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Beyond the Core Symptoms of the Diagnostic and Statistical Manual of Mental Disorders

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Avhandling for graden philosophiae doctor (ph.d.)
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## Scientific environment

Division of Psychiatry, Haukeland University Hospital and The Clinical Cognitive Neuroscience Group (C-CNS) at the Department of Biological and Medical Psychology have been my main affiliations during my work with this thesis. Professor Astri Lundervold, the head of the C-CNS, has been my supervisor together with professor Jan Haavik (Department of Biomedicine) and professor Maj-Britt Posserud (Department of Clinical Medicine). My project is part of the K. G. Jebsen centre for Neuropsychiatric Disorders, led by Professor Jan Haavik. I have been enrolled in the International Graduate School in Neuroscience (IGSIN) at the University of Bergen, and taken part in the Norwegian Research School in Neuroscience (NRSN). My project has been funded by a PhD grant from Helse Vest.


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In the final year of my PhD I have also been a guest at an office for Cognitive Neuropsychology PhDs at the Department of Psychology at the University of Oslo. I am very grateful for this opportunity and the friends I made there.

A huge thanks to my father for your continuing support. And in fond memory of my mother, who passed away during my PhD period. You have both given me a lot of encouragement and support.

# Preface

My motivation for this thesis developed as I stumbled upon the Wender Utah Rating Scale (WURS). As a recent clinical psychology graduate, I had certain expectations about psychiatry diagnoses in general and the diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) in particular. I thought for instance first and foremost that ADHD was a disorder of childhood, not appreciating it as a potentially persistent disorder, also affecting adults. I also supposed that the clinical phenomenon of ADHD would be sufficiently contained by the diagnostic symptom criteria set forth by the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases (ICD) diagnostic manuals. Thus, entering the adult ADHD project and stumbling upon the WURS that had been used for decades to retrospectively assess childhood symptoms of ADHD, I was taken by surprise by the apparent lack of face validity of this symptom checklist. Sure, there were questions of inattention in there, and some regarding hyperactivity/impulsivity as well. However, the main bulk of the 25 questions posed differed markedly from the 18 symptom criteria of inattention and hyperactivity/impulsivity of the DSM system. Thus, my curiosity was lit, and I was looking into a horizon that was already broader than the two main diagnostic systems in the field would have me think.

# Abstract

**Background/Introduction:** Attention Deficit Hyperactivity Disorder (ADHD) is a prevalent condition in both children (estimated prevalence of about 5%) and adults (estimated prevalence of about 3%). ADHD is characterized by impairing symptoms of inattention and hyperactivity/impulsivity. However, there are at least two caveats to this symptomatic description. First, as ADHD was initially considered a childhood disorder, these symptoms and their conceptualization may be more applicable to children than adults. Second, ADHD in children, adolescents and adults is comorbid in up to 75% of cases, and can also be understood as an underlying broad regulatory deficit, spanning multiple symptom domains. Thus, to understand and adequately address the needs of adult ADHD patients there is a need to go beyond the core symptoms of ADHD and investigate frequently associated and impairing symptom domains.

**Aims:** The overall aim was to investigate symptom domains in adults with ADHD including and expanding upon the core symptoms described in the Diagnostic and Statistical Manual of Mental Disorders (DSM). In the three papers the thesis investigates 1) the psychometric properties and the clinical utility of self-reported childhood symptoms versus current symptoms using two frequently used symptom checklists for adult ADHD; 2) the prevalence and clinical correlates of insomnia in adult ADHD; and 3) the genetic components of aggressiveness in ADHD.

**Materials and Methods:** This thesis is based on three separate papers. Paper I and II included 268 and 646 clinically diagnosed adult ADHD patients, respectively, as well as 202 and 908 population controls from the Medical Birth Registry of Norway, respectively. Paper III included a total of 1060 adult ADHD patients from three sites within an international multi-centre persistent ADHD collaboration (IMpACT): Germany, Norway, and Spain; and 750 adolescents with ADHD participating in the International Multicentre ADHD Genetics (IMAGE) study across Europe.

