Attention Deficit/Hyperactivity Disorder in Adults

Prevalence, Psychiatric Comorbidities and Long-term Outcome

DAN EDVINSSON
Attention Deficit/Hyperactivity Disorder (ADHD) was originally thought to occur only in children, but is increasingly recognised as causing functional impairment also in adulthood. The overall aim of this thesis was to achieve a comprehensive understanding of ADHD in adulthood.

A questionnaire based on the DSM-IV criteria of ADHD, reported childhood symptoms, reading and spelling problems, difficulties and suffering and general assessment of functioning (GAF) was distributed to three samples: the general population (GP), outpatient psychiatry (OPP) and female prison inmates. Symptoms consistent with ADHD were more than three times higher in the OPP sample than in the GP sample (6.6 versus 2.1%). ADHD symptoms and related problems occurred in 50% of the prison inmates.

A cohort of 168 patients diagnosed with ADHD in adulthood was interviewed about current ADHD symptoms and psychiatric comorbidity on axis I and II. The lifetime prevalence of psychiatric comorbidity on axis I was 92% and current comorbidity, including autism spectrum disorders and Tourette’s syndrome, was 47%. The sex-specific pattern of the comorbid disorders was similar to that in the general population. Forty-six per cent of the patients endorsed the specific criteria for at least one personality disorder.

After a mean follow-up of six years, there was remission of adult ADHD in about 30% of the patients, regardless of whether there was ongoing medication or not. There were no differences in function and quality of life, except for global general improvement, which was better in patients currently on medication.

The most prevalent long-term side effects of pharmacological treatment with mainly stimulants were decreased appetite, dry mouth, anxiousness/restlessness and an increase in pulse frequency. The discontinuation rate was about 50%: 29% discontinued because of a perceived lack of effect, followed by elevated mood or hypomania (11%). No detectable evidence of tolerance and increased need for dosage over time was observed.

To conclude, Symptoms of ADHD is highly overrepresented in OPP and in female inmates compared with the GP. Furthermore, adults diagnosed with ADHD have a high lifetime prevalence of psychiatric comorbidity. Long-term pharmacological treatment with stimulants is safe with relatively mild and tolerable adverse effects. Continued medication, however, is not related to remission.

Keywords: ADHD, adults, prevalence, inmates, psychiatric comorbidity, long-term outcome, side effects, adverse events, stimulants, atomoxetine.
With gratefulness and admiration, I dedicate this thesis to the persons who generously shared their life experiences and participated in these studies.
List of Papers

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


III Edvinsson D, Ekselius L. (2017) Six-Year Outcome in Subjects Diagnosed with Attention-Deficit/Hyperactivity Disorder as Adults. *Submitted for publication*.


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Papers I and II in this thesis, and a discussion on them, were the basis for a licentiate degree in medicine at Uppsala University, defended on October 11, 2012.
Abbreviations

AD/HD  Attention Deficit/Hyperactivity Disorder
ADD    Attention Deficit Disorder
ASD    Autism Spectrum Disorder
ASPD   Antisocial Personality Disorder
ASRS   Adult ADHD Self-Report Scale
AUDIT  Alcohol Use Disorders Identification Test
BPD    Borderline Personality Disorder
CAADID Conners’ Adult ADHD Diagnostic Interview for DSM-IV
CBT    Cognitive Behavioural Therapy
CD     Conduct Disorder
CGI-I  Clinical Global Impression - Improvement
DAMP   Deficits in Attention, Motor Control and Perception
DIP-I  ICD-10 Personality Interview
DIVA   Diagnostisk Intervju för ADHD hos vuxna
DSM    Diagnostic Statistical Manual of Mental Disorders
DUDIT  Drug Use Disorders Identification Test
ED     Emotional Dysregulation
ESSENCE Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examination
EQ-VAS EuroQol-Visual Analogue Scales
EQ-5D  EuroQol-5 Dimension Questionnaire
GAF    Global Assessment of Functioning
HKD    Hyperkinetic Disorder
HRQoL  Health-related quality of life
ICD    International Statistical Classification of Diseases and Related Health Problems
LD     Learning disability
MTA-study The multimodal treatment study of children with ADHD
ODD    Oppositional defiant disorder
PTSD   Posttraumatic stress disorder
RCT    Randomized controlled trial
SCID-I The Structured Clinical Interview for DSM-IV axis I
SCID-II The Structured Clinical Interview for DSM-IV axis II
SDS    Sheehan Disability Scale
SUD    Substance use disorder
Contents

Introduction ......................................................................................................................... 11
Background .......................................................................................................................... 12
   Historical perspectives on ADHD .............................................................................. 12
   Current diagnostic criteria of ADHD ...................................................................... 14
   Prevalence and impairment of ADHD ...................................................................... 14
   Aetiology ......................................................................................................................... 15
   Coexisting disorders and ADHD .............................................................................. 16
   ADHD in prison inmates ............................................................................................. 17
   Diagnostic assessment of ADHD in adulthood ......................................................... 18
   Multimodal treatment of ADHD .............................................................................. 19
   Pharmacological treatment of ADHD ...................................................................... 20
   Outcome predictors ....................................................................................................... 21
Aims and scope .................................................................................................................... 22
Method ................................................................................................................................. 23
   Study design and participants .................................................................................... 23
   Procedures and measurements .................................................................................... 25
   Statistics ......................................................................................................................... 28
   Ethics ............................................................................................................................... 28
Results ................................................................................................................................. 29
   ADHD-related symptoms (Paper I) ........................................................................... 29
   Sex differences (Paper II) ............................................................................................ 31
   Six-Year Outcome (Paper III) .................................................................................... 33
   Long-Term Tolerability and Safety (Paper IV) ............................................................ 37
Discussion ........................................................................................................................... 41
   Methodological considerations .................................................................................... 41
   General discussion and clinical implications .............................................................. 45
   Future aspects .................................................................................................................. 51
Conclusions ......................................................................................................................... 52
Acknowledgements ............................................................................................................. 53
References ............................................................................................................................ 55
Introduction

At the turn of the century, the knowledge of adult ADHD within psychiatry was almost non-existent, and sometimes even the existence of ADHD in adulthood was outright put in question. To optimize resources to obtain, assess and optimally use the new knowledge on ADHD in adulthood, and to develop and implement procedures for accurate evaluation and treatment, a specialized neuropsychiatric team was established within the Department of Psychiatry at Uppsala University Hospital. The first part of this thesis is the result of attempts to obtain relevant knowledge in order to ensure optimal clinical practice. Therefore, the two first papers in this thesis investigate the prevalence of adult ADHD in various settings and psychiatric comorbidity in adults previously not diagnosed with ADHD.

Effectiveness and safety of pharmacological treatment as well as predictors of favourable outcome are important issues to consider when planning for scientifically based treatment programs. In an increasing number of scientific publications, pharmacological treatment has been demonstrated to be effective and safe in the short term. The long term outcome and safety of pharmacological treatment is, however, still less well investigated. The second part of this thesis demonstrates the long-term outcome and safety of pharmacological treatment of a clinical sample of subjects diagnosed and treated for ADHD as adults.
**Background**

**Historical perspectives on ADHD**

The earliest description of attention difficulties in the medical literature, with reference to the present concept of ADHD, is the publication by the German physician Melkior Adam Weikard. In 1775, possibly even a few years earlier, he anonymously published the textbook *Der Philosophische Artzt* (English: *The Philosophical Physician*) [15]. In this textbook Weikard describes the symptoms of inattention and distractibility – *Attentio Volubilis*, which overlap part of the current inattentive ADHD diagnostic criteria. Interestingly, his clinical examples included adults. Environmental factors such as upbringing were identified as the cause of inattention but Weikard also discussed the possibility of a neurological impact of these external causes. Furthermore, he considered inattention to be more common in childhood than in old people and that the symptoms described should be treated with a distraction-free environment and physical exercise, among other measures [15].

In 1798, the Scottish physician Alexander Crichton published a chapter on inattention in his textbook *An Inquiry into the Nature and Origin of Mental Derangement* [41]. Crichton states that a patient suffering from “disease of inattention” is agitated by impressions and easily distracted, which causes mental restlessness and “fidgets”. He concludes that a person with the disorder “may be either born with it or it may be the effect of accidental diseases”. He further recommended special educational interventions in that physical punishment (“terrors of the rod”) seemed ineffective in these children.

Several descriptions of children with ADHD appeared later like the character *Struwwelpeter* (English: *Shockheaded Peter*) in the illustrated book *Lustige Geschichten und drollige Bilder* (English: *Funny stories and droll pictures*) by the German physician Heinrich Hoffman [72]. Since its appearance in 1845, the character has constituted a prominent part of the literature for children in German-speaking countries. Both the inattentive and the hyperactive/impulsive subtypes of ADHD can be clearly recalled from Hoffman’s poetic examples.

Until recently, the British physician Sir George Frederick Still was considered the first to present scientific descriptions of childhood ADHD. In a series of lectures delivered in 1902 and later published in the Lancet, Still describes a clinical panorama of children with a “defect of moral control” [135]. Many of these children were described as hyperactive and today
would probably be considered to suffer from comorbid oppositional defiant disorder (ODD). Of interest are Still’s observations of comorbid psychiatric disorders and criminality among adult relatives of these children [14; 135; 136].

In 1947, the book *Psychopathology and Education of the Brain Injured Child* was published by Alfred Strauss and Laura Lehtinen in which the concept “minimal brain damage” was introduced [137]. The concept was based on institutionalised children with distractibility, perseveration, hyperactivity and motor and learning problems for whom specific educational plans were later developed.

The concept of “minimal brain dysfunction” (MBD) appeared in an article by Clements and Peters in 1962 describing school-age children with specific learning, motor and coordination deficits together with “hyperkinesis”, impulsivity, emotional lability, distractibility, “equivocal” neurological signs and an EEG with a “6- and 14-per-second positive spiking pattern” [38]. DSM-II, published in 1968, included the entity “The hyperkinetic reaction of childhood”, mainly implying that symptoms were a reaction to the environment and usually outgrown later in life with increased developmental maturity [5].

In 1980, this concept was succeeded by the diagnostic entity “attention deficit disorder” (ADD), which was introduced in DSM-III: diagnostics were clarified by dividing the diagnosis into inattentional problems with and without hyperactivity [6].

DSM-III-R, published in 1987, introduced the diagnosis “attention deficit hyperactivity disorder (ADHD)”, with a unidimensional approach listing a total of 14 symptoms with a diagnostic cut-off of ≥8 diagnostic criteria [7].

In 1982, Gillberg and Rasmussen separately introduced the concept “perceptual, motor and attentional deficits” (PMAD) based on a survey of Swedish seven-year-old children [60]. This concept was changed to “deficit in attention, motor control and perception” (DAMP) in 1987 [58]. The DAMP concept is used mostly in Scandinavia. In DSM-IV and DSM-5 it approximately corresponds to ADHD in combination with “developmental coordination disorder” (DCD) [58].

