to cope with threats¹⁴¹. These strategies lead to either hyperactivation of the attachment system, as is the case for the anxious attachment style, or deactivation of the attachment system, which is the case for the avoidant attachment style¹⁴¹. Among other mental health problems, both symptoms of ADHD and depression have been found to be associated with insecure attachment styles in children and adolescents, as well as with insecure attachment styles of their parents¹⁴¹⁻¹⁴³. The role of the attachment style of adolescents for help-seeking from specialized mental health care is unclear.

4.3. Socio-cultural context and mental disorders

The socio-cultural context, as a part of the environment, also influences mental disorders and their identification^{22, 41, 144}. The same symptoms might be perceived differently depending on whether a boy or a girl exhibits them. For example, ADHD in the socio-cultural context of Western countries is more often recognized and perceived as “existing” among boys than among girls¹⁴⁵⁻¹⁴⁷. This phenomenon has been demonstrated in several studies. One study aimed to investigate the mental health literacy among adults with regard to adolescent depression and ADHD. The participants viewed videotaped vignettes of male and female adolescents expressing normal behaviour, symptoms of depression or symptoms of ADHD. Symptoms of ADHD were significantly less often recognized in adolescent girls than in boys expressing the same kinds of symptoms⁴¹. In a similar study that investigated teachers’ ability to recognize ADHD in children, teachers viewed video vignettes of children exhibiting symptoms of ADHD. When a girl exhibited typical symptoms of ADHD the behaviour was interpreted as oppositional, whereas when a boy was oppositional the behaviour was interpreted as ADHD¹⁴⁸.

Another study showed that regardless of the perception of symptoms of ADHD, which was equal in sons and daughters, mothers interpreted what they saw differently depending on the sex of the child. Girls’ ADHD symptoms were more often explained as a consequence of the environment, whereas boys’ symptoms were more often explained by medical or biological causes. Boys in the study were five times more likely to receive a diagnostic assessment than girls with the same symptoms¹⁴⁹. Because of

socio-cultural biases, the sex of the individual with ADHD is associated with its identification, and therefore with the individual's treatment, support and prognosis^{23, 41, 145, 148}.

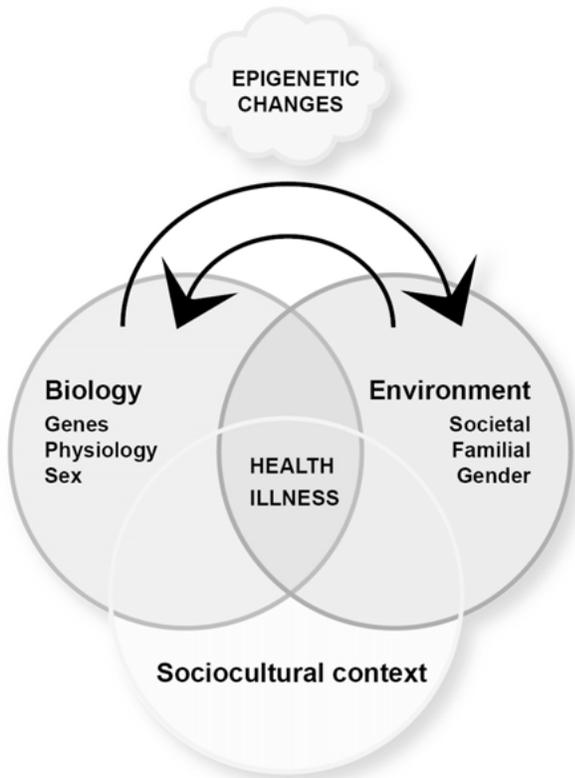


Figure 5. An aetiological model of mental disorders where biological and environmental factors interact in an epigenetic interplay. The socio-cultural context influences what is considered ill or healthy at a given time and place.

To sum up, genetic vulnerability, prenatal stress exposure and early attachment together with the sex of the individual, may be the foundation for later stress response patterns^{107, 141, 150}. From that platform, the eventual development of mental symptoms would depend on the balance of stress responses on positive and negative environmental factors throughout life, modulated by continuous epigenetic changes.

On the one hand, there is support for sex differences in biological and epigenetic risk factors for mental disorders. On the other hand, there are also differences in the environmental risk factors related to sex as well as to the socio-cultural construction of gender.

5. Help-seeking for mental disorders

Despite the high frequency of mental disorders in childhood and adolescence, only a minority seek help, even among severely impaired individuals^{146, 151, 152}. The reasons for help-seeking or otherwise can be described as “help-seeking facilitators” and “help-seeking barriers”¹⁵³.

Many studies report help-seeking barriers such as stigmatizing attitudes to mental illness, embarrassment, worries about confidentiality, difficulties in identifying symptoms as mental illness, distrust in the treatment and fears of being unkindly treated by health-care professionals^{153, 154}. A large proportion of adolescents, especially males, prefer self-reliance and handling the problem themselves or seeking informal help from family or friends^{153, 154}. Moreover, practical help-seeking barriers, such as worries about time, costs, transports and inconveniences, especially in rural areas, play a role¹⁵³.

Help-seeking facilitators are comparatively less well studied^{153, 154}. Socio-economic factors, such as higher levels of education in mothers, in combination with the severity of symptoms, have been found to be associated with help-seeking^{155, 149}. Perhaps the most important facilitator for mental health help-seeking is a positive past experience of mental health care, however social support from others to seek help also increases help-seeking. Confidentiality and trust in the health-care provider and positive relations with service staff are other facilitators. Mental health literacy (e.g., awareness of the difference between a personal problem and a mental health problem) increases help seeking. Additionally, female sex, ease of expressing emotions and, not surprisingly, a positive attitude towards help-seeking, are further facilitators¹⁵³.

5.1. Parent–adolescent relationship and mental health help-seeking

Verhulst and Koot developed a theoretical model for mental health help-seeking in children¹⁵⁶, which was revised by Zwaanswijk et al. to incorporate adolescents’ growing autonomy and influence on the help-seeking decision. Mental health help-seeking is described as a multistep process that

starts with *problem recognition* by the parents/adolescent and is followed by *awareness of service need* and finally, the *action of mental health help-seeking*. Parents' awareness of the problems of the adolescent precedes help-seeking¹⁵⁷. However, as Langeveld points out, the awareness of the parents may be influenced by characteristics of the parent–adolescent relationship¹⁵⁸. The information parents receive is influenced by the willingness of the adolescent to communicate with them. A small case–control study of adolescents, matched for sex, age and level of symptoms of depression and anxiety, found that adolescents who sought mental health assistance reported more caregiver warmth in relation to their parents, which supports the role of the parent–adolescent relationship in help-seeking from mental health services¹⁵⁸. In this context, Bowlby's attachment theory offers a well-established framework for the parent–adolescent relationship, although this has not been investigated in relation to help-seeking from mental health services¹³². Attachment style is a framework for the characteristics of the parent–adolescent relationship, whereby insecure attachment style is associated with symptoms of ADHD and depression, as well as a lower degree of trust in the communication with the parents. Insecurely attached adolescents are over-represented in clinical samples in comparison to the population¹⁴². However, only a minority of adolescents with symptoms of ADHD and depression seek help, and the reasons why some parents initiate help-seeking and others do not are unclear. As the likelihood of help-seeking is low, it is possible that secure attachment may enhance help-seeking due to characteristics of the parent–adolescent relationship.

5.2. ADHD, depression and help-seeking

Higher levels of psychiatric symptoms increase help-seeking^{146, 159, 160}. However, the nature of the symptoms and the sex of the adolescents influence the likelihood of mental health care use in different ways^{41, 145, 146, 153}. Depression in adolescence is at least twice as prevalent in girls as in boys, whereas the prevalence of ADHD is reversed^{27, 161}. At the same time, help-seeking is less frequent among adolescents with depression than among those who have ADHD^{145, 146}.

6. Assessment of mental disorders in children and adolescents

Psychiatric assessment, especially in children and adolescents is difficult out of several reasons. One of them is the lack defining line between normality and disorder as psychiatric symptoms are continuous variables³. In children and adolescents, complexity is added by the normal widespread differences in development³. Accordingly, the age of the affected individual also influences the judgement of symptoms, as symptoms can be deemed normal in one phase of development and indicate impairment and/or disease in another phase³.

Moreover, the diagnostic classification system, as set out in the Diagnostic and Statistical Manual of Mental Disorders (DSM)¹³, constitute agreements on valid entities for psychiatric disorders based on combinations of symptom criteria and diagnostic rules. Every symptom criterion precludes the rater's judgement, as meeting the threshold of a significant clinical symptom or not. Interrater variations in diagnostic judgement contribute further differences³. Therefore, the diagnostic methods also influence the estimate of prevalence of disorders^{3, 14}.

Psychiatric assessment through clinical interview without diagnostic tools, such as structured interviews and questionnaires, has been proven to be an unreliable method for the assessment of psychiatric diagnoses. Neither does the clinical interview identify comorbidity^{45, 48, 162, 163}. Semi-structured diagnostic interviews improve adherence to DSM-IV diagnostic criteria, are superior in identifying comorbidity and increase interrater reliability substantially^{45, 163-165}. There is also evidence suggesting clinical cost effectiveness in comparison to use of unstructured clinical interviews¹⁶². The Kiddie Schedule of Affective Disorders and Schizophrenia is a semi-structured diagnostic interview that is considered to be the best available diagnostic method for use in child and adolescent psychiatry^{3, 45, 165}.

In spite of the documented advantages of using structured diagnostic interviews, they are seldom part of clinical routine assessments in child and adolescent psychiatry^{163, 166}. Clinical diagnoses still rely mainly on unstructured clinical interviews only, which must be considered a method

with significant deficiencies^{45, 165}. Diagnostic methods that rely on only clinical assessment imply higher risks of unrecognized diagnoses as well as unidentified comorbidity^{45, 163, 165}.

Studies of ADHD and depression in adolescents have shown that up to two-thirds of all patients with depression are overlooked by the omission of a structured diagnostic interview as part of the diagnostic procedure^{165, 167}. Among children and adolescents with ADHD, the mean diagnostic delay has been found to be 33 months. Particularly strong predictors of increased diagnostic delay were comorbid symptoms of depression/anxiety. However, this study was retrospective and consisted of a clinical population of mainly male ADHD patients. Individuals who had still not been diagnosed with ADHD were not a part of the study population. Therefore, a median diagnostic delay of 33 months must be considered a conservative estimate¹⁶⁸.

6.1. Diagnostic procedures and diagnostic tools in child and adolescent psychiatry

Quality-assured diagnostic procedures in a clinic benefit from regular assessment meetings, where videotaped or audiotaped diagnostic interviews are assessed together by the group. The aims of the meetings are to maintain interrater reliability, develop diagnostic skills in the group through the exchange of knowledge, and educate and support the less experienced staff. These meetings lead to a collective understanding of disorders despite different professional backgrounds, and improve the conceptual language use in the clinic (e.g. definitions of symptoms and disorders)¹⁶⁵.

Reliable diagnostic tools have undergone a developmental process, and have been investigated according to their psychometric properties¹⁶⁹. Several characteristics have been investigated; validity, reliability and diagnostic accuracy. The validity of an instrument determines whether the instrument measures what it is supposed to measure. Reliability is a measure of consistency and precision¹⁶⁹. Diagnostic accuracy is conceptualized as sensitivity and specificity, which determine the precision with which the diagnostic tool discriminates true cases from non-cases¹⁷⁰.

Investigations of diagnostic tools should be performed in a population as similar as possible to the population for which the diagnostic tool is intended¹⁷¹. Consequently, a screening questionnaire for ADHD in adolescents with intended use in psychiatric settings should be validated in adolescent psychiatric patients because the psychometric properties that are found may not be generalizable to other settings¹⁷¹. For example, the positive

and negative predictive value are sensitive to changes in the prevalence of the disorder of interest¹⁷⁰. The prevalence of ADHD in a population-based sample may be 4–9%, whereas in a psychiatric clinic, the prevalence is amplified^{27, 172}.

7. Aim and scope of the thesis

The general aim of the thesis was to contribute to the knowledge about co-occurring symptoms of ADHD and depression in adolescence, focusing on sex differences, aetiology, help-seeking and identification. It was hypothesized that a substantial proportion of adolescent girls with symptoms of depression would have co-occurring symptoms of ADHD. Further, a validated screening tool for ADHD in adolescents in clinical settings is needed in Sweden.

7.1 Study-specific aims

The specific aims of the individual studies were:

To examine (a) the prevalence of co-occurring symptoms of ADHD and depression and (b) to examine associations of co-occurring symptoms of ADHD and depression with experiences of sexual abuse in a population-based sample of adolescents (Study I).