In Paper I we compared the Adult ADHD Self-Report Scale (ASRS) with the Wender Utah Rating Scale (WURS), testing the discriminatory ability for detecting and separating clinical ADHD patients from population controls. We used Receiver Operating Characteristics Area Under the Curve (AUC), Diagnostic Odds Ratio (DOR) and Likelihood Ratio (LH) as these methods are independent of the disorder prevalence in the sample studied. Principal Component Analysis (PCA) was used to validate the checklists.

In Paper II we used the Bergen Insomnia Scale (BIS) to measure insomnia and the Adult ADHD Self-Rating Scale (ASRS) to assess ADHD symptom domains.

In Paper III we performed a Genome Wide Association (GWA) study of a childhood aggressiveness phenotype in the adult ADHD sample, and compared this with GWA signals of dimensions of oppositionality (defiant/vindictive and irritable dimensions) in the adolescent sample.

**Results:** In Paper I we found that both symptom checklists had excellent screening properties, with the WURS having an AUC of .96, (95% CI: .95-.97) and the ASRS an AUC of .90, (95% CI: .89-.92). The WURS factors *Learning and Attention Problems* and *Aggressiveness and Social Problems* were found to be the strongest discriminants of ADHD.

In Paper II we found that insomnia was far more frequent among adults with ADHD (66.8%) than in a representative control sample (28.8%) ($P < 0.001$). Insomnia was more common in adults with the combined subtype of ADHD than in those with the inattentive subtype (79.7% and 55.6%, respectively) ($P = 0.003$). For self-reported current ADHD symptoms, inattention was strongly correlated to insomnia. Patients currently using stimulant treatment for ADHD reported a lower total insomnia score compared to patients without medication ($P < 0.05$).

In Paper III no single polymorphism reached genome-wide significance ($P<5.00E-08$). However, we did identify a number of biologically interesting markers (our top hits were rs10826548 within a long noncoding RNA gene; closely followed by

rs35974940 in the neurotrimin gene). As these markers possibly represent biological systems involved in childhood aggressiveness, they provide targets for further genetic explorations of aggressiveness across psychiatric disorders.

**Conclusions:** The results in the present thesis suggest that we need to broaden our approach and scope when investigating and treating patients with ADHD. We need to move beyond the classic symptom domains of inattention, hyperactivity and impulsivity, and recognize that patients meeting criteria for the ADHD diagnosis tend to also have other impairing problems across different symptom domains. These domains, such as aggressiveness and insomnia, need to be addressed in order to adequately aid adult ADHD patients' function in their daily life.

# List of publications

Paper I

Brevik, E.J, Lundervold, A.J, Haavik, J. & Posserud, MB (2017). Comparison of the psychometric properties of the ASRS and WURS scales in discriminating between adults with and without ADHD. *Submitted*

Paper II

Brevik, E.J., Lundervold, A.J., Halmøy, A., Posserud, MB., Instanes, J.T., Bjorvatn, B. & Haavik, J. (2017). Prevalence and clinical correlates of insomnia in adults with attention-deficit hyperactivity disorder. *Acta Psychiatrica Scandinavica.* doi:10.1111/acps.12756

Paper III

Brevik, E.J, van Donkelaar, M.M.J., Weber, H., Sánchez-Mora, C., Jacob, C., Rivero, O., Kittel-Schneider, S., Garcia-Martínez, I., Aebi, M., van Hulzen, K., Cormand, B., Ramos-Quiroga, J.A., IMAGE Consortium, Lesch, KP., Reif, A., Ribasés, M., Franke, B., Posserud, MB, Johansson, S., Lundervold, A.J, Haavik, J. & Zayats, T. (2016). Genome-wide analyses of aggressiveness in attention-deficit hyperactivity disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 171*(5), 733-747. doi:10.1002/ajmg.b.32434

Papers II and III are published in open access.