DSM-IV, published in 1994 [8], with a text revision, DSM-IV-TR in 2000 [9], lists nine symptomatic criteria of inattention and hyperactivity/impulsivity. The cut-off for a diagnosis is set at ≥6 items in each domain, resulting in the possibility of three subtypes: ADHD with predominantly inattention, ADHD with predominantly hyperactivity/impulsivity and the combined subtype (criterion A). The onset of symptoms causing impairment should be present before the age of seven years (criterion B). Impairment should be present in more than two settings (criterion C). There should be clear evidence of clinically significant impairment in social, academic or occupational functioning (criterion D). Symptoms that occur should not be accounted for solely by another mental disorder (criterion E). Because the
DSM-IV diagnostic criteria were originally adopted for children, questions were raised as to whether they are optimal for use in an adult population. This issue will be further addressed regarding the DSM-5 criteria (i.e. the current diagnostic criteria of ADHD).

Current diagnostic criteria of ADHD

DSM-5, published in 2013, presented some minor but important changes in the diagnostic criteria of ADHD. The childhood symptom items of criterion A are now supplemented by examples of how childhood symptoms can be presented in adults. Furthermore, only $\geq 5$ current items in each domain are required for older adolescents and adults aged $\geq 17$. Criterion B was changed to childhood symptom presentation to before 12 years of age. Criteria C and D were left unchanged. For criterion E, pervasive developmental disorders (PDDs), such as previous autism spectrum disorder (ASD), were removed as exclusion criteria [10].

The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) was published by The World Health Organisation (WHO) in 1992 and has been in clinical use in Sweden since 1997 [161]. The ICD-10 uses a narrower definition of ADHD, namely hyperkinetic disorder (HKD). A diagnosis of HKD requires symptoms of hyperactivity/impulsivity, and accordingly, ICD-10 does not recognise the predominantly inattentive subtype of ADHD. Thus, in comparison with DSM-IV (and partly DSM-5), HKD roughly corresponds to the combined and predominantly hyperactive/impulsive subtypes. The 11th Revision of the International Classification of Diseases (ICD-11) has been announced to be due out in 2018.

In addition, emotional dysregulation (ED) has been demonstrated to be linked to ADHD, although not formally included in the diagnostic criteria of DSM-5 and ICD-10. The "Wender Utah criteria" include ED as an important part of ADHD. ED has been demonstrated to respond to treatment with stimulants [118].

Prevalence and impairment of ADHD

ADHD is widely recognised as one of the most common psychiatric disorders of school-age children, with a prevalence rate of 3-7%. Data indicate that boys tend to be diagnosed [88] and treated more often than girls [11]. In adulthood, research presents a much more differentiated picture, which has been suggested to be explained by referral bias in combination with differences in assessment and methodology [154]. Although prospective studies indicate a frequent decline of ADHD symptoms with increasing age, signifi-
cant loss of functioning may remain despite sub-threshold diagnostic status [21; 50; 84]. Adult functioning after childhood ADHD varies but is generally worse with persistence of ADHD symptoms [70]. Thus, the functional impairment caused by ADHD in adulthood is increasingly acknowledged in a broad variety of domains. For example, motor vehicle accidents among adults with ADHD have been demonstrated to be substantially lower during periods of medication [34]. In summary, the prevalence of adult ADHD in the general population (GP) is estimated to be at least 2-4% [51; 83].

Aetiology
The aetiology of ADHD is still largely unknown, but it is widely recognized that there is a substantial genetic component. Follow-up studies of monozygotic and dizygotic twins report that persistent genetic influences explain between 45 and 90% of the total genetic variance in hyperactivity-impulsivity and inattention from childhood to adolescence [90]. The genetic structure of ADHD has proven to be complex, although gene studies of ADHD have produced evidence of the involvement of several genes in the aetiology of the disorder. Meta-analyses are supportive of the involvement of genes coding for serotonergic and dopaminergic receptors, together with various proteins involved in dopamine transportation and membrane fusion [104].

Environmental factors have also been reported to be important in ADHD. An increased risk of ADHD has been demonstrated in children with prenatal exposure to smoking [43], low birthweight [75], preterm birth [37], and low Apgar scores [65]. Furthermore, nutritional factors [123], TV and computer games have been discussed regarding ADHD [52; 140]. Severe institutional deprivation has also been reported to be related to persistent symptomatology of ADHD [80].

On a group level, ADHD children, regardless of sex, have been shown to have smaller brain volume compared with controls [31]. The most frequently replicated neuroanatomic deviations have been identified in brain areas involved in executive functioning (e.g., the dorsolateral prefrontal cortex, caudate nucleus, globus pallidus, corpus callosum and cerebellum) [126]. Neurobiological deviations have been identified with functional magnetic resonance imaging in boys with ADHD compared with age-matched non-ADHD controls while performing visual go-stop tests. Relative underfunctioning of the dorsomedial and left inferior frontal cortex, posterior cingulate and parietal brain regions has been demonstrated in persons with ADHD, and has been shown to be normalised with the use of methylphenidate, a central stimulant used for ADHD treatment [122]. Finally, positron emission tomography has demonstrated a decreased function in the dopamine reward path-
way in the brain in never previously medicated adults with ADHD [158], and has been associated with motivation deficits in adult ADHD.

Coexisting disorders and ADHD

Coexisting disorders in childhood ADHD

To clarify the broad spectrum of disorders coexisting with ADHD in childhood and symptom sharing across disorders, the concept and acronym ESSENCE (early symptomatic syndromes eliciting neurodevelopmental clinical examination) has been devised to cover children with impairing symptoms in defined areas/domains before age 3 to 5 years [59]. Major problems in at least one ESSENCE domain before age 5 years often signals major problems in the same or overlapping domains years later. The ESSENCE perspective is that one should not view neuropsychiatric symptoms in early childhood as discrete disorders or syndromes, but from a perspective of early brain dysfunctions that goes beyond syndromes. ESSENCE refers to deviance in syndromes included cover a wide spectrum comprising ASD and PPD, ADHD, ODD, specific language impairment, learning disability (LD), non-verbal LD, tic disorders, bipolar disorder, behavioural phenotype syndromes, epilepsy syndromes and reactive attachment disorders. This broad ESSENCE perspective is consistent with a report from the US on over 60,000 children aged 6 to 17 years, which concluded that 46% of children with ADHD had a LD, 27% a conduct disorder (CD), 18% an anxiety disorder, 14% depression and 12% speech problems. Thirty-three per cent of the ADHD children had at least one comorbid disorder, 16% two comorbid disorders and 18% three or more comorbid disorders. Comorbidity widely exceeded that of persons without ADHD [89].

Sex differences have been investigated in a study of 140 boys and 140 girls aged 6-17 years who were referred for and diagnosed with ADHD. Compared with boys, girls were more likely to have the predominantly inattentive subtype and less at risk for major depression, CD or ODD, whereas the risk of substance use disorder (SUD) was higher in girls with ADHD than in boys [22].

Coexisting disorders in adults with ADHD

Several studies have investigated psychiatric comorbidity in adult ADHD. In a German study clinically referred adults with ADHD were reported to have a lifetime comorbidity on axis I of 77% compared with 46% in age- and sex-matched controls [130]. Affective and eating disorders, together with SUD, were more frequently associated with adult ADHD, with a sex bias for SUD, which was more prevalent in men. Slightly lower figures were reported in a
Canadian study with a current and lifetime axis I comorbidity of 47% in adults with ADHD versus 27% in age- and sex-matched controls. Coexistence of axis II comorbidity was reported to affect half of the individuals [42]. Studies of subtype differences in comorbidity patterns have found externalising disorders (e.g., ODD, CD, SUD) and antisocial personality disorder (ASPD) to be more frequently associated with the combined subtype. In general, ADHD was more frequently associated with clusters B and C personality disorders, regardless of subtype, when compared with a non-ADHD comparison group [101]. Another study reported the combined subtype to be associated with significantly higher rates of lifetime CD, bipolar disorders and psychosis compared with the inattentive and hyperactive/impulsive subtypes [153]. Reversely, previously unidentified ADHD has been found to be prevalent in samples of persons diagnosed with various psychiatric disorders such as SUD [146], bipolar disorder [125], posttraumatic stress disorder (PTSD) [93] and borderline personality disorder (BPD) [111]. Another important clinical issue is the frequency of sleeping disorders in adult ADHD, which has been reported to be widely increased, especially in the combined and hyperactive/impulsive subtypes [27]. The aetiology is poorly understood but circadian rhythm disruption and an increased prevalence of restless legs syndrome have been proposed as possible explanations [40; 128; 129]. In accordance with the ESSENCE acronym, a high prevalence of learning disabilities [28; 99] and reading difficulties has been reported in children, adolescents, and adults with ADHD [45]. Studies have also indicated difficulties in written language expression in persons with ADHD [134].

ADHD in prison inmates

Several studies have reported an increased prevalence of ADHD in incarcerated men, affecting about 4 of 10 inmates [62; 120]. Female inmates have been studied less frequently but a German study of 110 incarcerated females found a lifetime prevalence of ADHD of 24.5% with 10% for persisting diagnostic criteria according to DSM-IV. The subjects reported a decline in the prevalence of persisting ADHD with age, from 17.9% (age ≤25 years) to 10% (age 26–45 years), and with none persisting above the age of 45 [121]. The coexistence of reading difficulties in male prison inmates has been reported [116]. In a meta-analysis, the estimated general prevalence in incarcerated patients was 25.5%, with no significant differences for sex and age, although with significant country differences [163]. Finally, pharmacological treatment of inmates with ADHD has been linked to positive long-term functional outcome [63].
Diagnostic assessment of ADHD in adulthood

Several screening instruments and diagnostic interviews are available for adult ADHD. The World Health Organisation Adult ADHD Self-Report Scale (ASRS) contains 18 items, one for each of the DSM-IV criteria, which can be used for interviews, treatment evaluation, or both [82; 84; 145]. There is also an abbreviated 6-item short screening version of current symptoms based on selected DSM-IV criteria (50). This has been reported to have a total classification accuracy of 97.9 % when applied to population survey data (50) but is less specific when used in subsamples of diagnostic entities such as subjects with SUD (51). The Brown ADD Scale concentrates on the inattentive aspects of ADHD [124]. Conners’ Adult ADHD Rating Scale is based on the 18 DSM-IV criteria with symptomatic descriptions adapted for an adult population [2]. The Wender Utah Rating Scale [100] is available for a retrospective screening of childhood ADHD, including additional symptoms often associated with ADHD (e.g., temper, affective lability and emotional overreactivity). Finally, the parent questionnaire "Five to Fifteen" is available for screening of symptoms and problems typical of ADHD and its comorbidities [77].

To secure diagnostic accuracy after positive screening, semi-structured interviews are available including the Conners’ Adult ADHD Diagnostic Interview for DSM-IV (CAADID) [47] and the Diagnostic Interview for ADHD in adults (DIVA). CAADID is not available in an authorized Swedish version and the original version in English is subject to copyright issues. DIVA has been translated into several languages, including Swedish, and is available free of charge on the Internet. The Spanish version of DIVA has recently been validated against CAADID [48; 115].

Apart from past and present symptoms of ADHD, the influence of psychiatric comorbidity, somatic disease, ongoing substance use and signs of behavioural phenotype syndromes must be considered before a clinical diagnosis of adult ADHD is established. Neuropsychological testing with evaluation of the cognitive level and profile often provides valuable information to facilitate the diagnostic procedure. Sometimes computerized continuous performance tests, e.g. QBtest [74], can be of value as part of the evaluation process.