To examine the interaction of polymorphisms of the *TFAP-2 β* genotype with symptoms of ADHD in relation to co-occurring symptoms of depression in two population-based samples of adolescents (Study II).

To examine the relation between the parent–adolescent relationship, symptoms of ADHD and/or depression in relation to help-seeking from specialized mental health services (Study III).

To investigate psychometric properties and diagnostic accuracy of the Swedish translation of the World Health Organization Adult ADHD Self-Report Scale for use in adolescent boys and girls in clinical psychiatric settings (Study IV).

8. Methods

8.1. Study designs

The Studies I-III were part of the Survey of Adolescent Life in Västmanland (SALVe) and had an epidemiological, cross-sectional design. SALVe aims to monitor the mental and somatic health of the adolescent population and is distributed biennially. The questionnaire was completed during school hours and participation was voluntary and anonymous. Study IV was a validation study in clinical psychiatric settings with cross sectional design. Patients were included from three sites, Sala and Västerås, both part of the Child and Adolescent Psychiatric Clinic Västmanland and the Enköping Child and Adolescent Psychiatric Clinic.

8.2. Description of the study participants

Study I- III

The target population for SALVe was all secondary school students aged 15–16 years and 17–18 years in 2001, 2006 and 2012. Students at special schools and pupils with insufficient knowledge of the Swedish language were excluded, as were students from schools and classes whose principals chose not to participate, in the flow-charts referred to as “administrative drop-out” (see next pages). At the time for the survey there were students absent from school or classes with practice period who did not participate, in the flow-charts referred to as “external non-respondents”. Out of the invited students between 77 % and 82 % participated in the Studies I-III. The teachers retained some questionnaires, and later administered them to students who had been absent from class during the original survey period. Questionnaires from the late respondents were returned by mail. Of the completed questionnaires, some did not indicate the student’s sex or were not adequately completed, in the flow-charts referred to as “internal non-respondents”. In study II group B it also refers to participants with failed genotyping (417 boys and 303 girls).

Study II group A

The target population for SALVe 2001 was all students aged 15–16 years and 17–18 years. Of those students, 785 volunteers agreed to participate also in a semi-structured in-depth interview and to give blood samples. All the students were classified with a risk index, based on the risk behaviours

(alcohol, narcotic, sexual, property offence, and violent offence) they reported in the questionnaire, and divided into four groups according to their respective risk index. After stratification for age, sex and deviant behaviours (focusing on individuals with high and low levels of deviant behaviour) 400 were randomly selected. The procedure of an initial risk survey was used to ensure that there would be enough participants from both ends of the deviant behaviour continuum. There were no explicit exclusion criteria. Two hundred individuals (119 girls and 81 boys) agreed to give blood samples and to take part in the interview. At the interview appointment, they were asked for informed consent a second time, consistent with the recommendations of the Human Ethical Committee of the Medical Faculty at Uppsala University.

A three-year follow-up study was performed by mailing a questionnaire with the Depression Self-Rating Scale (DSRS) and the Adult ADHD Self-Report Scale (ASRS) to the participants. One hundred and fourteen girls and 66 boys answered (19-year-olds and 22-year-olds). The analyses of the *TFAP-2 β* failed for five girls, leaving 109 girls in the final sample. There were no differences between the initial and final samples with regard to any of the variables used in this study, even when sex and age groups were analysed separately.

Study IV

Consecutively referred child psychiatric outpatients aged 12–17 years, from three Swedish child psychiatric clinics, Enköping, Västerås and Sala, were invited to participate. Patients in need of acute psychiatric or somatic in-patient care at the time of the diagnostic interview and those who were in need of a Swedish interpreter were excluded. The data collection took place between September 2011 and June 2013.

In Västerås and Sala, 433 adolescents were referred during the study period. Of those, 307 were invited and 157 (51%) agreed to participate. One hundred and sixty-nine adolescents were referred to the Enköping clinic during the study period, of whom 55 were invited and 28 (51%) gave consent to participate. In total, there were 185 participants. However 51 were excluded because they did not turn up for the K-SADS-interview, the time frame of 7 days between symptom rating and K-SADS was exceeded or because of missing/incomplete ASRS-A-symptom ratings, leaving a final sample of 134, 53 boys (40 %) and 81 girls.

There were no significant differences between participants and internal dropouts according to sex and age. However, there was a significant difference in sex between external dropouts and participants, with a lower proportion of boys in the participant group ($\chi^2 = 4.99, p < 0.05$). Further,

among boys, participants were younger than the non-participating boys ($t = 3.422, p < 0.001$). There was no such difference in mean age between participating and non-participating girls ($t = 0.078, p = 0.531$).

8.1. Flow-charts of participants study I-IV

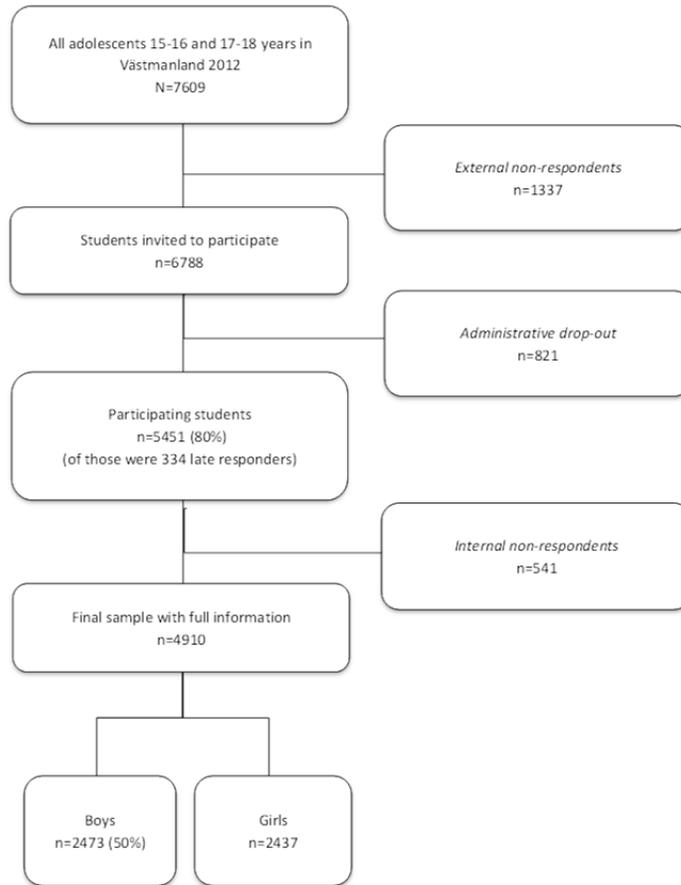


Figure 6. Flow-chart of the study population study I.

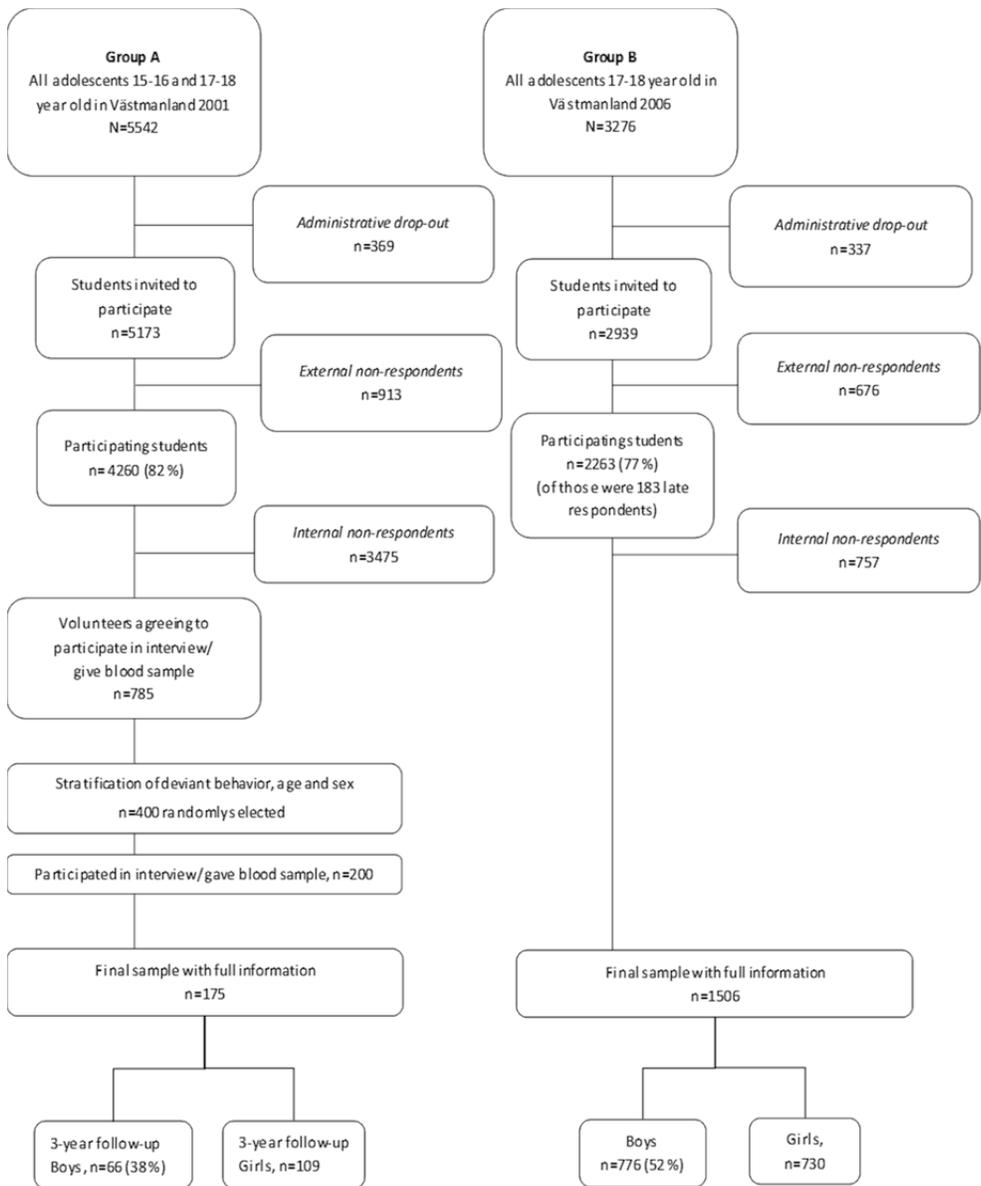


Figure 7. Flow-chart of the two study groups in study II.

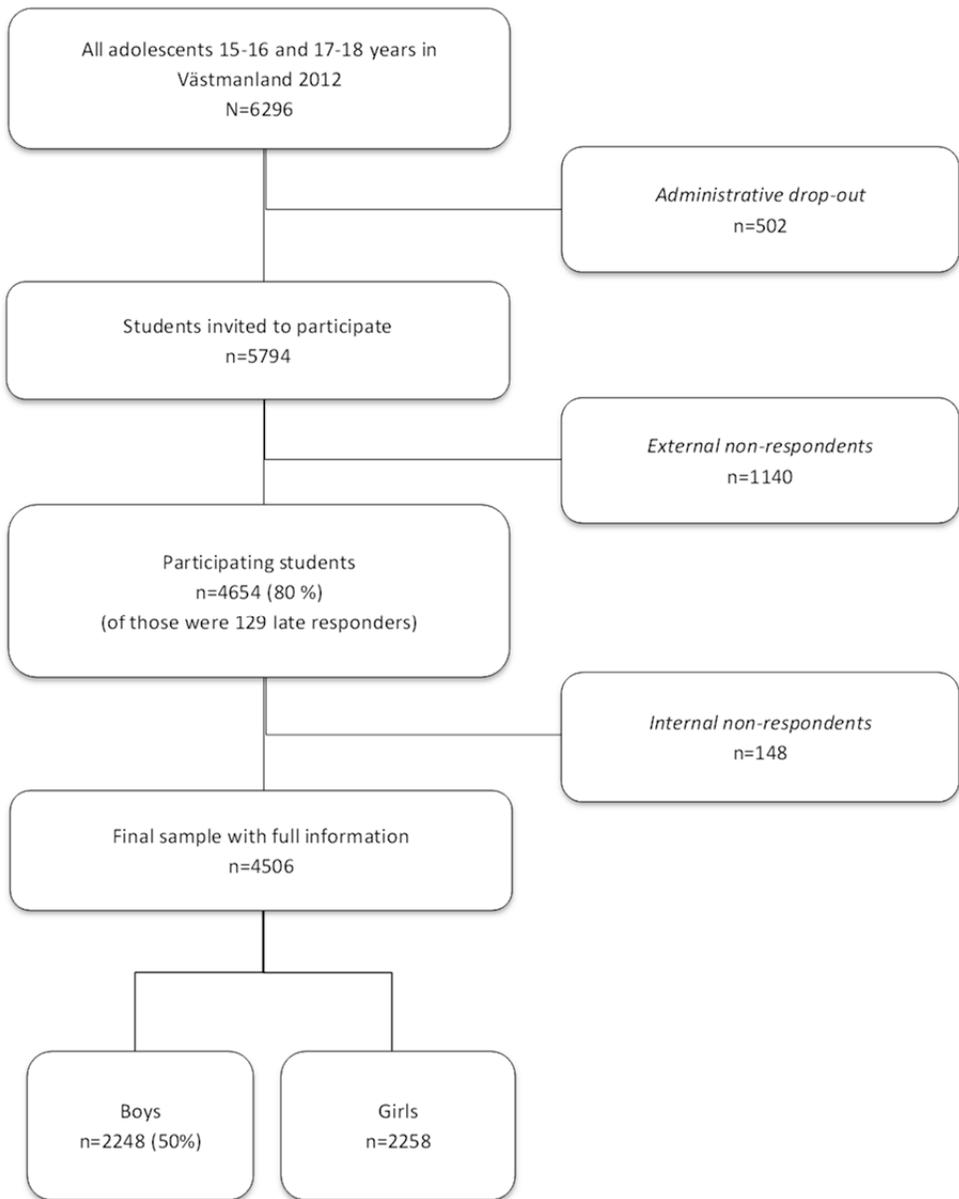


Figure 8. Flow-chart of the study population in study III.