**Related publications not included in this thesis:**

Bjorvatn, B., **Brevik, E.J.**, Lundervold, A.J., Halmøy, A., Posserud, MB., Instanes, J.T. & Haavik J. (In press). Adults with Attention Deficit Hyperactivity Disorder report High Symptom Levels of Troubled Sleep, Restless Legs and Cataplexy. *Frontiers in Psychology.*

Sørensen, L., Sonuga-Barke, E., **Brevik, E.J.**, Jensen, D., Haavik, J. & Lundervold, A.J. (2017, April) Poor quality of decision-making in adults with ADHD is linked to delay aversion and longer deliberation time. *Poster session presented at The 6th ADHD World Congress in Vancouver, Canada.*

Ahmad, S.I., Lundervold, A.J., Meza, J.I., Posserud, MB., **Brevik, E.J.** & Hinshaw, S.P. (2016). ADHD Symptom Dimensions Differentially Predict Adolescent Peer Problems: Findings From Two Longitudinal Studies. *Submitted*

Vildalen, V.U., **Brevik, E.J.**, Haavik, J. & Lundervold, A.J. (2016). Females With ADHD Report More Severe Symptoms Than Males on the Adult ADHD Self-Report Scale. *Journal of Attention Disorders*. doi:10.1177/1087054716659362

Lundervold, A.J., Halleland, H.B., **Brevik, E.J.**, Haavik, J. & Sørensen L. (2015). Verbal Memory Function in Intellectually Well-Functioning Adults With ADHD: Relations to Working Memory and Response Inhibition. *Journal of Attention Disorders*. doi:10.1177/1087054715580842

# Abbreviations

aADHD – Adult Attention Deficit Hyperactivity Disorder

ADD – Attention Deficit Disorder

ADHD – Attention Deficit Hyperactivity Disorder

ASRS – Adult ADHD Self-Report Scale

AUC – Area Under the Curve

BIS – Bergen Insomnia Scale

cADHD – Childhood Attention Deficit Hyperactivity Disorder

DOR – Diagnostic Odds Ratio

DSM – Diagnostic and Statistical Manual

GWA(S) – Genome Wide Association (Study)

HI – Hyperactive / Impulsive

HiTop - Hierarchical Taxonomy of Psychopathology

IA – Inattentive

ICD-10 – International Classification of Diseases and Disorders, Tenth edition

LH – Likelihood Ratio

NIMH – National Institute of Mental Health

NPV – Negative Predictive Value

OR – Odds Ratio

P-factor – One General Psychopathology dimension

PPV – Positive Predictive Value

RDOC – Research Domain Criteria

ROC – Receiver Operating Curve

SD – Standard Deviation

SNP – Single Nucleotide Polymorphism

WURS – Wender Utah Rating Scale

# Contents

# 1. Introduction

## 1.1 A brief history of Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013) by its symptoms of inattention, hyperactivity and impulsivity. These symptoms need to have a childhood onset, be impairing in two or more settings and not be better explained by other disorders (see Table 1). The diagnosis known as ADHD today had its formal beginnings with the name *Hyperkinetic Reaction of Childhood* in DSM-II. The name changed into Attention Deficit Disorder with or without Hyperactivity in the DSM-III (Wender, 1995). The ICD-10 still operates with the term Hyperkinetic Disorder (WHO, 1992), whereas the DSM-IV onward has named the disorder ADHD (American Psychiatric Association, 1994), and this is how it is most commonly known and researched to this day.

Going back in time, the phenomenon underlying the current diagnosis of ADHD, despite varying names, has a long history. This history dates back in the medical literature at least to a 1775 medical textbook by the German physician, Melchior Adam Weikard (Barkley & Peters, 2012). The Scottish physician Alexander Crichton described disorders of attention in his medical textbook dating back to 1798. The German psychiatrist Heinrich Hoffman wrote poems about Fidgety Phil in 1865. The English pediatrician George Still wrote medical papers describing a phenomenon closely related to today's conceptualization of ADHD in children in 1902, addressing the underlying behavioral problems as a moral deficit (Barkley & Peters, 2012). As a side note, Weikard himself "believed that people were more attentive in earlier times and less attentive in his time" (Barkley & Peters, 2012), a testament perhaps to human attention and point of reference, that we're all operating in the context of our own history and experiences. Regardless, it seems safe to say that distractibility has been a hallmark symptom of the disorder since its modern inception (Barkley & Peters, 2012). George Still emphasized passion, or emotional lability as we would

probably label it today, as the most common and noteworthy attribute among all the features of the disorder (Barkley & Peters, 2012). This is an important point that will be discussed later, as emotional dysregulation has never been fully recognized as part of the official core criteria of the ADHD (Barkley, 2017).