The European Network Adult ADHD was founded in 2002 to advance the recognition and treatment of adult ADHD in Europe. An extensive review article and consensus statement on the diagnostics and treatment of adult ADHD was published by members of the network in 2010 and an updated version is expected to be presented shortly [87].
Multimodal treatment of ADHD

A combination of pharmacological and non-pharmacological treatment, as well as psychosocial and pedagogic interventions are often considered the gold standard when treating subjects with ADHD. The multimodal treatment study of children with ADHD (MTA study) constitutes a cornerstone in the subsequent view on ADHD treatment [143]. The MTA group followed 597 children with the combined subtype over a period of 14 months. The children were randomised to one of four treatment strategies: 1) carefully titrated and monitored medication with stimulants, 2) intensive behavioural treatment, 3) a combination of strategies 1 and 2, and finally 4) standard community care (control group). The outcome demonstrated significantly greater ADHD symptom reduction in groups 1 and 3 compared with groups 2 and 4. There was no difference in symptom reduction when comparing groups 1 and 3, but combining carefully monitored treatment with stimulants with behavioural treatment reduced parallel symptoms (e.g., aggressive/oppositional and internalising symptoms) known to be frequently associated with ADHD in childhood.

Treatment of adults with ADHD has been the subject of several guidelines. The previously mentioned European Network has presented a treatment algorithm of psychoeducation, pharmacotherapy, coaching, cognitive behavioural therapy and family therapy. In this approach, the importance of considering treatment of coexisting psychiatric comorbidity is underlined [87]. The National Institute for Health and Care Excellence guidelines, published in 2008 and updated in 2016, advocate pharmacotherapy to be the first-line of treatment as a part of a comprehensive treatment programme addressing interventions and treatment of psychological, behavioural and educational or occupational needs [141]. Treatment recommendations of ADHD by the Swedish Medical Products Agency (Swedish: Läkemedelsverket) [98] underline pharmacological treatment as a component of a multimodal approach including psycho-social and pedagogic interventions.

The effect of non-pharmacological treatment has been investigated in patients receiving treatment with stimulants or placebo undergoing either behavioural group psychotherapy or individual clinical management. After three months of treatment, there was no difference in symptom reduction in those treated with group psychotherapy or individual clinical management. However, significantly decreased symptoms were found in patients treated with stimulants compared with those treated with placebo. These results were stable at a one-year follow-up [110].
Pharmacological treatment of ADHD

Mechanisms of action of stimulants and atomoxetine

Stimulants are thought to work primarily in dopamine and norepinephrine pathways, especially in striatal areas of the brain by blocking the reuptake of these neurotransmitters [155; 156; 157; 159].

The exact functional mechanism of atomoxetine remains unresolved but is thought to be a selective inhibitor of the norepinephrine transporter increasing norepinephrine causing $\alpha_2$-adrenergic receptor activation [56; 138]. In addition, atomoxetine appears to increase dopamine in the prefrontal cortex through nonspecific action of the norepinephrine transporter [12].

Effectiveness and safety of pharmacological treatment of ADHD in adulthood

Only a handful of randomised controlled trials (RCTs) of stimulants and atomoxetine have been conducted for ≥24 weeks in adults with ADHD [76; 61; 1; 23; 121; 162]. Moreover, some short-term trials of stimulants have been supplemented with open-label extensions confirming a similar pattern of relatively mild side effects [3; 29; 64; 149; 150]. The most frequent side effects reported for methylphenidate were headache, decreased appetite, dry mouth/mucosal dryness, nasopharyngitis and difficulty falling asleep; atomoxetine was linked to nausea, dry mouth, decreased appetite, headache and fatigue.

Despite evidence of beneficial effect and treatment safety, the clinical relevance of these short-term RCTs and/or open-label studies could be questioned since psychiatric comorbidity often excludes RCT participation. A few prospective and/or naturalistic studies have been published up to date. In a one-year study 30 % of participants experienced any side effect on methylphenidate and 12 % terminated treatment on any ADHD drug due to side effects [55]. Another study that included patients with a high degree of psychiatric comorbidity found that half of the patients remained on treatment with stimulants after two years. Only 15% discontinued treatment because of lack of effect and 17% did so because of anxiety or depression. The most frequently reported side effects during treatment were decreased appetite, dry mouth and initial insomnia [17]. Finally, a four-year outcome questionnaire study of pharmacologically treated adults with ADHD reported a 37% discontinuation rate at follow-up. Side effects were the most frequent reason for cessation of medication, followed by lack of efficacy and misuse [95].

Because ADHD medication has been associated with a moderate mean increase in blood pressure and pulse, questions on the long-term risks of cardiovascular adverse events have been rightfully raised [68].
Outcome predictors

Outcome predictors in childhood

A six-year follow-up study of a European cohort of children diagnosed with ADHD at a mean age of 11 years reported a correlation between younger baseline age, higher ADHD symptom severity and higher impairment at baseline and poorer overall functioning. Interestingly, pharmacological treatment demonstrated no impact on either ADHD symptom severity or overall functioning at follow-up [148]. Furthermore, a meta-analysis of studies on children identified ADHD severity, treatment for ADHD, comorbid CD and comorbid major depressive disorder to be predictors in childhood for ADHD persistence in adulthood [32]. In a longitudinal study of twins, adult persistence was associated with more symptoms and lower IQ [4].

Outcome predictors in adulthood

With an increasing number of adults seeking evaluation and treatment of ADHD, predictors at baseline for future outcome are clinically important to identify and consider in clinical practice.

Patients diagnosed with ADHD in adulthood reported better outcome on all measures when pharmacologically treated for two years or more compared with those with a shorter treatment time after a mean observation period of 4.5 years and at a mean age of 36.5 years at follow-up. In this study, comorbidity at baseline predicted poorer outcome [95]. A seven-year clinical study of patients diagnosed with ADHD at a mean age of 34 years reported that approximately 30% did not maintain ADHD criteria and 12% presented full remission (defined as <4 symptoms at follow-up). Predictors of diagnostic persistence were higher number of inattention and hyperactivity/impulsivity symptoms, previous ODD and social phobia at baseline [78].
Aims and scope

The overall aim of this thesis is to broaden the understanding of ADHD in adulthood by screening for prevalence and investigating psychiatric comorbidity in adults with ADHD, as well as to demonstrate long-term outcome and treatment safety in those diagnosed with ADHD as adults. The specific aims of this thesis follow a stepwise pattern closely coupled to experienced practical patient issues in everyday clinical practice.

The specific aims of this thesis are:

- To survey the frequency and severity of self-reported ADHD-related symptoms, difficulties and suffering, functional impairment and reading and spelling difficulties in patients seeking outpatient psychiatric care and in female prison inmates in comparison with a sample of the GP.

- To examine prevalence and sex differences of axis I and II comorbidity in a clinical sample of patients diagnosed with ADHD as adults. Specific interest was focused on analysing the prevalence and gender differences of personality disorders with and without fulfilment of the general diagnostic criteria.

- To assess long-term outcome with respect to symptom reduction and function in a well-defined sample of patients first diagnosed with ADHD as adults, to compare outcome in the patients who were still on medication versus those who discontinued medication, and also to identify potential baseline predictors of favourable outcome.

- To evaluate tolerability and safety of long-term treatment in adults with ADHD by assessing reasons for discontinuation as well as self-reported side effects in patients under current long-term treatment. To assess baseline predictors for adherence to treatment and to determine participants own perceived outcome since diagnosed with ADHD and subsequent treatment with stimulants and atomoxetine.
Method

Study design and participants

This thesis is based on cohort-studies performed in a piecemeal manner because of different and subsequent aims. An overview of the studies is given in Table 1.

Paper I contains three studies investigating the prevalence of ADHD symptomatology in three cohorts: the GP, adult psychiatric outpatients and female prison inmates. The GP sample included of 1000 patients between 18 and 55 years of age who were randomly selected from the population registry in Uppsala County by an independent company. The patients were reminded twice by mail after the initial request to participate. In all, 236 men and 281 women were included, representing a participation rate of 52%. The recruitment took place in autumn 2003. The psychiatric outpatient sample was made up of adult psychiatric outpatients in Uppsala County seeking care mainly for affective, anxiety, sleep and personality disorders, i.e. common comorbid disorders in adult ADHD. The reception personnel were instructed to inform every Swedish-speaking patient between 18 and 55 years of age about the study, both orally and in writing, and to invite them to participate. Four hundred and sixty-eight (n=468) patients were invited to participate in the study and 400 (85%) volunteered to take part. Of the 400 patients, 369 (92%) completed the study. However, 20 patients were excluded because of incomplete answers, leaving 77 men and 272 women for analysis, representing a participation rate of 75% (349/468). The recruitment took place in December 2003. The female prison sample comprised inmates from the Hineberg Prison, which is the largest prison for women in Sweden with the highest security level. The prison is intended for female convicts from the entire country who are sentenced to long-term (six years on average) imprisonment. The two most common crimes for which inmates were convicted were severe drug-related crimes (44%) and murder/manslaughter (21%). At the time of the study, there were 104 inmates; however, 17 had been transferred to a special unit for treatment of alcohol and drug addiction, 18 had been moved to an open-wing section because they had been convicted of minor crimes and 4 had been admitted to hospital. Accordingly, 65 high-security prisoners were available for the study and were invited to participate. Fifty women gave informed consent and the overall participation rate was 77% (50/65). The recruitment took place in March-May 2004.
<table>
<thead>
<tr>
<th>Paper</th>
<th>Sample</th>
<th>Included</th>
<th>Investigated sample</th>
<th>Response rate (%)</th>
<th>Females/males</th>
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<td>168</td>
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<td>78/90</td>
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<tr>
<td>III</td>
<td>Patients diagnosed with ADHD in adulthood</td>
<td>168</td>
<td>124</td>
<td>74</td>
<td>61/63</td>
</tr>
<tr>
<td>IV</td>
<td>Patients diagnosed with ADHD in adulthood with subsequent medication</td>
<td>168</td>
<td>112</td>
<td>67</td>
<td>57/55</td>
</tr>
</tbody>
</table>
Paper II included adults diagnosed with ADHD in adulthood. In 2002, a special outpatient clinic for referral of adult patients with suspected diagnoses of ADHD, ASD and Tourette’s syndrome was established at Uppsala University Hospital. Of 233 consecutively referred patients, 168 (78 women and 90 men) were diagnosed with adult ADHD and subsequently included in this study. The recruitment took place in April 2002-October 2010.

Paper III is a follow-up study of participants included in paper II. Of the 168 eligible patients, 124 (74%) participated in the follow-up. The recruitment took place in March-October 2013.

Paper IV included the same participants who took part in study II and III who had been put on medication after being diagnosed with ADHD in adulthood. Of the 168 patients diagnosed with ADHD in adulthood, 112 (67%) took part in the follow-up. The recruitment period was identical to paper III.