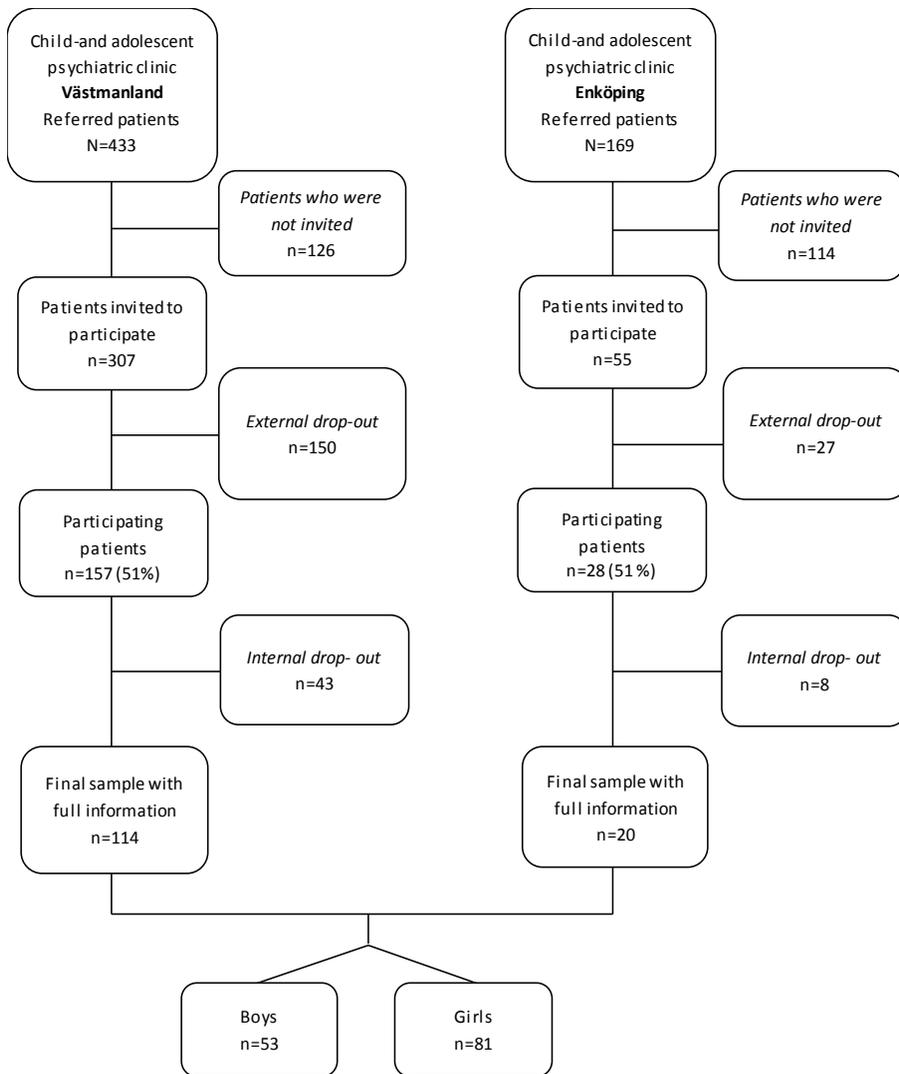


Figure 9. Flow-chart of the adolescent psychiatric patients participating in study IV.

8.3. Measures

The SALVe questionnaire (Studies I–III)

Most variables assessed were part of the SALVe questionnaire of the respective survey. One exception was group A in study II who were assessed with a 3-year- follow-up questionnaire for ratings of symptoms of ADHD and depression. Information on socio-demographic variables were selected from the questionnaire in order to adjust analyses for confounding factors. In study III, data that might influence the parent–adolescent relationship was selected from the SALVe questionnaire; parental employment status, immigrant status and civil status (e.g., separated parents), whether the family was living in a rented or owned house, occurrence of severe parental verbal conflicts, parental physical conflicts, presence of someone in the family with substance-related problems, experiences of parental physical abuse, sexual abuse, drug use/alcohol abuse and conduct problems.

Sexual abuse (Study I)

Participants were asked the following three questions: 1) Has anyone ever touched you or forced you to touch them in a sexual way against your will? 2) Has anyone ever attempted to have intercourse (oral, vaginal or anal) with you against your will? 3) Has anyone ever had intercourse (oral, vaginal or anal) with you against your will? The response alternatives were: 1) No; 2) Yes, once; 3) Yes, a few (2–4) times; 4) Yes, many (more than 5) times. Cut-off for the three questions was set at reporting sexual abuse at least once.

Symptoms of ADHD (Studies I–IV)

The Swedish version of the World Health Organization Adult ADHD Self-Rating Scale (ASRS) was translated from English by L. Nyberg and back into English by A. Fernholm¹⁷³. The ASRS has 18 items and is composed of two sub-scales: inattention (IA) and hyperactivity–impulsivity (HD), with nine questions each. The answers are on a 0–4 Likert scale with the alternatives: never, rarely, sometimes, often and very often. The total sum of the ASRS ranges between 0 and 72. The first six questions can be used alone as a short screening scale called the ASRS-S. The total sum of the ASRS-S ranges between 0 and 24.

Kessler recommends a summation based on dichotomized cut-off points for all items, shown as shaded areas on the questionnaire, and proposes a cut-off score of nine or more for ASRS (range 0-18) and a cut-off score of four or more for the ASRS-S (range 0-6)¹⁷⁴. This cut off was used in the Studies I-IV except for a number of analyses in study I.

In the original validation study (using the dichotomized cut off), the six-question ASRS-S and the 18-question ASRS had sensitivity scores of 68.7% and 56.3%, respectively, and specificity scores of 99.5% and 98.3%, respectively¹⁷⁴. In a clinical, drug-dependent population, the ASRS-S had a sensitivity of 66.7% and a specificity of 81.2%, with a positive predictive value of 41.8% and a negative predictive value of 92.6%¹⁷⁵. Minor adaptations of the ASRS wordings were made by K.W. Nilsson to suit adolescents; these are indicated by adding an “A” for adolescent, and the six-question screening version is abbreviated as “ASRS-A-S”.

Symptoms of ADHD, Study I

ASRS-A-S. The symptoms were rated according to “how it is now” (and not during the past 6 months). We also used a *narrow cut-off*, corresponding to an answer of “often” or more on all six screening questions, in Study I referred to as “symptoms of ADHD; narrow cut-off”.

Symptoms of ADHD, Study II

ASRS-A-S. The symptoms were rated according to “how it is now” (and not in the past 6 months).

Symptoms of ADHD, Study III

ASRS-A-S. The symptoms were rated according to the past 6 months.

Symptoms of ADHD, Study IV

ASRS-A and ASRS-A-S. The symptoms were rated according to the past 6 months.

Symptoms of depression (Studies I–III)

We used an adolescent adaptation of the Swedish translation of the Depression Self-Rating Scale (DSRS)¹⁷⁶, which is a self-report inventory based on the Diagnostic Statistical Manual IV (DSM-IV) criteria for depression. The DSRS has been validated in two versions, one assessing DSM-IV criteria A and C and one assessing only criterion A.

The DSRS assessing DSM-IV criteria A and C has a previously reported sensitivity of 86% and a specificity of 75%, and the DSRS assessing DSM-IV criterion A has a reported sensitivity of 96 % and specificity of 59 % in an adult psychiatric population¹⁷⁶.

The original DSRS was adapted for adolescents by including one question about irritable mood, because depression in adolescents is defined as either dysphoric or irritable mood. From paper III onwards, the adapted questionnaire was called the DSRS-A, to reflect the adolescent version. DSM-IV criterion A requires that at least one of the two general symptoms

is present, and is accompanied by at least four more symptoms. DSM-IV criterion C implies clinically significant suffering from functional impairment.

Depending on the DSRS-A version used, participants who fulfilled the DSM-IV criteria A and C, or only criteria A were classified as screening positively for depression, and were considered to have clinically significant symptoms of depression.

Symptoms of depression, Study I

DSRS-A assessing DSM-IV criteria A and C for depression.

Symptoms of depression, Study II

DSRS-A assessing DSM-IV criterion A and C for depression prevalence in the sample and an depression-index for the other analyses. The depression index consisted of a count of the depression symptoms of criterion A, ranging between 0-9. The internal consistency, measured with Cronbach's alpha, was 0.796 in group A and 0.807 in group B.

Symptoms of depression, Study III

DSRS-A assessing DSM-IV criteria A and C for depression. The internal consistency of the questions assessing DSM-IV criterion A in this sample, measured with Cronbach's alpha, was 0.822 (boys = 0.846, girls = 0.790).

Genotyping (Study II)

The *TFAP-2 β* intron 1 VNTR polymorphism was amplified from DNA using the following primer sequences: forward 5'-FAM-CA GAC GGC TCC GCT ACT C-3' and reverse 5'-CCA GAC CAT TCC GCT TAA AA-3'. Polymerase chain reaction (PCR) was performed in a 10 μ l reaction mixture with 1 μ l PCR Buffer 10 \times with MgCl₂; 2 μ l GC-rich solution; 1.4 μ l dNTP (5 mM tot); 0.2 μ l (10 μ M) of each primer and 0.08 μ l Fast Start Taq DNA polymerase (Roche Diagnostics, Germany).

The PCR reactions were performed on a Gene Amp 9700 (Applied Biosystems, Foster City, CA, USA) at the following profile: 95 °C for 4 min, followed by 40 cycles of 95 °C for 30 s, 58 °C for 30 s and 72 °C for 45 s, with final extension at 72 °C for 7 min. The PCR products were separated by capillary electrophoresis using an ABI PRISM@3700 DNA Analyzer (Applied Biosystems, Foster City, CA, USA) and genotypes were automatically determined using Gene Mapper Software v. 4.0 (Applied Biosystems, Foster City, CA, USA) with user-defined parameter specification of the stutter-peak ratio and peak-height ratio as quality controls.

All genotypes were also manually checked on chromatograms to detect ambiguities (e.g., in cases of low fluorescence signal to background ratio).

Help-seeking (Study III)

Participants were asked: Have you been in touch with any of the following during the past 3 months? 1) Emergency unit, 2) Paediatric clinic, 3) Child and adolescent psychiatric clinic, 4) Community youth counselling, 5) Community youth alcohol and drug centre, 6) General practitioner, 7) Social welfare, 8) School health care. Specialized mental health help-seeking was coded as present if contact with a child and adolescent psychiatric clinic was reported.

Measure of the parent–adolescent relationship (Study III)

The nine-item version of the Experiences in Close Relationships Scale for children and adolescents (ECR-RC9) was used.