As previously mentioned, the concepts behind, the criteria for, and the names of the syndrome of Attention-deficit Hyperactivity Disorder have been changed several times. Prior to the third edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-III, APA, 1980), the syndrome was conceptualized as composed of behavioral, motor, "perceptual", and cognitive impairments (Wender, 1995). What is now conceptualized as ADHD was variously designated as "minimal brain dysfunction", "hyperkinesis", and the "hyperactive child syndrome". The behavioral and cognitive abnormalities associated with the syndrome included, but were not limited to, overactivity, inattentiveness and distractibility, impulsivity, affective lability and moodiness, temper outbursts, "immaturity", poor peer relations, disobedience, defiance, hostility, "acting out" or delinquent behaviors, and dyslexia and other learning problems. (Wender, 1995).

DSM-III separated a cluster of symptoms from this potpourri which it designated as "Attention Deficit Disorder" (ADD), and grouped other behavioral problems under the category of "Conduct Disorder". DSM-III stated that the "essential features are signs of developmentally inappropriate inattention and impulsivity" (Wender, 1995). Hyperactivity was acknowledged as being frequently present (ADD-H) but not essential for the diagnosis. The identification of ADD as a diagnosis that might or might not be associated with hyperactivity avoided a former oxymoron or linguistic problem – that of the non-hyperactive "hyperactive child". The (frequently) associated features "vary as a function of age and include obstinacy, stubbornness, negativism, bossiness, bullying, increased mood lability, low frustration tolerance, temper outbursts, low self-esteem, and lack of response to discipline" (Wender, 1995). In addition, Specific Developmental Disorders, i.e. learning disorders, were found to be common. Conduct Disorder was considered a "complication" (Wender, 1995).

What was originally part of the same symptom cluster in the age of "minimal brain dysfunction" was split into separate categories of "attention deficit disorder" (ADD) (with or without hyperactivity) and "Conduct disorder" in the DSM-III (Wender, 1995). ADD was renamed Attention-deficit Hyperactivity Disorder (ADHD) with the DSM-III-R, under the revised assumption that hyperactive/impulsive symptoms were most often present (no subtypes were listed) (Hinshaw & Scheffler, 2014), and ADHD was classified together with Conduct Disorder and Oppositional Defiant Disorder as a member of "Disruptive Behavior Disorders" (Wender, 1995). The DSM-IV changed the name of the disorder to Attention-Deficit/Hyperactivity Disorder, opening up for inattentive, hyperactive-impulsive and combined subtypes. The DSM-IV also changed the disorder category to "Attention-Deficit and Disruptive Behavior Disorders" to avoid incorrectly implying that all patients with ADHD are disruptive (Wender, 1995). In DSM-5 ADHD has been placed in the new chapter called "neurodevelopmental disorders", reflecting the current conceptualization of the disorder (American Psychiatric Association, 2013).

## 1.2 Prevalence and persistence of adult ADHD

ADHD is currently one of the most prevalent disorders of child psychiatry with a world-wide prevalence rate estimate of about 5% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). About half of the children diagnosed with ADHD remain fully symptomatic in adulthood (Faraone et al., 2015), with an estimated persistence rate of 30-67% percent. Thus, it is an important disorder to be reckoned with also in adults, with an estimated prevalence of about 2-3% (Faraone, et al., 2015). There is, however, some variance across nations. A recent survey, (Fayyad et al., 2017) found an overall prevalence of 2.8 % of DSM-IV defined adult ADHD across a range of nations, spanning from 1.4% in lower income countries to 3.6% in higher income countries.