Procedures and measurements

In paper I, the first part of the study questionnaire covered the 18 symptoms of ADHD according to DSM-IV. Each question was supplemented with a short description of possible adult expressions of the symptoms. The response format was four-fold, depending on current presence and burden of symptoms of ADHD: “never/seldom”, “sometimes”, “often” and “very often”. Each answer corresponded to a score from 0 to 3. Thus, the scoring system is based on a minimum total score of 0 points and a maximum total score of 54 points (maximum score for hyperactivity-impulsivity=27 and inattention=27). A score of ≥2 for at least six of nine symptoms of inattention or six of nine symptoms of hyperactivity-impulsivity was required to be categorised as an inattentive or hyperactive type of adult ADHD. Questions about ADHD symptoms during childhood, as reported to the participant by parents or other informants, were asked separately. The GP sample and psychiatric outpatient sample were asked about childhood hyperactivity/impulsivity only, whereas the female inmates were also asked about childhood inattention. The first two samples were categorised as “hyperactive” if they endorsed hyperactivity in childhood or adulthood. The inmate sample was categorised as ADHD if they endorsed childhood hyperactivity or inattention or six of nine DSM-IV criteria as adults. The second part of the questionnaire contained questions on age and sex, as well as reading and spelling difficulties (dichotomised answers: yes/no). Functional impairment was assessed by asking the participants to rate difficulties and suffering caused by the current ADHD-related symptoms, using two 100-mm visual analogue scales (VASs) (end points: no difficulties/no suffering to totally handicapped), as well as to self-rate their social, occupation and psychological functioning using the Global Assessment of Functioning (GAF) scale during the past year and the past two weeks [25; 114]. The psychiatric pa-
tients were also asked about reasons for seeking care and about ongoing medication. The female prison inmates were screened for CD and ASPD by using relevant subscales of the self-report version of the DSM-IV and the ICD-10 personality questionnaire (DIP-Q) [8; 25].

In paper II, a multidisciplinary team made up of senior psychiatrists, clinical psychologists, social workers and occupational therapists performed all evaluations. The diagnostic procedure aimed at establishing best estimate diagnoses was confirmed by all participating professionals reaching consensus on the diagnostic outcome as well as on attributed impairment or suffering [92]. All patients underwent a physical examination that included basic neurologic status, as well as routine laboratory testing, including urine screening for drugs. All patients were interviewed about current symptoms and behaviours associated with ADHD using a semi-structured interview based on the 18 DSM-IV criteria [8]. The interview included realistic examples from everyday life that were obtained in clinical practice from adult patients. The patients were encouraged to give their own examples of adult ADHD with subsequent impairment in accordance with each diagnostic item. The answers were evaluated and rated according to four categories, depending on symptom frequency and impairment: “never”, “sometimes”, “often”, and “very often”. An answer of “often” or “very often” was categorised as a fulfilled criterion. Six or more of the maximum nine subtype criteria were required to fulfil a diagnosis of adult ADHD. A social worker or clinical psychologist collected and documented a developmental and social history from childhood to the present. The clinical version of the Structured Clinical Interview for DSM-IV axis I (SCID-I) [54], was administered by a senior psychiatrist (author, DE) with training in the use of this instrument to assess coexisting Axis I disorders. Evaluations of suspected ASD included semi-structured developmental interviews, i.e. the Diagnostic Interview for Social and Communication Disorders [94], and the Autism Diagnostic Interview-Revised [91], which were performed by senior clinical psychologists [91; 94]. Criteria for DSM-IV Axis II disorders were initially assessed by means of the DSM-IV and ICD-10 Personality Interview (DIP-I) [108]. It was later replaced by the Structured Clinical Interview for DSM-IV axis II (SCID II) [53], which is very similar to the DIP-I and was used for half (n=84) of the participating patients. ASPD was only considered if a previous history of CD had been confirmed. All interviews relative to personality disorders were performed by a senior psychiatrist (DE) with training in the use of the respective instruments.

In paper III, questionnaires were sent to the participants with questions about current symptoms of ADHD using a self-report version of the semi-structured interview used at baseline. Current functioning was assessed by a self-report version of the Global Assessment of Functioning Scale (GAF) [25; 114]. Potential improvement since baseline was measured by the Clinical Global Impressions Improvement scale (CGI-I). The CGI-I is a seven-
point scale from “very much improved” to “very much worse” [66]. Disability and impairment were investigated by the Sheehan Disability Scale (SDS) [96] a scale that covers three domains: work/school, social life and family life/home responsibilities. The SDS has recently been psychometrically evaluated in adult ADHD [39]. Health-related quality of life (HRQoL) was measured by EQ-5D and EQ-VAS [44; 142]. Alcohol consumption was assessed by the Alcohol Use Disorders Identification Test (AUDIT) [13] and drug consumption by the Drug Use Disorders Identification Test (DUDIT) [19]. When the questionnaires had been returned, a telephone interview was conducted covering demographics as well as details of the participants’ past and current medical condition. Participants’ information on previous medication periods was validated against data in their patient files if available. In case of contradictory data, we choose to rely on patient file data.

In paper IV, data from paper III were supplemented with information about each treatment period, defined as being of at least one month’s length and with an intervening one-month period of non-medication or more before another attempt of pharmacological treatment was considered. Patients’ information about previous medication periods and reasons for discontinuation were validated against data in their patient records. In case of contradictory data, we again choose to rely on patient record data. If there were several treatment periods, the final reason for discontinuation was registered for each pharmacological substance. In patients with ongoing medication, current adverse effects were assessed by a form covering 31 adverse effects which was used as part of the clinical routine in patients treated at the clinic for neuropsychiatry at Uppsala University Hospital. The frequency of adverse symptoms was categorised as “Never”, “Sometimes” (corresponding to 1-2 times/week), “Often” (corresponding to 3-6 times/week) and “Very often” (corresponding to daily/always). There were also questions on the patients’ experience of the effect of current medication, adherence and dosage pattern. Finally, participants were asked to respond to five statements about how their status had changed since baseline: “My quality of life has improved”, “My level of functioning has improved”, “My understanding of my way of functioning has increased”, “I have encountered greater understanding from the environment of my way of functioning” and “I find it worthwhile having been evaluated for ADHD”. Answers to the first four statements were categorised in a four-step scale from “Not at all” to “Exactly correct”; the last statement (…worthwhile having been evaluated…) was categorised in the opposite order from “Yes, indeed” to “Not at all”. Data on deceased participants’ cause of death among dropouts in paper III and their ongoing pharmacological treatment at the time of death were supplied by The Swedish National Board of Health and Welfare.
Statistics

All statistical analyses were performed using PASW Statistics, version 12.0.1 (paper I), version 18.0 (paper II) and version 23 (paper III and IV). P-values <0.05 were considered statistically significant.

Dichotomous data were analysed using chi-square test statistics or Fisher’s exact test when applicable with a cell count number of <5.

A Kolmogorov-Smirnov test was used to test for normality. When appropriate, the non-parametric Mann-Whitney U test was employed to determine group differences; otherwise, the t-test was performed for continuous data.

Inter-rater reliability of continuous scale data was tested by single-measure intraclass correlation and diagnostic agreement was tested using Cohen’s kappa.

Because symptom and GAF scores in paper I were not normally distributed, differences in mean scores were analysed using the Mann-Whitney U test for independent samples. Confounding by skewed sex proportions and a higher prevalence of hyperactivity in the outpatient sample was corrected using Mantel-Haenszel statistics. Because age was unevenly distributed among men and in the number of diagnoses on axis I in both sexes, the Mann-Whitney U test was used for analysis of sex differences in paper II. All baseline variables (e.g., age, sex, ADHD subtype and score, psychiatric comorbidity, sociodemographic data and treatment-related variables) were tested for possible inclusion in univariate logistic regression models with remission as the dependent variable in paper III and ongoing pharmacological treatment in paper IV. None of these variables were significantly related to either of the dependent variables, however.

Ethics

All studies included in this thesis were approved by the Regional Ethics Review Board at Uppsala University: 02-452 (paper I), 2006/241 (paper II), 2012/544 (paper III and IV).
Results

ADHD-related symptoms among adults in outpatient psychiatry and female prison inmates as compared with the general population (Paper I)

This study aimed to compare the prevalence of symptoms consistent with ADHD and related problems in adults in the GP, in outpatient psychiatry (where females are in the majority) and in female convicts. Detailed information concerning participating subject characteristics is given in paper I.

Prevalence of ADHD-symptomatology
One third (32.4%) of the participants in the outpatient psychiatry sample reported hyperactivity versus about one sixth (15.1%) in the GP sample. All three subgroups (childhood only, both childhood and adult and adult only) were more prevalent in the outpatient sample than in the GP sample. The prevalence of both adult and childhood hyperactivity/impulsivity was approximately three times higher among participants in the outpatient sample compared with the GP sample (6.6 versus 2.1%).

Fifty per cent of the female inmates reported symptoms of ADHD in childhood or as adults; 6 of the 50 participants (12%) reported inattention only in childhood. Fifteen participants (30%) had both childhood inattention and adult symptoms of ADHD. The frequencies of inmates endorsing the criteria for CD and ASPD, self-rated GAF values and reading and spelling difficulties in inmates, with and without symptoms of ADHD, are summarised in Table 2.

Difficulties and suffering attributed to ADHD-related symptoms
The levels of difficulties and suffering due to ADHD-related symptoms in the outpatient sample were significantly higher in those classified as hyperactive and in those not classified as hyperactive as compared with the GP sample. Within the GP sample, only the subgroup that reported both childhood and adult hyperactivity had significantly higher levels of difficulties and suffering as compared with the non-hyperactive group. In the outpatient sample, all subgroups had significantly higher levels of difficulties and suffering as compared with the non-hyperactive group. There were no major differences between men and women within the two samples. In the inmate
sample, difficulties and sufferings due to ADHD-related symptoms were significantly higher in the group classified as ADHD (p<0.001).

Table 2. The frequency of conduct disorder (CD) and antisocial personality disorder (ASPD), self-rated global assessment of function (GAF) values and reading and spelling difficulties in the groups of inmates with and without attention-deficit/hyperactivity disorder (ADHD) (from paper I).

<table>
<thead>
<tr>
<th></th>
<th>ADHD group (n=25)</th>
<th>Non-ADHD group (n=25)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD (%)</td>
<td>84 (21/25)</td>
<td>28 (7/25)</td>
<td>p&lt;0.001 b</td>
</tr>
<tr>
<td>ASPD (%)</td>
<td>76 (19/25)</td>
<td>20 (5/25)</td>
<td>p&lt;0.001 b</td>
</tr>
<tr>
<td>GAF in the past year*</td>
<td>62±17</td>
<td>81±17</td>
<td>p&lt;0.001 a</td>
</tr>
<tr>
<td>GAF in the past two weeks*</td>
<td>66±18</td>
<td>79±16</td>
<td>p&lt;0.01 a</td>
</tr>
<tr>
<td>Reading difficulties (%)</td>
<td>36 (9/25)</td>
<td>8 (2/25)</td>
<td>p&lt; 0.05 b</td>
</tr>
<tr>
<td>Spelling difficulties (%)</td>
<td>32 (8/25)</td>
<td>8 (2/25)</td>
<td>ns</td>
</tr>
</tbody>
</table>

* n= 24 in each group; a Mann-Whitney U-test; confirmed by b Fisher’s exact test

Self-rated global assessment of function (GAF)
The GAF scores were significantly lower among participants in the outpatient sample, both during the past year and during the past two weeks as compared with the GP sample. In the inmate sample, the GAF self-ratings for the past year and for the past two weeks were significantly lower in the group classified as ADHD (Table 2).