The 36-item ECR-R was developed to measure adult romantic attachment¹⁷⁷ and subsequently expanded to measure attachment dimensions in multiple contexts (ECR-RS)¹³⁸. A further adaptation of this version by Brenning¹⁷⁸, for use in children and adolescents, was called the ECR-RC, where “C” stands for children. It is possible to use a shorter nine-item version of the ECR-RC¹³⁸ when only one relationship is to be measured (ECR-RC9). The ECR-RC/ECR-RC9 is based on a continuous-dimensional approach of attachment anxiety and attachment avoidance. Ratings of both low attachment anxiety and low attachment avoidance indicate secure attachment¹⁷⁸. The ECR-RC has been validated in two samples of children (8–14 years old) in Belgium¹⁷⁸. The instrument was shown to have both construct and predictive validity¹⁷⁸. The shorter version, the ECR-RC9, has been translated into Swedish by A.G. Broberg at Gothenburg University. A validation study of children (n = 44) aged 10–12 years old and adolescents (n = 130) aged 13–17 years old indicated that the Swedish version of the ECR-RC9 has similar psychometric properties to the Belgian version (personal communication with Alfredsson et al., 2013).

The wording of the nine-item version of the ECR-RC questions is as follows: 1) It helps to turn to my mother in times of need; 2) I don't feel comfortable opening up to my mother; 3) I often worry that my mother doesn't really care for me; 4) I usually discuss my problems and concerns with my mother; 5) I prefer not to show my mother how I feel deep down; 6) I'm afraid that my mother may abandon me; 7) I talk things over with my mother; 8) I worry that my mother won't care about me as much as I care about her; and 9) I find it easy to depend on my mother. Participants also responded to analogous questions regarding the father.

Scoring instructions are available at the official web site¹⁷⁹. Responses were given on a Likert scale, ranging from “strongly disagree” (coded = 1) to “strongly agree” (coded = 7). The respondents were asked to answer the questions according to who they perceived as their emotional parent. The alternatives were “My biological mother/father”, “My adoptive mother/father”, “My stepmother/stepfather” or “Another woman/man”.

The internal consistency (Cronbach’s alpha) for secure attachment to mothers was 0.834 and for secure attachment to fathers was 0.865.

Gold-standard measure in Study IV: Kiddie Schedule for Affective Disorders and Schizophrenia for school-aged children (K-SADS)

The K-SADS is a semi-structured diagnostic interview that examines current and previous psychopathology in children and adolescents between the ages of six and 18 years¹⁸⁰. The K-SADS consists of one screening part and eight supplements. If general symptoms are assented to in the screening interview, questions from the appropriate supplement are used to verify the diagnosis. The K-SADS is regarded as the gold standard for child psychiatric diagnoses^{167, 180, 181}. To perform one K-SADS interview takes between one and a half and eight hours.

8.4. Procedures

Training and reliability of interviewers (Study IV)

All interviewers (n = 6) were trained in how to use the K-SADS before they started the data collection. The interviewers consisted of one specialist in child and adolescent psychiatry (KaS), two residents in child and adolescent psychiatry (IN and KoS), two clinical psychologists (SL and SO) and one clinical social worker (SV), all working in child psychiatric services. All interviewers completed their basic training according to the Swedish standard for K-SADS training, with four days of theory and practice. The specialist in child and adolescent psychiatry (KaS) had attended national training to become a trainer of other interviewers. She planned the training for the others and was considered the standard when calculating interrater reliability.

The training was based on viewing recorded interviews made by “master interviewers”. The ratings of these interviews were estimated individually and then discussed in the group. Next, the interviewers recorded themselves interviewing patients. The others assessed the recordings, and interrater reliability was calculated. Interrater reliability before the study started was based on five consecutive interviews. Interrater reliability was calculated as both kappa and prevalence- and bias- adjusted kappa (PABAK)¹⁸².

First, interrater reliability was calculated for each interviewer for each diagnosis; thereafter, the mean was calculated for all diagnoses. Finally, the mean interrater reliability for the group was calculated. For the five interviews before the study began, the mean interrater reliability for the group yielded a kappa of 0.84 (range = 0.51–1.00) and a PABAK of 0.90 (range = 0.77–1.00). For the diagnosis of ADHD, kappa was 0.83 (range = 0.54–1.00) and PABAK was 0.84 (range = 0.60–1.00).

Throughout the study, one joint assessment took place each month to ensure a continuous high level of agreement. In total, 25 interviews were rated by KaS, and the others rated between five and 22 interviews each. The mean number of interviews rated by the interviewers was 16 (SD = 7.0). The overall interrater reliability, based on all ratings, yielded a kappa of 0.84 (range = 0.73–1.00) and a PABAK of 0.91 (range = 0.86–1.00). For the diagnosis of ADHD, kappa was 0.81 (range = 0.70–1.00) and PABAK was 0.82 (range = 0.70–1.00).

Assessment procedure for psychiatric patients (Study IV)

Before the first appointment, the patients and/or their families were informed about the study. The first clinical assessment was a traditional non-structured psychiatric interview with the parent and adolescent together. At this appointment, the patients were invited to participate in the study. During the second visit, the parent and the adolescent were interviewed together using the K-SADS. From the autumn 2012 K-SADS was performed on the third visit due to changed clinical routine in the Västmanland clinic.

In Västerås and Sala, the ASRS-A was reported on during the initial appointment (after changed routine on the second visit). For 52 (39%) patients, the time period between the initial appointment and the diagnostic interview was more than seven days, which was considered the maximum time limit. In these cases, the ASRS-A questionnaire was filled out once more, immediately after the K-SADS interview. The K-SADS interviewers in Västerås and Sala were blind to the results of the ASRS-A.

In Enköping, the adolescents filled out the ASRS-A questionnaire immediately before the K-SADS interview started. Responses on the ASRS-A were withheld from the K-SADS interviewer by placing the questionnaire inside an envelope.

8.5. Statistical analyses

The analysis of Study I was carried out with SPSS software 16.0, and the analysis of Study II was carried out with PASW 18.0. Analyses of Studies III

and IV were carried out with IBM SPSS Statistics 20.0 (SPSS Inc., Chicago, IL, USA).

The significance level chosen for all tests was $p < 0.05$; however, for interaction effects in the multivariate regression analyses, the significance level was $p < 0.10$, as suggested by Fleiss¹⁸³.

Table 1. Overview of statistical methods used in Studies I–IV

	Statistical methods
Study I	Chi-square test Binary logistic regression
Study II	Cronbach's alpha Chi-square test General linear model Poisson log-linear regression Kruskal–Wallis test Mann–Whitney U test
Study III	Cronbach's alpha Chi-square test Student's <i>t</i> test Mann–Whitney U test Binary logistic regression
Study IV	Cohen's kappa Prevalence and bias adjusted kappa (PABAK) Chi-square test Student's <i>t</i> test Mann–Whitney U test Cronbach's alpha Spearman's rho Receiver operating characteristics (ROC) analysis Area under the curve analysis Sensitivity Specificity Positive predictive value Negative predictive value Binary logistic regression

8.6. Ethical considerations

In Studies I–III, surveys were filled out during school hours under the supervision of a teacher. Participation was voluntary, anonymous and could be interrupted at any time without explanation.

For traumatized individuals, some questions may have had potential to arouse emotions connected with experiences of former physical or sexual abuse, or a family member's alcohol or drug abuse. Adolescents were not informed of where to turn for support prior to completing the survey. This might have affected vulnerable individuals.

Studies I and II were approved by the Regional Ethics Committee of Uppsala University. The registration numbers of ethical approval are: SALVe 2001: Dnr: 00-325 and SALVe 2006: Dnr 2005:375.

Study III followed the Swedish guidelines for studies of social science and humanities, in accordance with the Declaration of Helsinki. According to Swedish regulations, this type of anonymous study does not require ethical approval by the medical faculty.

Prior to the start of the clinical study (Study IV), the health-care staff were concerned that the alliance with the families would be violated by the structured screening procedure (including the ASRS-A). Moreover, the screening questionnaire assessing physical and sexual abuse and drug use was considered to have the potential to be humiliating and/or harmful to the patients. The same considerations were relevant to the K-SADS interview, which followed on the second/third visit. Therefore, each family was administered a follow-up questionnaire, with results blind to the interviewer. The overall opinion of the structured screening visit and K-SADS interview was very positive.

The study was approved by the Regional Ethics Committee of Uppsala University. The registration numbers for ethical approval are: Study IV, Västmanland, Dnr 2008/214, Enköping: Dnr 2011/039.

9. Results

9.1. Co-occurring symptoms of ADHD and depression and associations with experiences of sexual abuse

In the total sample, the prevalence of ADHD symptoms was 21%, depression was 13% and sexual abuse was 21%; all these variables showed a preponderance of girls. According to the narrow cut-off, 6% of boys and 9% of girls were screened as positive on the ASRS-A-S, indicating high frequencies of current symptoms of ADHD. Seven per cent of boys and 19% of girls had a positive screening for depression. Co-occurring symptoms of ADHD and depression were reported by 1% of boys and 4% of girls. Experience of any sexual abuse was reported by 13% of boys and 29% of girls.

Girls with experience of sexual abuse had more ADHD or depression symptoms than boys. Among both boys and girls with co-occurring symptoms, approximately every other individual had experience of sexual abuse.

In logistic regression models of symptoms of ADHD, depression and co-occurring symptoms in relation to experiences of sexual abuse, there were higher odds ratios (ORs) for experiences of sexual abuse among those who reported symptoms of ADHD and/or depression. Boys who reported symptoms of ADHD and boys who reported symptoms of depression had ORs for sexual abuse that were double those of other boys. Boys who reported co-occurring symptoms had ORs of having experienced sexual abuse that were five to seven times greater than individuals with no symptoms.

Girls who reported symptoms of ADHD, depression or co-occurring symptoms had ORs for experiences of sexual abuse two to three times higher than girls with no symptoms. Girls with co-occurring symptoms had the highest probability of experiencing sexual abuse.

We also analysed the model with Kessler et al.'s cut-off for symptoms of ADHD¹⁷⁴ and adjusted our regression models for non-independent confounders (i.e., demographic factors such as separated parents, parental

unemployment, type of housing and non-Scandinavian ethnicity) without major impact on the results.

Interaction between sex and experiences of sexual abuse with symptoms of ADHD and symptoms of depression as outcomes, respectively (unpublished results)

Univariate analyses indicated that symptoms of both ADHD and depression were more common among girls who had experience of sexual abuse than among boys who had experience of sexual abuse. To investigate whether there was an interaction between sex and sexual abuse on symptoms of ADHD and depression, two more analyses were performed, and symptoms of depression and ADHD were outcome variables respectively.

Symptoms of ADHD as the outcome variable

The first logistic regression analysis was performed with symptoms of ADHD as the outcome (dichotomous variable) and sex, experiences of sexual abuse, interaction between sex and sexual abuse, and adjustment for non-independent confounders (i.e., the demographic factors of separated parents, parental unemployment, type of housing and non-Scandinavian ethnicity). The results showed a significant interaction between sexual abuse and sex, which implies that experiences of sexual abuse are associated with a higher probability of symptoms of ADHD in girls (OR = 1.59, 95% CI 1.110-2.264, $p= 0.011$).

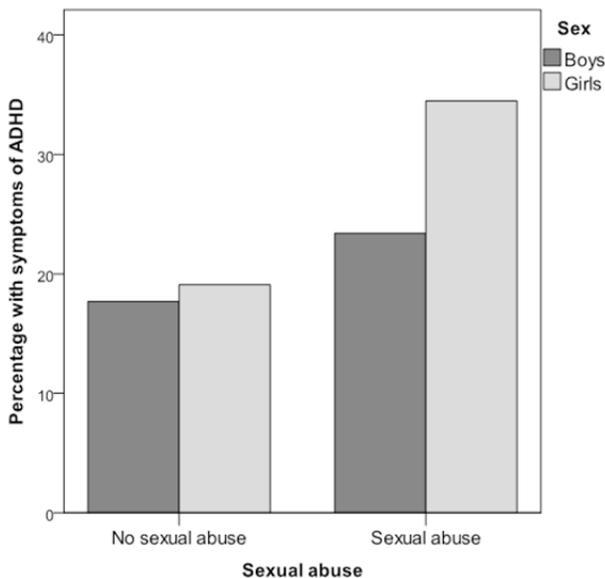


Figure 10. The proportion of symptoms of ADHD among boys and girls with and without experience of sexual abuse

Symptoms of depression as the outcome variable

A logistic regression exactly analogous with the regression model above, but with symptoms of depression as the outcome, was performed. The results of the interaction between sex and sexual abuse did not support any sex difference as a consequence of sexual abuse in relation to symptoms of depression (OR = 0.88, 95% CI 0.574-1.353, $p = 0.563$).