Although defined as a disorder with childhood onset, because contextual demands continue to increase in number, scope and complexity with age, coupled with decreased support systems, ADHD may often first be recognized and diagnosed in

adults (Turgay et al., 2012). Adult ADHD is associated with impaired functioning such as lower educational achievement, incarcerations/trouble with the law, unemployment, illicit drug use (Faraone, et al., 2015) and increased mortality (Dalsgaard, Ostergaard, Leckman, Mortensen, & Pedersen, 2015). Being a prevalent disorder with often debilitating outcomes, there is great need to obtain reliable and valid information to support the diagnosis of ADHD in adults based on both current symptoms and childhood symptoms.

The most effective treatment for ADHD in children and adults according to existing research is stimulant drugs (Hinshaw & Scheffler, 2014). As these drugs are non-specific, have side-effects and a potential for misuse, considerable controversy exist both in the popular press and academic literature concerning what ADHD is, and how it should be treated. Thus, a closer look into the diagnostic criteria of ADHD is warranted.

## 1.3 Different diagnostic traditions

Although both the DSM and ICD emphasize clinical utility, the scope of the clinical settings where the ICD is employed tends to be more varied and extensive than that of the DSM. The DSM is intended largely for use by highly trained mental health professionals. By contrast, the ICD is designed for health settings around the world, to be used not only by practitioners with widely divergent levels of expertise but also in cultural settings where assumptions about the etiology and the nature of disorders may be highly dissimilar from the Western milieu of the DSM. Accordingly, the ICD places stronger emphasis on public health applications than the DSM, and one reflection of this emphasis is the use of definitions that emphasize short text descriptions of each disorder rather than the polythetic symptom lists of the DSM (B. N. Cuthbert & Insel, 2013). A parallel tradition outside the DSM/ICD systems in diagnosing ADHD, still important and clinically relevant, is the Utah criteria (Wender, 1995). A description and comparison of the diagnostic criteria follows.

### 1.3.1 Diagnostic Criteria according to the DSM-IV and ICD-10

The following description is adapted from the DSM 4th edition text revision (American Psychiatric Association, 2000). This is the version used to diagnose the adult ADHD patients in this thesis. The criteria have remained unchanged in the DSM-5, with the addition of more relevant examples of behaviors displayed by adults.

**Table 1. Diagnostic Criteria according to the DSM-IV**

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

(1) Six (or more) of the following **symptoms of inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

(a) Often fails to give close attention to details or makes careless mistakes in school-work, work, or other activities

(b) Often has difficulty sustaining attention in tasks or play activities

(c) Often does not seem to listen when spoken to directly

(d) Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions)

(e) Often has difficulty organizing tasks and activities

(f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork and homework)

(g) Often loses things necessary for task or activities (e.g., toys, school assignment, pencils, books, or tools)

(h) Is often easily distracted by extraneous stimuli

(i) Is often forgetful in daily activities

(2) Six (or more) of the following **symptoms of hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

*Hyperactivity*

(a) Often fidgets with hands or feet or squirms in seat

(b) Often leaves seat in classroom or in other situation in which remaining seated is expected

(c) Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)

(d) Often has difficulty playing or engaging in leisure activities quietly

(e) Is often "on the go" or often acts as if "driven by a motor"

(f) Often talks excessively

*Impulsivity*

(g) Often blurts out answers before questions have been completed

(h) Often has difficulty awaiting turn

(i) Often interrupts or intrudes on others (e.g. butts into conversation or games)

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

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

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

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

In the most recent version, the DSM-5, the definition of ADHD has been updated to include descriptions of symptoms more accurately associated with the adult version of the disorder. The age of onset criteria of 7 years has been changed to 12, due to research showing no clinical differences between children identified by 7 years versus those identified later with regard to treatment response, course and severity or outcome (American Psychiatric Association, 2013). Another change in the criteria is the lower number of symptoms required for adult diagnosis; while children must present with at least six symptoms from one or both subgroup dimensions, older

adolescents and adults (over age 17 years) must present with at least five symptoms. Diagnostic Criteria according to ICD-10 differs from DSM in requiring symptoms from all three domains of hyperactivity, inattention and impulsivity. In addition, ICD-10 has an even stricter age of onset criterion of 5 years. Being originally published in 1992 (WHO, 1992), it does not have updated adult symptom descriptions.