Reading and spelling difficulties
There was a significantly higher prevalence of reading (p<0.001) and spelling (p<0.01) difficulties in the outpatient sample than in the GP sample. This result was repeated in the non-hyperactive group (reading, p<0.001; spelling difficulties, p<0.05). In the GP sample, the subgroups with childhood hyperactivity as well as childhood and adult hyperactivity had significantly higher frequencies of both reading (p<0.001 and spelling (p<0.001) difficulties than the non-hyperactive group. The data of the inmate sample are presented in Table 2. The reading difficulties were significantly higher in the group classified as ADHD than in the non-ADHD classified group (p<0.05). Differences in spelling difficulties did not reach statistical significance.
Sex differences of axis I and II comorbidity in subjects diagnosed with ADHD as adults (Paper II)

The aim of this study was to examine prevalence and sex differences of axis I and II comorbidity in a clinical sample of patients diagnosed with ADHD as adults.

Detailed patient characteristics are presented in paper II.

Of the 168 patients, 100 (60%) were diagnosed with an ADHD of combined type and 61 (36%) of the inattentive type. The remaining seven (4%) patients were diagnosed with ADHD (predominantly hyperactive-impulsive ADHD). The inattentive type was more common in men than the combined type and hyperactive type when compared with women (p<0.01).

ADHD symptom profiles by sex is depicted in Figure 1. The ADHD items with the greatest difference between women and men were the hyperactivity/impulsivity symptoms “talks excessively”, “blurts out answers” and “interrupts and intrudes” (all ps<0.01).

Figure 1. Percentage of individual ADHD items fulfilled as a function of patient’s sex (from paper II).
The lifetime prevalence of any comorbid axis I disorder was 95% in women and 90% in men (Table 3). The mean number of lifetime diagnoses, including ASD and Tourette’s syndrome, was 2.7±1.5 (range 1-7) in women and 2.7±1.8 (range 1-11) in men. Women were significantly more often diagnosed with mood and eating disorders, whereas men significantly more often fulfilled criteria for SUD (Table 3).

The presence of at least one current Axis I disorder, including ASD and Tourette’s syndrome was diagnosed in 47% (45% in the women and 49% in the men).

Table 3. Prevalence of psychiatric comorbidity on axis I in the clinical cohort of patients investigated from paper II.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
<th></th>
<th>χ²</th>
<th>p-value¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifetime</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any mood disorder</td>
<td>71 (91.0)</td>
<td>60 (66.7)</td>
<td>14.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any anxiety disorder</td>
<td>33 (42.3)</td>
<td>37 (41.1)</td>
<td>0.25</td>
<td>ns</td>
</tr>
<tr>
<td>Any somatoform disorder</td>
<td>2 (2.6)</td>
<td>1 (1.1)</td>
<td>0.05</td>
<td>ns</td>
</tr>
<tr>
<td>Any eating disorder</td>
<td>17 (21.8)</td>
<td>0 (0)</td>
<td>21.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjustment disorder</td>
<td>1 (1.3)</td>
<td>1 (1.1)</td>
<td>0.10</td>
<td>ns</td>
</tr>
<tr>
<td>Any psychotic disorder</td>
<td>1 (1.3)</td>
<td>2 (2.2)</td>
<td>0.21</td>
<td>ns</td>
</tr>
<tr>
<td>Any substance use disorder</td>
<td>26 (33.0)</td>
<td>45 (50.0)</td>
<td>4.76</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Any autism spectrum disorder</td>
<td>6 (7.7)</td>
<td>11 (12.2)</td>
<td>0.94</td>
<td>ns</td>
</tr>
<tr>
<td>Tourette’s syndrome</td>
<td>2 (2.6)</td>
<td>6 (6.7)</td>
<td>1.55</td>
<td>ns</td>
</tr>
<tr>
<td>Any Axis I disorder, including comorbid</td>
<td>74 (94.9)</td>
<td>81 (90.0)</td>
<td>1.39</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Current</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Axis I disorder, including comorbid</td>
<td>35 (44.9)</td>
<td>44 (48.9)</td>
<td>0.27</td>
<td>ns</td>
</tr>
<tr>
<td>neuropsychiatric disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹women vs. men

When the general diagnostic criteria for a personality disorder were considered, only six women (8%) and 10 men (11%) were diagnosed with an Axis II disorder. However, when only considering the specific criteria for at least one personality disorder, 36 women (46%) and 41 men (46%) fulfilled specific criteria (Table 4). The only observable sex differences concerned fulfilment of the specific criteria for histrionic personality disorder and for CD, with the former more common in women (p<0.05) and the latter more common in men (p<0.01). In addition, men more often fulfilled specific criteria for ASPD compared with women, but the difference was not statistically significant (p=0.06).
Table 4. Comorbidity of personality disorders without considering the general diagnostic criteria in the investigated group of patients (from paper II).

<table>
<thead>
<tr>
<th>Fulfilment of specific criteria</th>
<th>Women; n (%)</th>
<th>Men; n (%)</th>
<th>$\chi^2$</th>
<th>p-value $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisocial</td>
<td>5 (6.4)</td>
<td>4 (4.4)</td>
<td>0.32</td>
<td>ns</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>20 (25.6)</td>
<td>26 (28.9)</td>
<td>0.22</td>
<td>ns</td>
</tr>
<tr>
<td>Cluster B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antisocial</td>
<td>8 (10.3)</td>
<td>19 (21.1)</td>
<td>3.65</td>
<td>0.056</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>26 (33.3)</td>
<td>54 (60.0)</td>
<td>11.91</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cluster C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any cluster</td>
<td>23 (29.5)</td>
<td>17 (18.9)</td>
<td>0.11</td>
<td>ns</td>
</tr>
<tr>
<td>Any cluster</td>
<td>36 (46.2)</td>
<td>41 (45.6)</td>
<td>0.01</td>
<td>ns</td>
</tr>
</tbody>
</table>

$^a$ women vs. men.

Twenty-nine (17%) of the 168 patients were directly referred for evaluation of ADHD. The remaining 139 patients had a previous history in adult psychiatry (with a mean duration of 7.3±6.2 years, range 0-28) before being identified as potential ADHD patients and subsequently referred for evaluation by either adult psychiatry or primary health care. Twenty-seven women (35%) and 35 men (39%) reported previous contact with child and adolescent outpatient psychiatric clinics (one man had ongoing contact).

At the time of the evaluation, 110 (65%) of the patients were on medication. The five most common prescribed pharmaceuticals were medication for somatic disorders: for example, hypertensives and antibiotics, analgesics excluded, 25%, followed by antidepressants other than serotonin reuptake inhibitors (SSRIs, 21%), SSRIs (18%), benzodiazepines (14%) and hypnotics other than benzodiazepines (11%). Women were prescribed SSRIs more frequently than men (p<0.01); no other sex differences were identifiable.

Six-Year Outcome in Subjects Diagnosed with Attention-Deficit/Hyperactivity Disorder as Adults (Paper III)

The study aimed to assess long-term outcome for symptom reduction and function in a cohort of patients first diagnosed with ADHD as adults in relation to current medication (or not) and to identify potential baseline predictors of favourable outcome. The primary outcome measure was remission, which was defined as not fulfilling any ADHD subtype and a GAF score of ≥70 during the past year.
Participants constitute a subgroup of patients presented in paper II and detailed information of patient characteristics is presented in paper III.

Compared with baseline, there was a decrease in mean ADHD scores from 36.8±7.8 to 25.5±11.1; 33% of the patients (41/123) were in remission.

There was also a similar decrease in the number of patients who fulfilled each of the 18 DSM-IV ADHD criteria.

There was also an apparent change in ADHD subtype over time (Figure 2).

Figure 2. Number of patients with different ADHD-subtypes at baseline and at follow-up. Presentation as in [46]. Numerals are numbers of patients; sizes of squares and arrows represent approximate quantitative proportions.
In general, patients with a combined ADHD subtype at baseline remained as a combined subtype, changed into an inattentive subtype, or did not fulfil the criteria for a diagnosis of ADHD at follow-up. Patients with an inattentive ADHD subtype either maintained the diagnosis or did not fulfil criteria for a diagnosis of ADHD. There was no decline in the number of patients with the hyperactive type, whereas the number of patients with a combined ADHD subtype decreased from 71 to 21 (i.e. with 70%) and the number of patients with an inattentive ADHD subtype decreased from 47 to 31 (i.e. with 34%). Patients in remission reported similar ADHD scores at baseline as those who were not in remission (Table 5). Furthermore, there was no difference in current medication between the groups (51 versus 43%). Patients in remission reported significantly better global functioning, less disability, better quality of life (QoL) and better clinical improvement than those who were not in remission. There was no difference in mean alcohol consumption, as measured by AUDIT scores, and drug use, as assessed by DUDIT scores. Scores above limits for harmful drinking [13] however, were observed in 7% of those in remission versus 24% of those who were not (p=0.03), and risk scores for potential drug-related problems [19] in 2% of those in remission versus 11% of those who were not (p=0.16).

Reciprocally, there was no difference in remission rate between patients in the current medication group, (37%) and in those not currently medicated (30%). Medicated patients reported similar ADHD scores as those without ongoing medication, both at baseline and at follow-up. They also reported similar global functioning, disability and QoL than those not medicated, although medicated patients showed better clinical improvement (Table 6).

All baseline variables and treatment-related variables were tested for possible inclusion in a regression model with remission as the dependent variable. None of these variables were significantly related to remission.
Table 5. Data for the patients that responded to the enquiry at follow-up by state of remission (from paper III).

<table>
<thead>
<tr>
<th></th>
<th>Remission (n=41)</th>
<th>Not remission (n=82)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time on treatment (months)</td>
<td>51±31</td>
<td>41±30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time on treatment (per cent of follow-up)</td>
<td>65±35</td>
<td>55±35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADHD score at baseline</td>
<td>35.8±7.7</td>
<td>37.2±7.8</td>
<td>0.41</td>
</tr>
<tr>
<td>ADHD score at follow-up</td>
<td>15.6±7.5</td>
<td>30.5±8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current medication</td>
<td>21 (51%)</td>
<td>35 (43%)</td>
<td>0.44</td>
</tr>
<tr>
<td>CGI-improvement</td>
<td>2.2±1.3</td>
<td>3.2±1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GAF past year</td>
<td>84±10</td>
<td>61±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GAF past two weeks</td>
<td>82±17</td>
<td>62±16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work/school</td>
<td>1.7±3.1</td>
<td>4.5±3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Social life</td>
<td>1.7±3.4</td>
<td>4.5±3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family life/home responsibilities</td>
<td>1.5±2.7</td>
<td>4.0±3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EQ-5D index</td>
<td>0.82±0.19</td>
<td>0.55±0.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EQ-5D VAS</td>
<td>78±14</td>
<td>57±21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AUDIT score</td>
<td>3.5±3.8</td>
<td>4.0±4.4</td>
<td>0.67</td>
</tr>
<tr>
<td>DUDIT score</td>
<td>0.2±0.7</td>
<td>1.3±4.3</td>
<td>0.12</td>
</tr>
</tbody>
</table>

^1 Mann-Whitney U test; ^2 n=35; ^3 n=76; ^4 n=38; ^5 n=80;

Table 6. Data for the patients that responded to the enquiry at follow-up by state of medication (from Paper III).