9.2. Co-occurring symptoms of ADHD and depression and associations with a polymorphism of the *TFAP-2 β* genotype

In the gene for *TFAP-2 β* , located at intron 1, there is a VNTR polymorphism with eight, nine or ten repeats. The variant with nine repeats (9R) has been reported to be functional and has been tested against the rest (non-9R-variants)⁹².

Co-occurring symptoms of ADHD and depression were reported by 6.1% of group A and 7.8% of the adolescents in group B. The genotype frequencies were in Hardy–Weinberg equilibrium.

Table 2. Prevalence of symptoms of ADHD, depression, co-occurring symptoms and the *TFAP-2 β* genotype with 9R in study groups A and B.

Group A (N = 175)	Boys n (%)	Girls n (%)	Total n (%)
No symptoms of either ADHD or depression	43 (65.2)	71 (65.1)	114 (65.1)
Symptoms of ADHD	17 (25.8)	21 (18.6)	38 (21.2)
Symptoms of depression	3 (4.5)	9 (8.0)	12 (6.7)
Co-occurring symptoms of ADHD and depression	3 (4.5)	8 (7.1)	11 (6.1)
<i>TFAP-2β</i> nine-repeat variant	23 (34.8)	41 (37.6)	64 (36.6)
Group B (N = 1506)			
No symptoms of either ADHD or depression	549 (70.7)	445 (61.0)	994 (66.0)
Symptoms of ADHD	117 (15.1)	94 (12.9)	211 (14.0)
Symptoms of depression	65 (8.4)	119 (16.3)	184 (12.2)
Co-occurring symptoms of ADHD and depression	45 (5.8)	72 (9.9)	117 (7.8)
<i>TFAP-2β</i> nine-repeat variant	228 (29.4)	180 (25.7)	408 (27.1)

Groups A and B were comparable according to genotype frequency distribution, except for the 9/10R and 10/10R variants. In group A, an over-representation of 9/10R variants was found, whereas in group B there was an over-representation of 10/10R variants.

There was a sex difference of *TFAP-2β* in relation to symptoms of ADHD: the *TFAP-2β* 9R variant was found in lower proportions among girls with symptoms of ADHD than among girls with no symptoms of ADHD, whereas no such differences were found among boys.

Interaction between TFAP-2β and ADHD symptoms in relation to the depression index

General linear model (GLM) analyses of symptoms of ADHD and interaction with *TFAP-2β* polymorphism (9R versus non-9-repeat variants) on the depression index showed non-significant results for both groups.

When boys and girls were analysed separately in both study groups, symptoms of ADHD and the interaction effects between symptoms of ADHD and *TFAP-2β* polymorphism were associated with symptoms of depression among girls, but not among boys. In both samples, girls with symptoms of ADHD in combination with the 9R variant showed lower scores on the depression index.

To avoid scaling artefacts and to validate our findings, we performed Poisson log-linear regression analyses and the non-parametric Kruskal–Wallis test of the interaction between *TFAP-2β* genotype and ADHD symptoms in relation to the depression index. We also adjusted for population stratification. Neither the validation analyses nor the adjustment for population stratification affected the result.

9.3. The parent–adolescent relationship and help-seeking from specialized mental health services

In the total sample ($n = 4506$, equal proportions of boys and girls) 5% of adolescents ($n = 213$), with a preponderance of girls, reported seeking specialized mental health-care help over the last three months.

Nineteen per cent of the study population had symptoms of ADHD, 14% had symptoms of depression and 6% reported co-occurring symptoms of ADHD and depression, all with preponderances of girls. The proportion of help-seekers with symptoms of depression (including co-occurring symptoms of ADHD and depression) was larger than that with symptoms of ADHD (including co-occurring symptoms of depression). Among help-seeking girls, symptoms of depression were more common than symptoms of ADHD, whereas among boys it was the other way around. Among help-seeking adolescents with symptoms of depression, approximately 40% of the boys and 50% of the girls had co-occurring symptoms of ADHD. Among help-

seeking girls with symptoms of ADHD 71% had co-occurring symptoms of depression in contrast to 30 % among the boys.

Immigrant and accommodation status did not differ between help-seekers and non-help-seekers in the total sample, and parental unemployment did not differ among girls. However, among adolescents who were help-seekers, there were higher frequencies of stressful psychosocial family characteristics as well as alcohol abuse, drug use, more conduct problems and substantially higher frequencies of sexual abuse. The same pattern was found when boys and girls were analysed separately.

Parent–adolescent relationship measured as secure attachment cognitions

Help-seeking adolescents had lower mean scores of secure attachment than non-help-seeking adolescents. Additionally, adolescents with significant symptoms of depression or ADHD had lower mean secure attachment scores than adolescents without these symptoms.

Contrary to our hypothesis, the mean secure attachment score among specialized mental health help-seekers was lower than among those who did not seek help.

There were differences in mean secure attachment scores according to symptom presence. The lowest mean secure attachment scores were found among those with co-occurring symptoms; then, in ascending order, for those with symptoms of depression and those with symptoms of ADHD. The highest mean scores were found among adolescents without symptoms of ADHD or depression.

Associations with help-seeking form specialized mental health services

The highest probability for help-seeking was associated with co-occurring symptoms of ADHD and depression (OR = 5.4), symptoms of depression (OR = 4.8) and symptoms of ADHD (OR = 2.6), as well as any experience of sexual abuse (OR = 1.7) and being female (OR = 1.6). Secure attachment to parents, assessed with the ECR-RC9, did not increase help-seeking. Furthermore, in interaction analyses, secure attachment to parents in combination with experiences of sexual abuse and/or conduct problems, or being female and having symptoms of ADHD, decreased the probability of help-seeking.

As the co-occurrence of symptoms of ADHD and depression was a predictor of specialized mental health help-seeking, and the prevalence of co-occurring symptoms was substantially higher among girls, separate univariate regression analyses were performed for boys and girls. For both sexes, symptoms of depression increased help-seeking more than symptoms of

ADHD. The analyses showed that, for girls, the OR for specialized mental health help-seeking for co-occurring symptoms of ADHD and depression was 9.2 (95% CI 5.8–14.5), for symptoms of depression without ADHD it was 6.3 (95% CI 4.0–10.0) and for symptoms of ADHD without symptoms of depression it was 2.1 (95% CI 1.2–3.7). For boys, the OR for help-seeking from specialized mental health services for co-occurring symptoms of ADHD and depression was 7.2 (95% CI 3.2–15.8), for symptoms of depression without ADHD it was 7.5 (95% CI 3.7–15.1) and for symptoms of ADHD without depression it was 4.9 (95% CI 2.7–8.6).

9.4. Validation of the World Health Organization Adult ADHD Self-Report Scale for adolescents

The study population comprised 134 psychiatric patients, 53 boys and 81 girls, with a mean age of 15 years. According to the assessment with the K-SADS interview, 47 (35%) patients had ADHD, 24 boys (45 %) and 23 girls (28%). The mean number of disorders was three for girls and two for boys. Among ADHD patients, the mean number of disorders was increased, though still with higher rates among girls than boys. Four per cent of boys with ADHD had four or more disorders, whereas 39% of girls did.

Psychometric properties of the ASRS-A-S and the ASRS-A

Internal consistency for the ASRS-A-S, measured with Cronbach's alpha, was 0.79 (boys = 0.81, girls = 0.79). For the inattention subscale, internal consistency was 0.79 (boys = 0.84, girls = 0.76) and the hyperactivity subscale yielded a score of 0.68 (boys = 0.71, girls = 0.65). Internal consistency for the ASRS-A total scale, measured with Cronbach's alpha, was 0.92 (boys = 0.91, girls = 0.92). For inattention, it was 0.87 (boys = 0.88, girls = 0.87), and for hyperactivity, it was 0.89 (boys = 0.89, girls = 0.89).

Concurrent validity, measured by Spearman's rho, for the correlation between the total K-SADS ADHD symptom severity score and the total sum of all ASRS-A-S ratings was 0.51 (boys = 0.58, girls = 0.47). Spearman's rho for the correlation between the total K-SADS ADHD symptom severity score and the total sum of all ASRS-A ratings was 0.60 (boys = 0.64, girls = 0.58).

Diagnostic accuracy of the ASRS-A-S

For the total sample, the Area under the curve (AUC) was 0.73 (95% Confidence interval CI 0.64–0.81, $p < 0.001$), with a score of 0.68 for boys (CI 0.54–0.83, $p < 0.023$) and a score of 0.76 for girls (CI 0.64–0.89, $p <$

0.001). The sensitivity allowed discrimination of 7 out of 10 patients with ADHD according to the gold standard, and a negative predictive value (NPV) which allowed correct identification of 8 out of 10 patients who did not have ADHD. However, the specificity and the positive predictive value (PPV) were relatively low, indicating that a substantial number of individuals without ADHD scored above the cut-off. The psychometric properties were better among girls than among boys. See Table 3 for sensitivity, specificity, PPV, NPV and the ORs for an ADHD diagnosis.

Diagnostic accuracy of the ASRS-A

For the total sample, AUC was 0.78 (CI 0.70–0.87, $p < 0.001$), with a score of 0.77 for boys (CI 0.65–0.90, $p = 0.001$) and a score of 0.81 for girls (CI 0.70–0.93, $p < 0.001$). The ASRS-A demonstrated an ability to identify 8 out of 10 patients with ADHD according to the gold standard, and at the same time 8 out of 10 patients without ADHD were correctly discriminated. However, the specificity and the PPV were lower as a result of a substantial proportion of false positives. The psychometric properties among girls were better than among boys. See Table 4 for sensitivity, specificity, PPV, NPV and the ORs for an ADHD diagnosis.

Table 3. Sensitivity, specificity, PPV, NPV and odds ratios for an ADHD diagnosis using the ASRS-A-S

ASRS-A-S	Sens.	Spec.	PPV	NPV	OR	95% CI	<i>p</i>
0–6 points, cut-off ≥ 4							
Total sample N = 134	74%	59%	49%	81%	4.132	1.890– 9.034	< 0.001
Boys n = 53	71%	55%	57%	70%	2.989	0.951– 9.390	0.061
Girls n = 81	78%	60%	44%	88%	5.478	1.784– 16.821	0.003
ASRS-A-S rated before K-SADS n = 82	75%	53%	40%	84%	3.444	1.195– 9.924	0.022
ASRS-A-S rated after K-SADS n = 52	74%	69%	65%	77%	6.296	1.861– 21.298	0.003

Table 4. Sensitivity, specificity, PPV, NPV as well as the odds ratio for an ADHD diagnosis of the ASRS-A.

ASRS-A	Sens.	Spec.	PPV	NPV	OR	95% CI	<i>p</i>
0–18 points, cut-off ≥ 9							
Total sample N = 134	79%	60%	51%	84%	5.497	2.422– 12.475	< 0.001
Boys n = 53	75%	59%	60%	74%	4.250	1.302– 13.874	0.017
Girls n = 81	83%	60%	45%	90%	7.228	2.178– 23.992	0.001
ASRS-A-S rated before K-SADS n = 82	79%	57%	43%	87%	5.016	1.647– 15.278	0.005
ASRS-A-S rated after K-SADS n = 52	78%	66%	64%	79%	6.840	1.955– 23.927	0.003

10. Discussion

10.1. Symptoms of ADHD and/or depression–relations to sex and the socio-cultural context of gender

The epidemiological Studies I–III showed high frequencies of self-reported symptoms of ADHD and depression as well as co-occurring symptoms, with an overall preponderance of girls. The findings of more symptoms of depression among girls are consistent with previous research^{27, 184}. However, the prevalence of symptoms of ADHD exceeded that of previous research findings. Definitions and assessments of ADHD in previous research vary greatly, and this contributes to large differences in estimates of ADHD prevalence¹⁴. The diagnosis of ADHD assessed with structured interviews yields lower prevalence rates than ADHD symptom ratings¹⁴. In Studies I–III, symptoms of ADHD were based on self-reports, rather than on the diagnosis, which may partly explain the high prevalence of symptoms of ADHD¹³. In Finland, a population-based study found an ADHD prevalence of 18% among adolescents when they used lower thresholds for diagnosis but still required impairment. Moreover, the lower threshold reduced the sex ratio between boys and girls from 1 girl to 5–6 boys to 1 girl to 3 boys, indicating that girls may show fewer symptoms and still be impaired compared with boys²⁶.