### 1.3.2 Diagnostic Criteria according to the Utah Criteria

The following description is adapted from the Appendix in Paul Wender's 1995 book on adult ADHD (Wender, 1995).

**Table 2. Diagnostic Criteria according to the Utah Criteria**

**I.** Childhood Characteristics

Childhood history consistent with ADHD in childhood. Obtaining reliable historical data usually requires input from the individual's parents or older siblings. The following are [our – Wender and colleagues] diagnostic criteria for ADHD in childhood:

**A:** Narrow Criteria (DSM-III)

That the individual met DSM-III-R criteria (or DSM-IV when he wrote the book, probably DSM-5 now) for ADHD in childhood.

**B:** Broad Criteria

Both characteristics 1 and 2, and at least one characteristic from 3 through 6.

1. Hyperactivity
2. Attention deficits
3. Behavioral problems in school
4. Impulsivity
5. Overexcitability
6. Temper outbursts

**II.** Adult characteristics

**A:** The presence in adulthood of both characteristics 1 and 2, which the patient observes or says others observe in him, together with two of characteristics 3 through 7.

1. Persistent motor hyperactivity

2. Attentional difficulties
3. Affective lability
4. Disorganization, inability to complete tasks
5. Hot temper, explosive short-lived outbursts
6. Emotional overreactivity
7. Impulsivity

**B:** Absence of the following disorders:

1. Antisocial Personality Disorder
2. Major Affective Disorder

**C:** Absence of signs and symptoms of the following disorders:

1. Schizophrenia
2. Schizo-affective disorder

**D:** Absence of Schizotypal or Borderline Personality Disorders or traits

**E:** Associated features: Marital instability; academic and vocational success less than expected on the basis of intelligence and education; alcohol or drug abuse; atypical responses to psychoactive medications; family histories of ADHD in childhood, alcoholism, drug abuse, Antisocial Personality Disorder and Briquet's syndrome.

**F:** Child Temperament Questionnaire (Conners Abbreviated Rating Scale.)

Although not necessary for diagnosis, a score of 12 or greater as rated by the patient's mother is helpful for diagnostic purposes and may be predictive of treatment response.

The Wender Utah criteria require a childhood history of ADHD including both inattentive and hyperactive symptoms, with one of the following additional symptoms: behavior problems in school, impulsivity, over-excitability or temper outbursts. Secondly, it requires an adult history of persistent attention problems and motor hyperactivity with at least two of the following symptom domains: affective lability, hot temper, stress intolerance, disorganization and impulsivity (Ward, Wender, & Reimherr, 1993). In other words, Ward and colleagues presented a quite strict definition of which symptoms should be present to qualify for an ADHD diagnosis. These criteria were originally presented as a list of 61 items in a

questionnaire, which was subsequently reduced to the 25 items that best distinguished an ADHD sample from control samples (i.e. healthy controls and depressed patients). Most of the final 25 items are thus actually not directly tapping into the core ADHD symptoms as described in the DSM or ICD, but were rather chosen for their discriminative ability in case-control samples. In sum, the Wender Utah criteria are more in line with the ICD criteria, and both are stricter than the DSM criteria. Despite these comprehensive diagnostic criteria, Wender proposed in his 1995 book that the adult prevalence of ADHD is between approximately 2 and 6-7 %. (Wender, 1995).

## 1.4 Diagnostic challenges

### 1.4.1 Heterogeneity

Basing diagnoses of heterogeneous forms of psychopathology on rigid, highly specified lists of operationalized criteria means substituting a higher interrater reliability for the exclusion of a significant number of individuals, who by less stringent criteria would be counted as affected (Hyman, 2010). Problems created by strict overspecification are demonstrated by comparing diagnoses made with DSM-IV and ICD-10 for disorders in which the intention was to detect the same patients. Although there are some disagreements between the DSM-IV and the ICD-10, many of the differences in operationalized criteria appear to be the accidental results of having two parallel processes of criterion writing (Hyman, 2010). Slade and Andrews (2001) used a single structured interview, the Composite International Diagnostic Interview, administered to a community sample of 10,641 people to derive DSM-IV and ICD-10 diagnoses. They found that minor alterations in wording resulted in the identification of different individuals as being affected. In a smaller sample enriched for prevalence of mental disorders, Andrews, Slade, and Peters (1999) found a concordance between DSM-IV and ICD-10 criteria of 83% for a depressive episode, but only 64% for obsessive-compulsive disorder, and as low as 35% for posttraumatic stress disorder. Thus the rigidly operationalized criteria of the DSM-IV and the ICD-10 seem to exclude large numbers of plausibly affected individuals (indeed identified by the other system) who are likely in need of treatment (Hyman, 2010). In sum,