<table>
<thead>
<tr>
<th></th>
<th>Current medication</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=56)</td>
<td>No (n=67)</td>
</tr>
<tr>
<td>Time on treatment (months)</td>
<td>63±24</td>
<td>20±22</td>
</tr>
<tr>
<td>Time on treatment (percent of follow-up)</td>
<td>84±19</td>
<td>19±27</td>
</tr>
<tr>
<td>ADHD score at baseline</td>
<td>36.5±8.6</td>
<td>37.2±7.2</td>
</tr>
<tr>
<td>ADHD score at follow-up</td>
<td>24.5±11.0</td>
<td>26.4±10.9</td>
</tr>
<tr>
<td>Do not fulfil criteria for ADHD at follow-up</td>
<td>31 (55 %)</td>
<td>33 (49 %)</td>
</tr>
<tr>
<td>Remission</td>
<td>21 (37 %)</td>
<td>20 (30 %)</td>
</tr>
<tr>
<td>CGI-improvement</td>
<td>2.4±1.5</td>
<td>3.3±1.6</td>
</tr>
<tr>
<td>GAF past year</td>
<td>69±16</td>
<td>68±17</td>
</tr>
<tr>
<td>GAF past two weeks</td>
<td>69±18</td>
<td>68±20</td>
</tr>
<tr>
<td>SDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work/school</td>
<td>3.2±3.7</td>
<td>3.8±3.8</td>
</tr>
<tr>
<td>Social life</td>
<td>3.4±3.6</td>
<td>3.7±3.8</td>
</tr>
<tr>
<td>Family life/home responsibilities</td>
<td>2.8±3.3</td>
<td>3.4±3.4</td>
</tr>
<tr>
<td>EQ-5D index</td>
<td>0.68±0.30</td>
<td>0.60±0.33</td>
</tr>
<tr>
<td>EQ-5D VAS</td>
<td>67±19</td>
<td>62±24</td>
</tr>
<tr>
<td>AUDIT score</td>
<td>4.1±4.5</td>
<td>3.6±4.0</td>
</tr>
<tr>
<td>DUDIT score</td>
<td>1.5±5.1</td>
<td>0.4±1.2</td>
</tr>
</tbody>
</table>

^1 Mann-Whitney U test; ^2 The 55 who had discontinued their treatment; ^3 n=56; ^4 n=64;
Long-Term Tolerability and Safety of Pharmacological Treatment of Adult Attention-Deficit/Hyperactivity Disorder (Paper IV)

The aim of this study was to evaluate tolerability and safety of long-term treatment in adults with ADHD by examining patient reasons for discontinuation as well as self-reported side effects in patients currently on long-term treatment. The study also assessed baseline predictors for adherence to treatment and attempted to determine participants’ perceived outcome since being diagnosed with ADHD.

Participants constitute a subgroup of patients presented in paper II and III. Detailed information on patient characteristics is presented in paper IV. Data on dropouts in paper III revealed that five persons had died since their ADHD diagnosis and only one by way of natural causes.

Fifty-seven patients were currently on treatment and 55 had discontinued treatment. There were no significant differences in baseline data between current treatment and the off-treatment patients. Time on medication was longer in patients on treatment compared with those who had discontinued (63±24 versus 24±22 months).

Of the currently medicated patients, 46 were on treatment with methylphenidate, 8 with amphetamine and 3 on a combination of methylphenidate and atomoxetine. Of the eight patients currently treated with amphetamine, seven had previously been on methylphenidate. Five patients had previously been treated with atomoxetine but discontinued. Of the currently medicated patients, 56 had a lifetime history of treatment with methylphenidate, 13 with amphetamine and 8 with atomoxetine.

The maximum dosage during treatment was 84±37 mg for methylphenidate, 43±10 mg for amphetamine and 68±23 for atomoxetine. The current dose was 60±32 mg for methylphenidate, 42±9 mg for amphetamine and 38±13 mg for atomoxetine.

Most patients on treatment with methylphenidate were treated with medium- or long-acting agents. All patients treated with amphetamine were on short-acting tablets.

Seventy-eight per cent of the patients took their medication once or twice daily. Eighty-four per cent of the patients stated that they took their medication in the exact dosage as prescribed, whereas 16% reported that they used a lower dosage. Eighty-eight per cent reported daily adherence to treatment.

The total time on treatment was 61±24 months for stimulants, i.e. time of treatment with methylphenidate and amphetamine added together; for atomoxetine, the time was 9±17 months for the first treatment period. The number of stimulant treatment periods was 2±1). When corrected for overlapping time of treatment with stimulants and atomoxetine, the total treatment time increased to 63±24 months.
Current adverse effects during pharmacological treatment of patients diagnosed with ADHD as adults are presented in Table 7. The most common adverse effects related to methylphenidate were decreased appetite (28%), dry mouth (24%) and anxiousness/restlessness, increased pulse frequency (19%).

Finally, 81% of the patients reported a pronounced beneficial effect of their ongoing medication and an additional 16% reported a moderate beneficial effect.

The dosage at the time of discontinuation for those patients without current medication was 68±42 mg for methylphenidate, 47±18 mg for amphetamine and 57±28 mg for atomoxetine. The total time on treatment with stimulants was 22±21 months; the total time on treatment with atomoxetine was 6±12 months. The number of treatment periods was 2±1 for stimulants (no patients had been treated with atomoxetine more than once). When corrected for overlapping time of treatment with stimulants and atomoxetine, the total treatment time increased to 24±22 months.

The reasons for discontinuation of treatment are given in Table 8. The top three reasons for discontinuation of treatment with methylphenidate were lack of effect (29%), elevated mood or hypomania (11%) and not being able to maintain contact with the prescriber (9%). None of the patients who discontinued methylphenidate or amphetamine because of elevated mood or hypomania had been diagnosed with a bipolar disorder before medication. One patient had been diagnosed with bipolar type II and one with bipolar NOS at baseline; these two patients were treated with methylphenidate only. In both these cases, depressive symptoms were the reason for discontinuation. Fifteen patients had been treated with atomoxetine and the most common reason for discontinuation was, as with stimulants, lack of effect. Further reasons for discontinuation were widespread, but in almost half of the patients discontinuation was related to psychiatric side effects.

The statements, "My quality of life has improved", "My level of functioning has improved" and "Encountered increased understanding" were endorsed to a higher degree among those patients still on medication.
Table 7. Current reported adverse effects during pharmacological treatment of 57 subjects diagnosed with ADHD as adults. Several symptoms could be reported simultaneously from each individual patient (from paper IV).

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>MPH²</th>
<th>MPH+ATX³</th>
<th>AMPH⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects; n (%)</td>
<td>46</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td><strong>Psychiatric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiousness/restlessness</td>
<td>9(19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased sexual desire</td>
<td>8(17)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Depressed mood</td>
<td>5(11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated mood</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficult getting to sleep</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased need for sleep</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased sexual desire</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apathy</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dermatological</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perspirations</td>
<td>7(15)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Skin heating</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitive/dry mucous membranes</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Pale skin</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cold hands/feet</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sensitive skin</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13(28)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>11(24)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased pulse frequency</td>
<td>9(19)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypertonia</td>
<td>4</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Heart beats “strongly”</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypotonia</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Sexual function problems</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Vertigo/unsteadiness</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tics</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clumsiness</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficult to accommodate (vision)</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

1 = Only those with symptom frequencies classified as “often” (3-6 times/week) or “very often” (daily/always) are included. 2 = Methylphenidate, 3 = Methylphenidate + Atomoxetine, 4 = Dexamphetamine,
Table 8. Reasons to discontinue pharmacological treatment in subjects diagnosed with ADHD as adults (n=55; from paper IV).

<table>
<thead>
<tr>
<th>Reason/Adverse effects</th>
<th>MPH(^1)</th>
<th>AMPH(^2)</th>
<th>ATX(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects; n (%)</td>
<td>55</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Lack of effect</td>
<td>16(29)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>No perceived need for further medication</td>
<td>1(2)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lost contact with prescriber</td>
<td>5(9)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated mood or hypomania</td>
<td>6(11)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Depressed mood</td>
<td>4(7)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>2(4)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2(4)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1(2)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased obsessive-compulsiveness</td>
<td>1(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug abuse</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>“Mentally affected as influenced by drugs”</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Dermatological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>1(2)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Loss of hair</td>
<td>1(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perspirations</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3(6)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Weight gain</td>
<td>1(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecific gastrointestinal symptoms</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertonia</td>
<td>3(6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations/arrhythmia</td>
<td>3(6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2(4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>1(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amnesia</td>
<td>1(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecific pain</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

\(^1\)MPH = methylphenidate, \(^2\)AMPH = dexamphetamine, \(^3\)ATX = atomoxetine
Discussion

The principal aim of this thesis was to aid in the understanding of ADHD in adulthood by screening for prevalence and investigating psychiatric comorbidity in adults with ADHD, as well as demonstrating long-term outcome and treatment safety in persons diagnosed with ADHD as adults.

Methodological considerations

Design, samples and methods

For practical reasons, we decided in paper I to restrict participants in the GP and outpatient sample to persons residing in Uppsala County and belonging to a certain age group, which per se entails a selection bias. The age span of 18-55 years was arbitrarily chosen to diminish the risk for confounding disorders occurring in older age groups. Uppsala County spans a widely diverse geographic area that includes an expanding university city as well as less populated areas with traditional industry, much like the rest of the country of Sweden. This diversity would, to some extent, contribute to ensuring that both the GP sample and the outpatient sample are representative of the Swedish population.

Anonymous participation was chosen in all three samples to extract truthful and honest answers as well as a high participation rate. This approach unfortunately prevented attrition analyses. Concerning dropouts, ADHD-related symptoms in combination with reading difficulties might be more frequent in non-participants. Previous studies on attrition that examined other psychiatric disorders have reported a number practical issues [160], where low income, low education level and a previous psychiatric diagnosis were associated with lower participation rates [18]. From our own experiences in the follow-up study, it cannot be ruled out that non-participants in paper I may have had an even higher prevalence of ADHD symptomatology than the patients included in the study.

Furthermore, it is important to stress that symptom reporting in paper I did not include clinical evaluations, but describes patient self-reports of symptomatology in accordance with ADHD. Self-report questionnaires, in general, are easily administered and time-saving, but they have some inherent issues that must be considered. Apart from various degrees of validity
and reliability of each instrument, systematic biases can be pronounced [36]. Another point to consider concerns issues such as who; the patient of next of kin, in reality answered the questionnaires, how the questionnaires were administered, and the fact that respondents used the questionnaires to freely comment and communicate on symptom patterns and experiences. At the time of Study I there were no validated screening instruments for current symptoms of adult ADHD available for a Swedish population. The ADHD questionnaire used by us in this study was constructed and based solely on the DSM-IV diagnostic criteria but shared the disadvantage of not being validated. The scale questions were, however, similar or almost identical to the official WHO rating scale to evaluate adult ADHD, ASRS, that was published later [82].