Contrary to previous research, we found a preponderance of symptoms of ADHD among girls^{14, 27}. In Western countries, including Sweden, the phenotype of ADHD is attributed to the male gender to a large extent. Studies show that even if girls exhibit symptoms of ADHD, they are not recognized as such by parents, teachers or other adults, whereas boys who exhibit ADHD symptoms or oppositional defiant symptoms are recognized as “ADHD”^{41, 148}. Parents recognize impairment due to ADHD equally well in sons and daughters. Despite this, the sex/gender of the child predicts how it is handled by the parents, and boys have a substantially higher chance of being assessed than girls¹⁴⁹. The socio-cultural perception of “ADHD” is most probably mixed up with common comorbidity profiles of ADHD with behaviour disorders among boys, which is more easily identified. Girls with ADHD more often have comorbid internalizing disorders such as depression, which is less evident to peers, teachers and parents^{58, 185}. In the clinical

sample, girls with ADHD were diagnosed with many more comorbid disorders, indicating a longer delay before help-seeking for girls.

As expected, ADHD was much more prevalent in the clinical sample in Study IV assessed by structured interviews than in the epidemiological samples. Additionally, contrary to the epidemiological samples, there were more boys than girls with ADHD. Even if self-assessment is less reliable, this raises questions about whether girls with ADHD are both under-identified and are under-utilizing child psychiatric services.

On the other hand, adolescent girls may be more reflective about their own symptoms, and boys with ADHD are known to under-report their symptoms more often compared with girls, which may attenuate the preponderance of girls in Studies I–III¹⁸⁶. These differences may also have biological underpinnings, as typically developed girls' physical, neurological and psychosocial development precedes the same development among boys. Skills that depend on maturation are impaired among individuals with ADHD. This contributes to the under-recognition of girls with ADHD, as they are more mature than boys with ADHD of the same age. Consequently, the comparison of suspected ADHD symptoms in girls should be made with other girls of the same age, rather than with boys^{29, 187}.

There is evidence of sex differences in brain morphology and function, as well as neurochemistry, and sex differences in prevalence and/or nature of psychiatric disorders^{188, 189}. Profound effects of sex hormones on the organization of the brain during development are known, as well as the effects of diversity and fluctuations in circulating sex hormones on sex differences in behaviour, stress responses and mental illness^{107, 111, 112, 189-191}. Moreover, it is suggested that girls' elevated levels of sex hormones in puberty, which are associated with central nervous system changes in dopamine receptors, may increase the symptoms in girls in adolescence, whereas in adolescent boys there is a decrease in dopamine receptors, which is associated with a reduction in hyperactivity/impulsivity symptoms^{26, 29}.

In Studies I–III, the prevalence of co-occurring symptoms of ADHD and depression ranged between 2% (boys 1%, girls 4%) and 8% (boys 6%, girls 10%), with some of the variation depending on differences in the ADHD and depression self-report measures. However, in all studies, there was a preponderance of girls. These findings are consistent with those of previous studies, with a female preponderance of ADHD and comorbid depression in adolescents and adults with ADHD^{26, 58}.

10.2. Sexual abuse—an environmental stress factor and its relation to symptoms of ADHD and/or depression

From the epidemiological sample in Study I, one-fifth of adolescents reported having experienced sexual abuse, with twice as many girls as boys. Previous research report large variations of the prevalence of sexual abuse in children and adolescents and our results are within the range of other studies, including a preponderance of females^{116,212}. The variations in prevalence of sexual abuse may apart from real differences in prevalence in different countries or cultures also depend on differences in definition of sexual abuse, study population and assessment methods^{116,212}. Among adolescents with co-occurring symptoms, half of all individuals reported experiences of sexual abuse, with equal numbers of boys and girls. Symptoms of ADHD or depression were associated with a two–threefold higher probability of experiences of sexual abuse. This was most evident among individuals with co-occurring symptoms of ADHD and depression in both boys and girls, with the greatest likelihood among boys. These findings are consistent with previous research reporting associations between experiences of sexual abuse and mental disorders, including ADHD and depression^{66,127,128}.

For girls, there was less variation in the extent to which symptoms of ADHD, depression or co-occurring symptoms were associated with experiences of sexual abuse, compared to among boys. In girls, sexual abuse was more strongly related to symptoms of ADHD than symptoms of depression, whereas among boys it was the other way around. In addition, there was an interaction between sex and sexual abuse, increasing the probability of symptoms of ADHD in girls compared with boys. According to the literature, sexual abuse is more strongly associated with the kind of symptoms that are most uncommon in that respective sex¹⁰⁶. Etiologically, sex differences in stress responses may play a role; however, the cross-sectional design of the study did not allow any conclusions on developmental pathways. Theoretically, experiences of sexual abuse in childhood and adolescence have the potential to cause severe intermittent stress^{66,106}. In animal laboratory settings, stress responses to severe intermittent stress during periods analogous to childhood and adolescence are distinguished from stress responses to mild chronic stress, have sex-specific patterns and show long-lasting effects on stress sensitivity¹⁰⁶. In response to severe intermittent stress, male rodents exhibit behaviour associated with internalizing symptoms, whereas females exhibit increases in escape behaviour. The results imply that severe stress, such as sexual abuse, may cause stress responses other than those most typical of females, or of males, who are subjected to mild chronic stress^{106, 111}.

10.3. The *TFAP-2β* gene —a biological characteristic and its relation to symptoms of ADHD and/or depression

The findings of Study II suggest that the presence of the 9R variant of the *TFAP-2β* genotype polymorphism, which is associated with increased gene expression, protects girls with symptoms of ADHD from developing symptoms of depression. Consequently, girls with symptoms of ADHD who carry the 8- and 10-repeat variants might have a higher probability of developing co-occurring symptoms of depression.

The *TFAP-2β* gene is known to influence embryonic development of the central nervous system, and it remains possible that different gene variants may influence neuroarchitectonic development in ways that may predispose the individual to the development of psychiatric disorders, such as comorbid ADHD and depression¹⁹². *TFAP-2β* also influences postnatal monoaminergic transmission, several genes with relevance for monoaminergic function and regulation have binding sites for *TFAP-2β*⁷¹ and several observations confirm a relationship between levels of the *TFAP-2β* protein and aspects of monoaminergic function¹⁹³. One finding of particular relevance in this context is that the protein may play a crucial role in mediating the effects of the serotonin transporter gene polymorphism, which, in several studies of both human and non-human primates, appears to influence the development of depression and anxiety in a sex-specific way^{64, 112, 194, 195}. A positive correlation between *TFAP-2β* and dopamine and serotonin turnover in the frontal cortex of rats has been shown, as well as an effect of antidepressant treatment on *TFAP-2β* levels in the brain of rats¹⁹³.

In comparison with the recent GWAS finding on shared genetic risk of ADHD and depression⁸⁴, Study II is free of selection bias regarding sex or gender, including referral bias^{41, 148, 149}. Our study also embraces all subjects in a defined population without selection biases for other possible comorbidities. Some parts of the data in the GWAS, which aimed to study ADHD, excluded subjects with depression. Further, the present sample consists only of adolescents, which is important when considering the changes in the prevalence and sex ratio of depression from childhood to adolescence. The co-occurrence of symptoms of ADHD and depression may therefore be more evident in an adolescent population, as younger subjects with ADHD may not yet have developed the comorbidity.

The results of Study II are consistent with studies on shared genetic risk for ADHD and depression^{57, 84}, which indicate a role for calcium channel signalling genes and specific single-nucleotide polymorphisms (SNPs) in

both disorders. There is also support for the existence of several pathways to ADHD supported by GWAS analyses, where both common and rare copy number genetic variants have been associated with ADHD. Additionally, ADHD with comorbid severe conduct disorder has been showed to share genetic risk via the COMT genotype⁸⁵.

In Study II, the finding seemed to be specific to women. In fact, sex differences in neuroscience are a rule rather than an exception, although the neurobiological underpinnings and pathophysiological mechanisms are largely unknown^{188, 190}. However, epigenetic changes caused, for example, by differences in exposure for boys and girls to the potentially severe intermittent stress of sexual abuse, may interfere in a sex-specific way in our results. Future studies may reveal eventual sex-specific interactions between the *TFAP-2β* polymorphism and sexual abuse on the probability of symptoms of ADHD and/or depression.

10.4. Parent–adolescent relationship and help-seeking from specialized mental health services

Only a minority of adolescents who reported significant symptoms of ADHD and/or depression sought specialized mental health care. However, the symptoms still explained more service utilization than all other psychosocial factors examined. Contrary to our expectations, willingness to communicate with parents about problems, assessed by secure attachment, did not increase help-seeking.

As expected, girls sought more help than boys^{196, 197}. In accordance with the literature for both sexes, co-occurring symptoms of ADHD and depression increased help-seeking the most^{146, 159}. Larson et al. found an increased use of mental health care that followed the number of comorbid disorders, including depression and ADHD¹⁵⁹. Merikangas et al., who studied North American adolescents, found that comorbidity, particularly with behaviour disorders, was associated with increased use of specialized mental health care¹⁴⁶. Another finding in the same study by Merikangas et al. was that girls with ADHD reported lower service use than boys, which is consistent with our results. In contrast to previous studies^{145, 146}, symptoms of depression increased help-seeking more than did symptoms of ADHD. Socio-cultural differences according to stigma, as well as literacy of depression and its treatment, may play a role¹⁵³.

Among help-seeking adolescents with symptoms of depression, approximately 40% of the boys and 50% had co-occurring symptoms of

ADHD. Among help seeking girls with symptoms of ADHD a majority had co-occurring symptoms of depression, in contrast to the boys. This finding is in line with the results in Study IV, where girls with ADHD had substantially higher comorbidity than the boys. Among individuals with ADHD who had four or more disorders, girls outnumbered boys in a ratio of almost 10:1. One might speculate that boys with many comorbid disorders had been referred to psychiatric care at a younger age than girls, which would be consistent with the larger proportion of child allowances due to ADHD from younger ages among boys compared to among girls¹⁴⁷.

Help-seeking adolescents reported less secure attachment to their parents. Insecure attachment has been found to be associated with higher rates of both depression and ADHD, which we also found in our study^{141, 198, 199}. We do not know whether there are state effects of depressed mood on self-reports in attachment questionnaires. However, no interactions between symptoms of ADHD and/or depression and attachment to either of the parents were significant predictors of specialized mental health help-seeking.

One Norwegian case-control study with 39 pairs of help-seeking and non-help-seeking adolescents matched on internalizing symptoms found an association between caregiver warmth, measured by the Parental Bonding Instrument (PBI), and specialized mental health help-seeking. The PBI may measure different characteristics of the adolescent-parent relationship than does the ECR-RC9. Parental attitudes towards mental health care are also known to influence help-seeking^{41, 200, 201}. None of the family characteristics examined explained help-seeking; however, there were no measures of family attitudes towards psychiatric services, either in this study or in the Norwegian study¹⁵⁸.

10.5. Validity of ASRS-A and ASRS-A-S

The ASRS-A and the ASRS-A-S showed similar high internal consistency and concurrent validity to the original English ASRS¹⁷⁴. However, the sensitivities were higher and the specificities were lower. Another difference, compared with the original ASRS, was better psychometric properties for the total scale in comparison to the screening version. Moreover, the ASRS-A-S and the ASRS-A had superior psychometric properties among girls.

Studies among adults, even when performed in different countries, have found stable internal consistencies for the ASRS²⁰², similar to those found in this adolescent sample. However, the diagnostic accuracy of the ASRS-A found in Study IV differed from that of previous studies^{174, 175}. The only other study performed in the same age group²⁰³ consisted exclusively of

ADHD patients, with a preponderance of males; moreover, adolescents perceived as unreliable reporters of their ADHD symptoms had been excluded, which suggests that comparisons may be coarse. Differences between participants, such as adolescents versus adults and males versus females, may influence sensitivity and specificity, because some characteristics of the ADHD diagnosis might differ between groups. Further, the prevalence of the diagnosis of ADHD varies between population-based and clinical samples, and influences PPV and NPV. Increasing prevalence increases PPV but decreases NPV. Consequently, the difference in diagnostic accuracy between the adolescent clinical sample in Study IV and previous studies may be explained by differences in the studied populations.

Whether the proposed narrow cut-off used in Study I or a count of the total score of the ASRS-A and the ASRS-A-S would show higher diagnostic accuracy than the investigated dichotomized cut-off used by Kessler et al.¹⁷⁴, remains to be investigated. Nor do we know whether the diagnostic accuracy would change by lowering the prevalence of ADHD, as in the epidemiological samples. Evaluation of the diagnostic accuracy of alternative scoring methods could be a focus of future studies, as could evaluation of parent report versions of the ASRS-A and the ASRS-A-S.