when you create rigid sets of narrow categories you create plenty of opportunities for diagnostic overlap. These overlaps are often referred to as comorbidities; the coexistence of two or more distinct psychiatric diagnoses (Maj, 2005).

### 1.4.2 Practical implications of diagnostics and classifications

It is widely recognized that ADHD both in children and particularly in adults, is more often than not accompanied by comorbid disorders (Singh, 2008; Sobanski, 2006). Thus, there is a need to investigate, research and further our knowledge into the various aspects that are associated with adult ADHD to illuminate its characteristics. As such, questions arise as how to differentiate between controls and ADHD patients (paper I), meaningful phenotypes within ADHD (such as aggressiveness in paper II), and comorbidities related to ADHD (such as insomnia in paper III).

As is apparent from the diagnostic checklists presented above, psychiatric diagnoses are polythetic, not monothetic. Monothetic describes a category that shares the same identifying features across all its members, like birds, etc. Polythetic means that you have separate classes of symptoms, e.g. inattention and hyperactivity/impulsivity, where only a few (e.g. 5/6 of 9) of the symptoms need to be present from one class in order to qualify for a diagnosis, resulting in considerable heterogeneity. Several people can thus have non-overlapping symptomatologies and still qualify for the same categorical description. A further point is that psychiatric diagnoses in general are descriptive, consensus based entities meant to increase inter-rater reliability. They are not defined from biological understandings of the underlying etiologies, as this would have been premature, not to say impossible to determine, at least at the inception and inclusion of these categories in diagnostic manuals. Thus, the underlying etiological substrates leading to a diagnosis of e.g. ADHD may vary considerably between people defined within the same categorical diagnosis. The diagnostic heterogeniety is further complicated by the fact that there is no reliable litmus test for ADHD; a comprehensive clinical assessment based on the DSM criteria remains the gold standard for the diagnosis (Haavik, Halmoy, Lundervold, & Fasmer, 2010).

Extensive research shows that adults with ADHD appear to benefit from treatment with stimulant medications in similar ways as children (Kooij et al., 2012), including significant improvements on driving performance and other associated problems. Pharmacological treatment of ADHD, albeit found to be efficacious, involves regulated substances such as methylphenidate and amphetamines. Such drugs have a potential for abuse and misuse, e.g. as cognitive performance enhancers. Although fear surrounding the abuse of stimulants is an important issue, evidence suggests that children with ADHD who are treated with stimulant medication are less likely to develop a substance use disorder in adolescence and adulthood (Biederman, Wilens, Mick, Spencer, & Faraone, 1999). The benefits observed with ADHD treatment, however, emphasize the importance of recognition and treatment of adult ADHD (Kooij, et al., 2012).

According to present diagnostic manuals, childhood symptoms of ADHD are particularly important to establish. Several other disorders that appear in adulthood may display symptoms similar to the core ADHD symptoms (e.g. affective disorders, substance use disorders and sleep disorders) (Sobanski, 2006). To add to the complexity, these disorders may often also be comorbid to ADHD (Halmoy et al., 2010; Haavik, et al., 2010; Sobanski, 2006). The Wender Utah Rating Scale (WURS) was developed as a diagnostic aid to retrospectively evaluate the presence and severity of childhood symptoms of ADHD in adult patients (Ward, et al., 1993). It was developed independently from and partly in parallel with the diagnostic criteria of the DSM, but with some important differences between these sets of criteria as mentioned previously.