To optimise the length of the questionnaire, it only focused on present symptoms of ADHD. Regarding childhood history, we chose to use a dichotomous Yes/No approach because we feared that an almost duplicated questionnaire which also included questions on lifetime problems would markedly increase attrition. The mixed sex samples of the GP and outpatients were only asked about childhood hyperactivity as there was an initial focus on the combined and hyperactive/impulsive subtypes according to DSM-IV, which are equivalent to the HKD of ICD-10. In the all-female prison inmate sample, a question on childhood inattention was supplemented. It is regrettable that this was not done in the first two samples. To distinguish between shortcomings attributable to symptoms of ADHD and other reasons for reduced functioning, the participants were asked to report about difficulties and suffering exclusively caused by current ADHD symptoms. For this purpose, we decided on a scale with a construction similar to the GAF. Self-rated GAF scores have been shown to constitute a valid and reliable instrument [114]. Outpatients and prison inmates with known ongoing substance abuse, a feature which is recognised as being associated with high prevalence rates of ADHD and related problems, were not included in the present surveys and may have biased the observed prevalence rates. The advantage of that decision was, however, that we could demonstrate that ADHD and related problems among non-addicts and patients in abstinence of drugs are common and need to be recognised. On the other hand, there were no questions on SUD in any of the questionnaires, why it is possible anyway that a number of unidentified patients with SUD were included.

Paper II is a descriptive study of a prospective sample of patients evaluated and diagnosed with ADHD as adults. The study design was based on information that could be extracted from the patient files. Selection bias may have been introduced into the sample because the majority of the patients were referred and had a previous history of psychiatric treatment, although not diagnosed with ADHD. Still, by using consecutive inclusion, we hoped to reduce the risk of further selection bias. All evaluations were performed in the same outpatient clinic with a multi-professional neuropsychiatric team. A
reliable process to diagnose ADHD in adulthood in a scientific way was complicated as there was no validated semi-structured interview available for adults in Swedish in 2002 when the evaluations started. CAADID was published in English in 2001 but was, and is, restricted to copyright law and not available in Swedish. We chose to do the evaluation of adult ADHD symptoms using a self-constructed and semi-structured interview according to DSM-IV, which was similar to the questionnaire distributed in the previous studies. Because this interview had not previously been validated, diagnostic validity was ensured through interviews being videotaped and independently and blindly rated by a second senior psychiatrist with long experience in clinical encounters with patients suffering from neuropsychiatric disorders. Inter-rater reliability was excellent for individual ADHD items, as well as the final diagnostic outcome (paper II).

Another potential problem concerns the possibility for patient recall bias, particularly regarding retrospective assessment of lifetime axis I disorders. This problem has been noticed in a previous study where a birth cohort was followed from age 18 to 32 years, and where the prevalence of lifetime psychiatric disorders almost doubled when assessed prospectively as compared to when assessed retrospectively [102].

Another limitation was the lack of a specific assessment of overall functioning (e.g. GAF) in the patient records. However, complete and extensive demographic data were collected and analysed, indicating, at least indirectly, some measure of overall social functioning. Only 34% of the participants were working full or part time, which is lower than figures reported from previous comorbidity studies [83; 132], where 61% and 72% respectively were working.

Best estimate diagnoses were established by members of the professional team who independently participated in the evaluation process. In general, we consider the best estimate diagnostic process for all the participating patients to provide reasonable evidence of functional impairment in accordance with ADHD. Psychiatric comorbidity was investigated by SCID-I and SCID-II interviews to secure validity of axis I and axis II disorders.

Paper III and IV included a follow-up of the sample described in paper II. The follow-up was based across a broad spectrum of instruments. Being a long-term follow-up study with a mean time of six years (range up to 11 years), the study design was subject to several practical and important issues. Previously documented everyday difficulties which were presented by patients with ADHD were challenges to be considered in order to maximise participation rate. The protocol was therefore designed to optimise data collection. In addition, we assumed that a potential part of the participants would have moved far away from the original catchment area and maybe even abroad. We therefore decided on a two-step study design with initial self-questionnaires to be followed by an interview and validation of the answers given to the items in the questionnaires. In this way, missing infor-
mation, obvious misunderstandings and other potential problems in the first step of the protocol could be resolved in the protocol’s second step. This approach proved to be successful as it became clear that a number of participants needed assistance (e.g., telephone, a personal visit at the clinic or a home visit) to complete the questionnaires. Another issue is that baseline ADHD symptoms had been obtained using a semi-structured interview; while the symptoms at follow up were obtained using a self-report questionnaire, although with the same questions. Here it must be considered that adults with ADHD have been found to be their best informants regarding their symptoms but tend to underreport the severity of their symptoms [86]. Adding informant reports from partners and significant others, as in the diagnostic process, would probably had accessed additional information.

To assess function apart from GAF, we choose to use the SDS because it had recently been psychometrically evaluated in adult ADHD. This scale is a comprehensive but short instrument measuring everyday functioning domains applicable to any psychiatric as well as somatic disorder. The Weiss Functional Impairment Rating Scale (WFIRS) [144] would probably have yielded more detailed and specific information on impairment related to ADHD but was omitted because our protocol already contained a large number of questionnaires.

We choose the ERQ-5D to assess HRQoL. EQ-5D is short and easy to administer. We also choose AUDIT and DUDIT instruments for screening of alcohol and substance abuse, respectively. These are regarded as the gold standard for screening, and have been used for this purpose in numerous studies.

The fact that there was no information on overall or cognitive functioning at baseline might have influenced and biased the comparison in the different groups at follow-up. Information from a parallel non-pharmacological treatment and support arm, as well as an evaluation of psychiatric comorbidity at follow-up would have contributed to more precise analyses. Obviously, an RCT with a placebo treated control group would have been the most optimal design to collect comparison data on long-term outcome. However, such a design would be both practically impossible over a period of up to 11 years and ethically extremely questionable. Another option, such as that used in follow-up studies of the original MTA study, would be to attach a normal matched control group to compare outcome [139]. This would have been a more elaborate and extensive study design to demonstrate long-term outcome of adult ADHD and would have facilitated interpretation of the data obtained and demonstrated in papers III and IV.

Finally, no formal calculation of statistical power was performed before designing any of the studies. In paper I, we assumed that a sample of 1000 patients in the GP would be sufficient based on a previously reported prevalence rate of ADHD in children of 3-7%. In the outpatient sample, we hypothesised a potentially higher prevalence rate and thus restricted the num-
ber of distributed questionnaires to 400. The female inmates constituted all high-security internees at the only prison available for investigation at the time. Patients in paper II, III and IV were those that were consecutively evaluated and diagnosed over a specific period. Nevertheless, it is highly probable that a higher number of participants would have facilitated detailed sub-analyses and identification of potential outcome predictors in the regression analyses in paper III and IV.

Ethical considerations

Because anonymous screening of psychiatric disorders can evoke the necessity for psychiatric evaluation, all participants in paper I in the GP sample and within outpatient psychiatry were invited to contact a specialised unit for questions and assistance. The female inmates had access to health care facilities within the prison for the same purpose. In preparation for paper II, it was clearly stated in the application to the Ethics Committee that research on data from patient files is an ethically delicate matter and must be carefully considered based on the potential scientific outcome. To secure anonymity, all study data were decoded from individual patient information before analysis. In paper III and IV, the principal ethical issue concerns evoking potential memories and emotional reactions when addressing and contacting patients who have undergone diagnostic procedures and long periods of treatment. Generally, most participants expressed gratitude for being contacted. Some participants conveyed a need for renewed medical contact and treatment, and accordingly, were assisted with referrals to psychiatric outpatient clinics in their residential area. Some of the participants had a need to express opinions and share their experiences with the interviewer since being diagnosed with ADHD in adulthood. As many participants saw themselves as being among the first individuals in the country to be diagnosed with ADHD as adults, it was felt that many of the participants perceived themselves as "pioneers", a fact that probably contributed to the high participation rate.

General discussion and clinical implications

The principal aim of this thesis was to expand our understanding of ADHD by investigating prevalence, psychiatric comorbidity and long-term outcome and safety of pharmacological intervention in persons diagnosed with ADHD as adults.
Prevalence

Our data confirm the high prevalence of ADHD-related symptoms associated with increased difficulties and suffering, lower general functioning and increased frequencies of reading and spelling difficulties in outpatient psychiatry, regardless of sex. These findings were also observed in female prison inmates. No major sex differences were identified in outpatient psychiatry versus the GP. The high prevalence of reading difficulties in those with ADHD symptoms was not unexpected and concurs with the ESSENCE concept. Half of the female prison inmates reported symptoms of ADHD in childhood or as adults, and approximately 30 % reported inattention in childhood and symptoms of ADHD as adults. This is similar to the previously mentioned meta-analysis with an average ADHD prevalence rate of 25.5 % in prison inmates [163]. High prevalence rates of ADHD in both patients and inmates prompt awareness of potential ADHD-related problems. Such awareness should be beneficial in attaining optimal treatment, care and rehabilitation in patients who are in contact with outpatient psychiatry as well as prison establishments [62; 106]. Currently, the awareness of ADHD as an important factor for outcome in correctional treatment has increased substantially. In addition, treating inmates diagnosed with ADHD has demonstrated successful long-term outcome [63]. Finally, pharmacological treatment of patients with ADHD has been linked to lower criminality rates in both men and women compared with periods when patients are off medication [97].

Comorbidity

In our clinical sample of patients diagnosed with ADHD in adulthood, 9 out of 10 patients had experienced at least one lifetime axis I disorder, and usually in the form of a mood disorder. This supports a published observation of a genetic correlation of ADHD and bipolar disorder [147]. Thus, identifying and treating potential coexisting mood disorders is an important part of adult ADHD, especially as register data suggest that stimulant medication is related to a decreased risk of suicide [35]. Our data reveal few sex differences for an axis I disorder but confirm the results of previous studies in which mood and eating disorders were more frequent in females [117; 119] and SUD more common in males [20; 67; 117]. Accordingly, a recent study related to the ESSENCE concept performed on adults with ADHD, ASD, or both confirmed that almost one fifth of the participants reported severely or moderately disturbed eating behaviour [79].

The relatively low prevalence of ongoing substance use in our material might be explained by compulsory drug screening and the request for drug abstinence during the evaluation period. Although ADHD has been demonstrated to be overrepresented in patients with SUD, a prospective study of twins has linked the risk of alcohol problems during adolescence to external-
ising behaviour rather than to core ADHD symptoms [113]. Moreover, proposed concerns of evoking SUD or provoking relapse of previous SUD by treating ADHD with classified drugs has not been confirmed [33; 112].

In our sample, ASD and Tourette’s syndrome greatly exceeded the prevalence rates in the GP [16; 85]. Conversely, there is an increased risk for ADHD in patients with ASD and their relatives [57] suggesting a genetic overlap of the two disorders. This finding underscores the need to consider coexisting symptoms of ASD and tics when treating patients diagnosed with ADHD as adults.

Nearly half of the patients confirmed the specific criteria for one or more personality disorders but only one tenth was considered to fulfil a best estimate diagnosis. The low prevalence of personality disorders in the present study is probably explained by the restrictive methodology applied, separating specific personality criteria from a best estimate diagnosis on axis II. The diagnostic overlap between personality disorder criteria and ADHD has not been sufficiently examined, especially in relation to cluster B disorders such as ASPD and BPD. Borderline development in ADHD has been reported to be related to certain environmental factors such as emotional abuse in childhood [111]. To elucidate and explain the variable extent of emotional lability in ADHD, a gradient model of "cool" and "hot" executive functions with different neuroanatomical correlations has been proposed [109]. The former would be correlated to classical ADHD while the latter would be tied to antisocial and borderline functioning. In parallel, non-emotional and emotional processing would involve the basal ganglia with modulatory effects of the dopamine system. In all, this dual concept would be a model to stepwise integrate ADHD with emotional lability, ASPD and BPD.