10.6. Methodological considerations

Strengths and limitations, Studies I–III

Considerations of design and representativeness

In Studies I–III, all school pupils were recruited from a county that is considered representative of Sweden because of its distribution of educational, income and employment levels, and its urban and rural areas²⁰⁴. Thus, our studies contribute important information by their use of a large, representative community sample, and offer an opportunity to generalize our results to other adolescent populations.

The response rate was high. However, there were some drop-outs, and it can be assumed that adolescents with severe mental illness were over-represented among those students who were missing from the original administration of the survey and from the “late responder” group. In Study I, the prevalence of experience of forced intercourse was higher among the late responders, which is an indication of an association between not being at school and more severe sexual abuse. This, in turn, is associated with mental illness, including symptoms of ADHD and depression. This means that the results of Studies I–III are likely to underestimate the symptoms of ADHD, symptoms of depression and prevalence of sexual abuse. In Study III, the

rates of help-seeking is probably lower than they would be if the drop-outs had been present in the analyses.

However, the restricted age range of participants, with only 15–16-year-olds and 17–18-year-olds included in the study, may have influenced the results. In these age groups, depression increases and ADHD decreases^{14, 37}, which might explain why more help-seekers reported depressive symptoms.

Nevertheless, the large samples and high participation rates are strengths of the present studies, which also gave high statistical power in the analyses. As the design of the studies was cross-sectional, analyses of associations could be performed, however analyses of developmental trajectories of symptoms of ADHD and/or depression were not possible.

Considerations of the measure of ADHD symptoms

One limitation of the Studies I-III is that the measure for symptoms of ADHD, the ASRS-A-S, lack validation in a Swedish adolescent non-clinical population. The ASRS-S for self-report of ADHD symptoms has been validated in an adult population in the U.S. and showed good psychometric properties¹⁷⁴. There is only one other study of the ASRS in adolescents, which has major methodological shortcomings²⁰³. In Studies I-III, the prevalence of symptoms of ADHD was 19–22%, which is higher than in most population-based studies of ADHD^{14, 27}. This suggested a higher sensitivity and a lower specificity of the ASRS-S among adolescents than among adults. In Study IV, the ASRS-A and ASRS-A-S were examined in a clinical sample, however the accuracy in a non-referred population remains to be investigated.

It is possible, that symptoms of ADHD as well as symptoms of depression and anxiety in adolescence are captured by the ASRS-A-S, due to overlapping symptoms. This notion would be supported by the results in the clinical Study IV where the highly comorbid girls with ADHD had the best diagnostic accuracy measures of the ASRS-A and the ASRS-A-S. Accordingly, the findings in Studies I-III can not rule out that symptoms due to other disorders than ADHD may play a role for the scoring on the ASRS-A-S. Consequently, it may exist other ADHD phenotypes than that of co-occurring symptoms of ADHD and depression. According to the literature, psychiatric comorbidity, and overlapping psychiatric symptoms, is common^{10, 44}. However, the methodologies of Studies I-III did not allow controlling for anxiety etc. Future research may address these issues.

Furthermore, in the Studies I-III the majority of girls reporting symptoms of ADHD is contrary to the findings of most studies¹⁴. A self-report measure is free of observer bias, which may contribute to more pronounced sex differ-

ences in ADHD than actually exist among children and adolescents¹⁸⁵. The sex ratio of ADHD is more equal among adults who, to a larger extent, report their symptoms themselves²⁰⁵. Moreover, it is also possible that some individuals in the sample scored high on the ASRS-S because of shared symptoms, such as impaired attention ability and/or physical restlessness in those who suffer from depression or anxiety.

Further, in Studies I and II, we asked the participants for current symptoms instead of their symptoms over the past 6 months. This change of pretext was expected to contribute to the high prevalence of symptoms of ADHD according to the cut-off used by Kessler et al.¹⁷⁴. However, in Study III, the adolescents were asked to report their symptoms over the past 6 months. The total prevalence of symptoms of ADHD (using identical cut-off) was reduced from 21-22% to 19%. This indicates a limited influence of the pretext time period varying between now and 6 months, probably due to recall bias.

In Study I, we aimed to find adolescents with evident symptoms of ADHD—a narrow cut-off was introduced to identify individuals with more pronounced symptoms—however, whether this really increased the specificity of the instrument according to a diagnosis of ADHD measured with gold standard method, will be investigated in future studies.

Considerations of the measure of depression symptoms

The lack of validation of the DSRS against structured interviews in non-clinical adolescent samples is a limitation. The DSRS has been validated among adult psychiatric patients but not in an adolescent population. Consequently, comparisons made with other population-based studies are coarse.

In Studies I, II group B and III, symptoms of depression were reported by 12% - 14% respectively, which is similar to the 12% found in a Swedish epidemiological study of 16–17-year-olds³³. However, self-assessment increases the prevalence, and the true proportion fulfilling the depressive episode criteria is not known. In the Swedish study by Olsson et al., diagnostic interviews were conducted in a subsample, revealing a depression prevalence of 6%^{33, 206}. Among our 12–14%, we do not know the proportion of individuals who had a diagnosis of major depression. In addition, we did not control for symptoms of anxiety, which is the most prevalent mental health problem in adolescence²⁷.

There was a distinct preponderance of girls with symptoms of depression in all samples, which is consistent with previous research based on self-report scoring in this age group³³. Furthermore, screening through self-reports has

been suggested to be superior to physician-rated diagnoses, even when the physicians have been trained beforehand²⁰⁷.

In Study II, group A had a lower prevalence of symptoms of depression than expected in comparison with our large population-based surveys and with other research on self-reported symptoms of depression³³. This is probably an effect of the stratification of that group, over-emphasizing both ends of the deviant behaviour continuum (“angels and evils”).

However, the validations of the DSRS may be a focus of future research in order to full fill a need of a validated screening tool for depression to use in non-clinical and clinical samples of adolescents.

Considerations of the measure of sexual abuse

Our choice to code any presence of sexual abuse as “experience of sexual abuse” includes individuals with heterogenic experiences of sexual abuse, and most likely heterogenic responses. Moreover, the retrospective design of Study I is a limitation, as sexually abused individuals in general tend to forget, belittle or deny their experiences²⁰⁸, which may render our results conservative according to the true prevalence of sexual abuse. However, failure by children to disclose their experiences in interviews of sexual abuse might have diverse explanations. Professionals will most likely never be able to identify all cases of sexual abuse on the basis of children's answers in interviews²⁰⁸. Therefore, the anonymous self-reports of sexual abuse in the present study may be more reliable than non-anonymous reports^{208, 209}.

Considerations of genotyping, drop-outs and statistical methods

The interpretation of the results in Study II should be considered in the context of several limitations. First, genetic association studies have been haunted by failures of replication²¹⁰. In response to this, several ways of avoiding false positive findings have been suggested. The most important of these are: (1) replications of novel findings in independent samples; (2) a plausible biological theory behind candidate gene approaches; and (3) control for population stratification. In the present study, we investigated the associations studied in two independent population-based samples, stated a plausible biological risk factor and, finally, controlled our findings for population stratification. The fact that Study II was performed in two population-based samples makes generalizability to other similar populations possible.

A second limitation is the number of drop-outs or non-participants, which affects the representativeness and generalizability of the results. However, an analysis of the 183 students in group B who were absent from school on the day the questionnaire was distributed but who completed the questionnaire at

a later time and returned it together with their saliva sample by mail, and a comparison of those with detectable DNA and those who did not give saliva samples or had failed DNA analysis, showed no differences in symptoms of ADHD or depression.

Third, it is a delicate matter to choose statistical methods in a study of main and interaction effects, where the outcome measures are on a skewed ordinal or interval scale. Interactions are efficiently estimated by a GLM. However, the inference should be interpreted with caution if the assumption of normally distributed residuals is violated. The dependent variable data (depression index) were used on an ordinal scale, which was positively skewed, and outliers were present within each predicting subcategory. Neither a log nor a log–log transformation produced a normally distributed outcome measurement. Moreover, a log transformation seriously impinges the possibility of detecting interaction effects. The choice of statistical methods was therefore intricate, and we used both parametric and non-parametric methods. We validated our analyses with Poisson log-linear regression, which is suitable for ordinal-scaled variables and the kind of distribution that was found in the present study, and with the Kruskal–Wallis test. The Kruskal–Wallis test also has to be interpreted with caution, because it compares independent subgroups' mean rank of the dependent variable rather than testing for interaction effects. However, the procedure with complementary statistical approaches helps to overcome the shortcomings of individual statistical methods and helps to eliminate scaling artefacts, one of the most ubiquitous sources of artefacts in interaction research. Furthermore, the Kruskal–Wallis test, the Poisson log-linear regression and the GLM test all showed similar results, in the same direction, giving further support for the presented findings among females. In addition, after adjusting the model for possible non-independent confounders, the interaction effect between the *TFAP-2 β* and ADHD status remained significant and of equivalent magnitude, indicating a solid finding.

Bonferroni adjustments for multiple statistical analyses could have been considered in Study II. However, the data resulted in a positive outcome of a distinct hypothesis, and the second, larger population sample replicated the findings from our first sample. Furthermore, the observed power of the interaction was not alarmingly low (52–66%). Therefore, it may be argued that results could be presented without Bonferroni corrections, as such analysis would involve a serious risk of Type II errors²¹¹.

There is, however, a need for careful consideration of whether our findings are theoretically plausible or whether the significant findings were random or unexpected.

Considerations of the measure of the parent–adolescent relationship

A limitation of Study III is the lack of a gold standard for the assessment of adolescents' willingness to communicate with their parents. We used the ECR-RC9 as a measure of attachment cognitions, but its Swedish validation has not yet been published. However, an appraisal of face validity for the nine questions indicated that they assessed willingness to communicate. Moreover, we do not know if attachment style is reported differently by depressed and non-depressed adolescents. To our knowledge, there is no prospective longitudinal study that explores state effects on self-reported attachment in adolescents. Additionally, whether one particular insecure attachment style is a help-seeking facilitator or a barrier remains to be investigated.

However, Study III contributes new knowledge to the research area on specialized mental health help-seeking. To the best of our knowledge, this is the first study on the influence of the parent–adolescent relationship, measured by secure attachment, on specialized mental health help-seeking.

Methods, strengths and limitations, Study IV

The external drop-out rate of Study IV was high. Severely disordered patients might have dropped out more frequently, resulting in a less impaired study sample than the true patient population. Moreover, some adolescents are not motivated help-seekers themselves but are brought to the clinic by their parents, which may result in less reliable ASRS-A self-reports. This might have occurred more often in boys, who more often chose not to participate. Symptoms of ADHD have been shown to be under-reported by adolescent boys. Therefore, parents are considered more reliable¹⁸⁶. By interviewing the adolescent and their parent together, the reference standard was more likely to be valid. Furthermore, almost half of the participants filled in the ASRS-A after the K-SADS interview, which may have sensitized them to their symptoms and influenced their answers. However, there were no differences according to mean symptom level in the ASRS-A between the group who answered the ASRS-A before the K-SADS interview and the group who answered the ASRS-A afterwards, nor did the diagnostic accuracy change.

With regard to the different psychometric properties among boys and girls, caution must be exercised regarding sample size, with fewer boys than girls, which implies greater distribution variety among boys. Additionally, the comorbidity rates were considerably higher among girls than among boys and were most pronounced among the patients with ADHD. Comorbidity may influence the ratings of the ASRS-A because of the overlapping symptoms of comorbid disorders. Boys with severe ADHD and high

comorbidity rates may seek help more often before adolescence compared with girls with severe ADHD and high comorbidity rates^{146, 147}. Therefore, help-seeking boys and girls in adolescence may have different characteristics. The internal consistency of the ASRS-A was high for both boys and girls, which indicates that the ASRS-A is reliable for both sexes. Finally, it is unclear whether the dichotomized scoring method of Kessler et al is the optimal scoring method among adolescent psychiatric patients.

A strength of the present study was that the ASRS-A-S/ASRS-A was compared with a gold-standard diagnosis of ADHD made by K-SADS interviewers, with good interrater reliability before and during the data collection. Moreover, the time between the index test and the reference test was not more than seven days. Another methodological strength was that the K-SADS ADHD diagnosis uses information from two informants, the adolescent and a parent. Additionally, the fact that the patients from three different sites—two small towns and one large city—were included was a strength that may enhance the generalizability of the results. As a great amount of research on ADHD has been performed in solely or predominately male samples, the present study contributes with more knowledge about the less often studied, yet equally impaired females with ADHD. Finally, the present study fulfils the need for validation studies of the Swedish translation of the ASRS-A-S/ASRS-A.