The adult ADHD concept

Recently, data from a small number of studies have raised the question of whether onset of ADHD could occur first in adulthood, an issue which would further complicate the diagnostic procedure insofar as symptom requirement before the age of 12 is still requested according to DSM-5 [4; 32; 49; 103]. Further studies are required to elucidate factors that influence age of symptom onset and phenotypic expression of ADHD. Genetic research is intense and several candidate genes have been proposed but still with limited success in detecting common genetic variants for the diagnostic phenotype of ADHD [26]. Accordingly, viewing ADHD as a dimensional rather than as a categorical construct, together with increases in study sample sizes, have been proposed for future genetic research [69]. In addition, to identify specific genetic correlations and biological markers predicting pharmacological treatment response would be important to clinical practise. Polymorphism of catechol-O-methyltransferase (COMT) has been linked to treatment response to methylphenidate in children [81]. In adults, polymorphism in the gene
SLC6A3 has been reported to be associated to methylphenidate response [86].

**Long-term outcome**

The principal outcome of the long-term follow-up is that one third of the patients first diagnosed with ADHD as adults went into remission during a mean observation period of six years. This result is consistent with findings of a recently published seven-year longitudinal study of adults with ADHD [78]. After being taken off medication and re-evaluated, one third of the latter patients did not maintain ADHD criteria and 12% were in full remission. Another important finding in this thesis is that, despite a high percentage of psychiatric comorbidity at baseline, adult ADHD in general seems to have a favourable long-term functional outcome as judged from the GAF scores at follow-up, which were similar to scores reported from the GP in paper I. Furthermore, the domain means on the SDS were below the cut-off for significant functional impairment when assessed at follow-up, and independent of ADHD remission. The EQ-5D index, a health status index related to HRQoL, was similar to population sample scores [30] in patients in remission, but lower in those not. This finding must be given an interpretation with caution, however, because substantial variability was noted between individuals for these measures, indicating that some of the patients still perceived substantial impairment in disability and HRQoL. Altogether, the results reflect the complexity of adult ADHD with all its nuances beyond core symptomatology when evaluating aspects of treatment and treatment outcome. A somewhat unexpected finding was that alcohol consumption (as measured by AUDIT) in patients with ADHD was similar to that in the GP. On the other hand, a DUDIT score which reflected any use of drugs was reported in 14% overall, and in 17% of non-remitters, which is higher than the 3% in the Swedish GP [19].

A noteworthy finding was that the remission rate and the ADHD scores were similar in patients currently undergoing treatment with central stimulants and in those not treated. Our data add to the present literature with presently no accepted evidence based on longitudinal assessments, suggesting that there are long-term benefits from medication in individuals first diagnosed with ADHD as adults [71]. Moreover, a six-year follow-up study of participants with ADHD combined type in late adolescence and early adulthood found no effect of pharmacological treatment on either ADHD symptom severity or overall functioning despite an increasing rate of pharmacological treatment over time [148]. In addition to that, time on medication did not predict persistence of ADHD in the previously mentioned study [71]. This finding is, however, in contrast with those from another recent study in adults with ADHD [95] which reported that 56% of the patients currently on medication were below a cut-off for ADHD after a mean obser-
vation time of 4.5 years compared with 34% of those without ongoing medication, and also a better outcome on all measures in patients treated for two years or more compared with those given shorter pharmacological treatment.

Although patients who were currently on medication did not report better ADHD or SDS scores, they did report higher improvement as measured by the CGI-I scale. This result may suggest that there are medication-related improvements beyond core symptomatology of inattention and hyperactivity/impulsivity. It is also possible that the patients’ ratings contain a placebo-related mechanism in the compliant patients as suggested and discussed in reference [73]. There may also be differences in patient characteristics that are not discerned, and also a variable amount and quality of psychoeducational measures and information that may have affected the tendency to discontinue medication. Psychiatric comorbidity at follow-up and data on the participants’ cognitive level and profile, which were not assessed by us, are also factors that could have influenced coping strategies and adherence to medication.

It is particularly noteworthy that no baseline factors predicted outcome six years after the patients were first diagnosed with ADHD in adulthood. This observation is discordant with studies showing that psychiatric comorbidity at baseline is a negative prognostic factor [95; 78]. An explanation could be that comorbidities are registered and diagnosed differently in different studies. Another issue can be that the primary outcome measure differed between studies. It has been recommended that clinical research in ADHD should use remission as the primary outcome [133], which also was used in this study. Our paper defined remission as not fulfilling any ADHD subtype and a GAF value of ≥70 during the past year. Nevertheless, we also calculated persistence of symptoms as performed and defined by Biederman et al. [24] in the form of full or subthreshold ADHD based on the DSM-IV diagnostic criteria, or failure to attain functional remission (GAF score ≤60). Irrespective of how outcome was assessed there was no significant difference between patients who were on current medication and those who were not (data not shown).

Pharmacological treatment

Half of the medicated patients were still on medication at follow-up, which is consistent with previous data [17]. Most of these patients perceived a pronounced or moderate effect on their ADHD, with a mean stimulant dosage within recommended limits. Adherence to treatment was reported excellent in this group, both with respect to dosage and to regularity of intake. Self-reported adverse effects during treatment demonstrated a broad spectrum of symptoms of the sort reported in previous studies: the five most common complaints were decreased appetite, dry mouth, anxiousness, increased pulse frequency and decreased sexual desire [76; 121]. The results indicate the
importance of a wide and systematic evaluation of adverse effects when treating adults with ADHD. Most importantly, our data do not indicate that there is tolerance or a need for increased dosage over time to preserve treatment effect, but rather the contrary. The reason for this could only be speculative, but possibly long-term medication creates "a window" that enables and increases the possibility to profit by other non-medical interventions and treatments. Further research will likely increase our knowledge of factors influencing the dose required for clinical effect over time. Nevertheless, this thesis confirms that the long-term pharmacological treatment of patients diagnosed with ADHD in adulthood, and who present a high degree of psychiatric comorbidity at the time of the diagnostic evaluation, is safe and tolerable after a mean period of six years. Being based on a clinical sample with no exclusion criteria attached, the present results seem representative of a typical patient sample from an adult outpatient psychiatric clinic.

The other half of the participating patients had discontinued treatment at follow-up. This observation is similar to observations made in other long-term studies [17; 95]. We noticed a mean treatment time of two years in this group, suggesting that there had been sufficient time to evaluate treatment and to adjust dosage of the pharmaceuticals used to be in accordance with dosage used in everyday clinical practice. It also raises the question of whether the efficacy of treatment diminishes over time, or if, once again, the non-pharmacological interventions that run parallel with medication, affects the perceived need for pharmacological support. Furthermore, lack of effect was the most common cause for discontinuation. Only one patient discontinued methylphenidate and one amphetamine because they saw no need for further medication.

Notably, none of the patients who had reported elevated mood or hypomania had been diagnosed with a bipolar disorder at baseline, whereas those two who had been diagnosed with a bipolar disorder at baseline discontinued treatment because of depressed mood. This finding agrees with results of a report suggesting that comorbidity of bipolar disorders and ADHD is more frequently linked to depressive episodes than to manic episodes [125]. The necessity of treating patients who present with comorbid bipolar disorder and ADHD with mood stabilisers before stimulants has recently been demonstrated [152]. It can also be discussed whether some patients with SUD were offered optimal treatment in that data on patients with ADHD and SUD indicate that dosage in the higher range may increase adherence to treatment with methylphenidate [127].

Another important observation is that nearly one tenth of the participants had discontinued treatment because of the perceived inability to stay in contact with the prescribing physician. It cannot be ruled out that a change in the panorama of comorbidity over the six-year period may have influenced adherence to treatment as well as the reported adverse effects. Furthermore, differences in non-pharmacological treatment or supporting interventions
since baseline are potential factors that could have biased the results. Conversely, combined data on pharmacological and non-pharmacological treatment have demonstrated medication to be superior in outcome (at least for one year) compared with supportive interventions and psychological treatment [110].

Finally, patients’ own perception was that of an increased QoL, an increased level of functioning and better understanding from the surroundings in those with ongoing medication. This observation must not be underestimated as an important feature of adult ADHD is the general effect of the disorder on both the patients and their family members.

Future aspects
ADHD in adulthood may be a more complex diagnostic entity to evaluate and treat than in childhood as it is associated with a wider spectrum of comorbidity and also with secondary consequences of SUD and somatic conditions.

The role of epigenetics in ADHD is still relatively unknown but has slowly emerged over the past years. Taking this into account, ADHD in adulthood often displays a heterogeneous clinical presentation with aspects to consider that go beyond the present categorical diagnostic system and core symptomatology of inattention and hyperactivity/impulsivity. Reports on possible adult onset of ADHD further complicates this issue. Future clinical studies of ADHD in adulthood therefore need a wide spectrum of approaches concerning genetics, diagnostics, treatment, and psychiatric as well as somatic comorbidity. Not to mention the link between cognitive impairment and the clinical presentation and treatment outcome.

In the present study four persons had died of unnatural causes since diagnosed with ADHD, which is in line with the perspective that ADHD is related to suicidal behaviour or other adverse health outcomes [105]. Key issues to investigate are to further assess whether such an association is the effect of comorbid psychiatric conditions, e.g. mood disorders and SUD, and if so, to what extent a comorbid ADHD only acts as a risk amplifier.

A key issue is that the characteristics of ADHD as such contain elements that affect adherence to structured treatment protocols negatively. Any treatment protocol that only reaches half of those in need is in vain for a substantial subgroup of patients. Research on how to organize care, and how to effectively reach patients with psychoeducational interventions and coaching in order to improve adherence to protocols is highly desired [107] The rapid technological development allows for new approaches in such psychoeducational interventions and coaching. To date, some success has e.g. been reported for Internet-based interventions and coaching [151; 131].
Conclusions

- There is a high prevalence of ADHD-related symptoms associated with increased difficulties and suffering, lower general functioning and increased frequencies of reading and spelling difficulties in psychiatric outpatients, regardless of sex. These findings were also observed in female prison inmates.

- There was a high prevalence of psychiatric comorbidity in both women and men diagnosed with ADHD as adults, with women more vulnerable to mood disorders and men more at risk for substance-use disorders. Nearly half of the patients fulfilled specific personality disorder criteria, with few differences between sexes.

- Patients diagnosed with ADHD as adults report diagnostic remission in about 3 of 10 cases after a mean period of six years, irrespective of ongoing pharmacological treatment at follow-up, and despite a high percentage of psychiatric comorbidity at baseline.

- Long-term pharmacological treatment (mainly with stimulants) of adults with ADHD is safe with generally mild and tolerable adverse effects. The discontinuation rate of about 50%, with almost a third of which due to perceived lack of effect of methylphenidate, suggests that close surveillance and a strategy to change drugs, drug combinations and dosages should be assessed as a way to increase retention to treatment. Long-term data do not indicate tolerance or a need for increased dosage over time to preserve the treatment effect, but rather the contrary.
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