11. Conclusions

The phenotype of co-occurring symptoms of ADHD and depression is common with doubled frequency among girls compared to boys. Among both boys and girls with co-occurring symptoms of ADHD and depression, approximately 50% also have experiences of sexual abuse, indicating that this is a group with multiple risk factors for long-term impaired mental health. Results support biological sex differences, as girls, but not boys, with symptoms of ADHD and a common polymorphism of *TFAP-2 β* (absence of a 9R variant) reported more symptoms of depression.

Further, a large majority of adolescents with symptoms of ADHD and/or depression were not seeking help from specialized mental health services. The co-occurrence of symptoms of ADHD and depression was the strongest predictor of help-seeking over and above all other psychosocial factors investigated, including secure attachment cognitions to parents. Among help seeking adolescents with symptoms of depression, 40 % of the boys and 50 % of the girls had co-occurring symptoms of ADHD.

The validation study of the ASRS-A/ASRS-A-S showed promising results for further validation.

From a public health perspective, school health-care-based screening for ADHD and depression would have the potential to identify adolescents with co-occurring symptoms of ADHD and depression. Identification would enable evaluation of the need for psychiatric and/or psychosocial interventions, and provide a step towards equalizing health care. From a clinical perspective, this thesis shows that help-seeking girls with ADHD comprise a group with major comorbidity. It suggests the need of reliable diagnostic methods that identify complex comorbidity.

In the light of previous research results of the present thesis show that girls with ADHD express different phenotypic profiles associated with biological factors, compared to boys with ADHD. The phenotypic profiles in girls with ADHD may, in combination with sociocultural differences related to ADHD and gender, contribute to the under recognition of girls with ADHD.

12. Summary in Swedish (Sammanfattning)

Flickor som har ADHD upptäcks i betydligt lägre omfattning jämfört med pojkar som har ADHD. Samtidigt är depression ett vanligt tillstånd, speciellt bland tonåriga flickor. Både ADHD och depression uppvisar hög samsjuklighet, d.v.s. de förekommer ofta samtidigt med andra psykiatriska tillstånd. Hypotesen som ligger till grund för avhandlingen är att det bland tonåriga flickor med symtom på depression, finns många som har samtida symtom på ADHD. Därför är syftet med avhandlingen att öka kunskapen om samtida symtom på ADHD och depression hos ungdomar samt att belysa eventuella könsskillnader, vilket är fokus i de första tre delarbetena. Det avslutande delarbetet är en klinisk valideringsstudie av ett skattningsformulär för ADHD hos ungdomar (ASRS-A/ ASRS-A-S).

Teoretiska modeller för orsaker till psykisk sjukdom innefattar påverkan via biologi, miljö och epigenetik. Dessutom sker samspelet mellan dessa områden inom ramen för individers sociokulturella sammanhang där genuskonstruktioner utgör en sorts miljöfaktor. Såväl biologi som miljö, inklusive den miljö som är kopplad till genus, innehåller aspekter som är olika för pojkar och flickor.

De tre första delarbetena baserades på enkätundersökningar bland hela årskullar av ungdomar i Västmanland i åldrarna 15-16 och 17-18 år. Studie I undersökte förekomsten av samtida symtom på ADHD och depression samt association med en stress faktor i miljön; sexuella övergrepp. Studie II undersökte associationer mellan en biologisk faktor; en polymorfism i genen för transkriptions faktor aktiverande protein-2 β (*TFAP-2 β*) och samtida symtom på ADHD och depression. Studie III undersökte ungdoms- och föräldrelationens betydelse för vårdsökande till barn- och ungdomspsykiatri, i relation till symtom på ADHD och/eller depression. Studie IV undersökte överensstämmelsen mellan självskattade ADHD symtom via formulären ASRS-A och ASRS-A-S med diagnosen ADHD ställd med gold standard metod; den diagnostiska intervjun ”Kiddie Schedule of Affective Disorders and Schizophrenia” (K-SADS).

Studie I-III visade att fenotypen med samtida symtom på ADHD och depression var vanlig och dubbelt så frekvent bland flickor jämfört med pojkar. Vidare uppgav ca 50 % av individerna med samtida symtom på ADHD

och depression att de hade erfarenheter av sexuella övergrepp, likaledes med majoritet av flickor. Flickor som rapporterade erfarenheter av sexuella övergrepp, hade ökad sannolikhet för att ha symtom på ADHD jämfört med pojkar.

Studie II stödjer att det finns biologiska könsskillnader kopplade till samtidiga symtom på ADHD och depression, då avsaknaden av *TFAP-2-beta* med 9 upprepningar ökade risken för flickor med symtom på ADHD, men inte för pojkar, att uppvisa samtidiga symtom på depression.

Studie III visade att 5 % av alla ungdomar med symtom på ADHD och/eller depression sökte hjälp från barn- och ungdomspsykiatrin. Då föräldrar är avgörande initiativtagare till att söka vård, hade vi hypotiserat att ungdomar som gärna anförtrorde sig/kommunicerade med sina föräldrar skulle vara mer vårdsökande. Detta kunde inte bekräftas. Istället var samtidiga symtom på ADHD och depression den faktor som var starkast associerad med hjälpsökande från barn- och ungdomspsykiatrin (BUP) av alla undersökta psykosociala faktorer. Bland dem som sökte vård på BUP var flickor den största gruppen och bland dem var det vanligare med symtom på depression jämfört med symtom på ADHD, tvärt om jämfört med bland pojkarna. Hos ungdomar som sökte vård på BUP som hade symtom på depression, hade 40 % av pojkarna och 50 % av flickorna samtidiga symtom på ADHD.

Detta är i linje med fynd i den kliniska studien (IV) där patienterna diagnostiserades med hjälp av en diagnostisk intervju. Där var samsjukligheten också högre bland flickor jämfört med pojkar, särskilt hos de patienter som hade ADHD. Allra tydligast var skillnaden hos patienter med ADHD som hade fyra eller fler diagnoser vilket förekom hos 4 % av pojkarna och hos 39 % av flickorna.

Studie IV visade att ASRS-A hade något bättre psykometriska egenskaper än den korta ASRS-A-S, i motsats till valideringsstudien av originalversionerna av ASRS och ASRS-S för vuxna. Både ASRS-A och ASRS-A-S hade hög intern konsistens, extern validitet och förmåga att urskilja 7-8 patienter av 10 som hade diagnosen ADHD enligt gold standard (den diagnostiska intervjun; K-SADS). Vidare urskiljdes 8 av 10 patienter som inte hade diagnosen ADHD korrekt. Bland dem som skattade över gränsvärdet i respektive formulär fanns dock en relativt stor proportion av individer som trots detta inte hade ADHD. Vidare hade ASRS-A och ASRS-A-S bättre psykometriska egenskaper bland flickor. Sammantaget visar båda skattningsformulär lovande psykometriska egenskaper men bättre diagnostisk effektivitet vore önskvärd. Alternativa sätt att räkna ihop poäng respektive gränsvärden behöver utvärderas i fortsatt valideringsarbete.

Ur ett folkhälsoperspektiv skulle en generell screening av ADHD och depression inom skolhälsovården öka jämställdheten till chans för upptäckt av vårdbehov hos flickor och pojkar. En screening skulle kunna identifiera gruppen med samtida symtom på ADHD och depression; individer som uppvisar multipla riskfaktorer för långvarig psykisk ohälsa. Det skulle möjliggöra tidig bedömning inom skolhälsovården av behov av remittering till barnpsykiatri och/eller kontakt med socialtjänst.

Ur ett kliniskt perspektiv, visar avhandlingen att flickor som har ADHD som söker vård på BUP till en stor andel utgörs av individer med mycket hög samsjuklighet. Det indikerar behov av diagnostiska metoder som identifierar komplex samsjuklighet på ett tillförlitligt sätt.

Sammanvägt med annan forskning på området visar resultaten, att flickor med symptom på ADHD har en annan fenotypisk profil jämfört med pojkar, vilken är associerad med biologiska skillnader. Den fenotypiska profilen hos flickor med ADHD, tillsammans med skillnader förknippade med genus i det sociokulturella sammanhanget, bidrar sannolikt till att flickor med ADHD identifieras i lägre omfattning och får mindre hjälp jämfört med pojkar med ADHD.

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ASRS-A

Besvara frågorna nedan genom att skatta dig själv med hjälp av skalan till höger. För varje fråga, sätt ett kryss i den ruta som bäst beskriver hur du känt och betett dig de senaste 6 månaderna.

	Hur ofta....?	Aldrig	Sällan	Ibland	Ofta	Mycket ofta
1.	har du svårigheter med att riktigt avsluta en uppgift/ett projekt när du är nästan färdig?					
2.	har du svårigheter med att få ordning på saker och ting när du ska utföra en uppgift som kräver planering?					
3.	har du svårigheter att komma ihåg avtalade möten, t.ex. skolsystem, eller om du bestämt att träffa en kompis?					
4.	händer det att du låter bli eller inte sätter igång med en uppgift där du behöver tänka mycket?					
5.	händer det att du sitter och pillar med något, eller skruvar på dig och rör händer eller fötter när du är tvungen att sitta en längre stund?					
6.	känner du dig sprallig och tvungen att fara runt som om du har "spring och hopp" i kroppen?					
	Hur ofta...?	Aldrig	Sällan	Ibland	Ofta	Mycket ofta
7.	gör du slarvfel när du arbetar med en tråkig eller svår uppgift?					
8.	har du svårt att hålla kvar uppmärksamheten när du gör tråkiga eller enformiga sysslor?					
9.	har du svårt att koncentrera dig på vad folk säger även när de pratar med dig?					
10.	slarvar du bort eller har svårt att hitta saker hemma eller i skolan?					
11.	störs du av händelser eller ljud i din omgivning?					
12.	lämnar du din plats under lektionen eller i andra situationer där andra tycker att du skall sitta kvar?					
13.	känner du dig otålig, rastlös eller har svårt att vara stilla?					
14.	har du svårt att ta det lugnare och koppla av när du har en stund över?					
15.	pratar du för mycket när du är med andra?					
16.	avslutar du meningar åt dem du pratar med, innan de själva hinner prata färdigt?					
17.	har svårt att vänta på din tur när andra tycker att du borde vänta?					
18.	avbryter eller stör du andra när de är upptagna?					

DSRS-A

Följande frågor handlar om hur du känt dig de senaste två veckorna:

Har du under de senaste två veckorna känt dig nedstämd, ledsen eller tom, mest hela tiden, i stort sett varje dag? Ja Nej

Har du under de senaste två veckorna känt dig irriterad, arg eller uppriven mest hela tiden, i stort sett varje dag? Ja Nej

Har du under de senaste två veckorna, så gott som dagligen, känt dig påtagligt mindre intresserad av det mesta i tillvaron eller haft svårt att glädjas åt sådant som du vanligtvis tycker om? Ja Nej

Har du haft minskad aptit så gott som varje dag under de senaste två veckorna eller har du gått ner 2 kg eller mer i vikt (utan bantning) under denna tid? Ja Nej

Har du haft ökad aptit så gott som varje dag eller har du gått upp 2 kg eller mer under denna tid? Ja Nej

Har du under de senaste två veckorna, i stort sett varje natt haft svårt att somna, vaknat till under natten eller vaknat tidigare än vanligt på morgonen? Ja Nej

Har du under de senaste två veckorna sovit mer än vanligt, i stort sett varje natt? Ja Nej

Har du under de senaste två veckorna så gott som dagligen känt så orolig och rastlös att du haft svårt att vara stilla? Ja Nej

Har du under de senaste två veckorna, så gott som dagligen varit mer i stillhet och rört dig mindre än vanligt? Ja Nej

Har du under de senaste två veckorna, så gott som dagligen haft god nattsömn? Ja Nej

Har du under de senaste två veckorna, i stort sett varje dag känt dig svag eller haft bristande energi? Ja Nej

Har ditt självförtroende varit sämre än vanligt under de senaste två veckorna? Ja Nej

Har du under de senaste två veckorna haft återkommande skuld känslor eller känslor av värdelöshet? Ja Nej

Har du under de senaste två veckorna haft svårigheter att tänka, fatta beslut eller att koncentrera dig? Ja Nej

Har du under de senaste två veckorna haft återkommande tankar på döden eller tänkt att det skulle vara bättre att vara död? Ja Nej

Har du under de senaste två veckorna haft återkommande tankar på att ta ditt liv? Ja Nej

Har du svarat JA på en eller flera av frågorna ovan, ber vi dig också ta ställning till följande fråga:

Har de symtom som du besvarat med JA inneburit ett påtagligt lidande för dig, eller medfört svårigheter i ditt sätt att fungera i dina dagliga uppgifter eller i din relation till andra människor? Ja Nej

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