In addition to establishing childhood presence of symptoms, questionnaires and symptoms checklists are often used to assess current symptoms of ADHD. The DSM criteria were based on concurrent childhood symptoms of ADHD, and have later been adapted to fit with behavioral characteristics of adults with ADHD. The Adult ADHD Self-Report Scale (ASRS) is one of the most commonly used instruments of current symptoms of ADHD in adults, and represents the official screening instrument of the World Health Organization (WHO) (Ronald C. Kessler et al., 2005). The ASRS

includes the 18 items representing current symptoms of ADHD according to the DSM and ICD, and has been extensively validated, albeit with an important caveat: most studies have used the short 6 item screener, not the full version with all 18 symptoms (e.g. (R. C. Kessler et al., 2007)) Thus, important information on the full ASRS screening properties is largely lacking from the research literature.

### 1.4.3 Comorbidities and differential diagnostics

A myriad of comorbid conditions such as impulse-control problems, personality disorders, anxiety, mood disorders, substance abuse, learning disorders and sleep disorders overlap with adult ADHD (Kooij, et al., 2012). Furthermore, a number of such conditions have symptoms that can directly mimic those of ADHD, including hyperactivity, impulsivity, inattention, and disruption of circadian rhythm, adding to the complexity of recognition and diagnosis of ADHD in adults. Accordingly, disorders frequently comorbid to adult ADHD span several diagnostic bounds/categories, and create serious impairments on their own. Thus it is obvious that there can be uncertainties when assessing patients, untangling all of these different strands of clinically important information and potential treatment targets. Even though researchers such as Kooij, et al. (2012) list extensive comorbidities, two vital problem domains conspicuously lacking from their review are insomnia (only sleep-onset insomnia is briefly mentioned) and aggressiveness.

Comorbidities and symptom overlap between disorders may imply that there is a problem with the classification system, rather than any meaningful association between underlying diseases indexed by that classification. The fact that we are not dealing with clearly validated disease entities does not, however, mean that there is no point studying psychiatric comorbidity. Indeed, the opposite is the case, since understanding the presence of comorbidity between psychiatric conditions offers a means of correcting and validating psychiatric nosology. The study of comorbidity does not depend upon the existence of well-validated disease entities, but may actually be particularly informative in the case of poorly validated disorders (Angold, Costello, & Erkanli, 1999). Even if many, or even all, examples of comorbidity turn

out to be alternative expressions of some unitary underlying psychopathological process or processes, the phenomenon currently called “comorbidity” will still need to be explained (Angold, et al., 1999). However, there is no reason to suppose that comorbidities will go away (Angold, et al., 1999). “Diseases” are not obvious “natural” categories in any branch of medicine. Boundary problems are abound in relation to all medical disease, just as they are in mental disorders (Angold, et al., 1999). All normally distributed phenomena struggle with boundary issues, where clear cut-offs are illusive and non-existing.

A problem with not recognizing ADHD, CD, ODD and Learning Disorders as separate disorders is that the etiology, epidemiology, biological substrates and natural history or response to treatment is left unknown for ”pure” instances of these disorders, if they are only studied when lumped together (Wender, 1995). However, the reverse is more common and can also be quite problematic. If a research design is contingent upon identifying and characterizing only patients with ”pure” phenotypes of an arbitrarily defined categorical diagnosis, the naturally occurring overlaps between the diagnosis in question and other diagnoses may be neglected, overlooked, underappreciated and understudied. This is particularly problematic when a bulk of research shows that a categorical diagnosis in psychiatry usually does not come alone (Angold, et al., 1999).

This recognition has been co-existing alongside the categorical diagnostic systems for quite a while, especially in child- and adolescent psychiatry. To address this problem, Gillberg for example has introduced the concept of ESSENCE (Gillberg, 2010). ESSENCE stands for Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations. This alerts the clinician to meaningful symptoms spanning several psychiatric/pediatric categories that should elicit clinical attention and care to ensure an optimal developmental trajectory. To split syndromes into more precise diagnoses in a state-of-the-art way will only be possible if there is anything meaningful to start splitting from. In this sense a relevant group of cases “lumped” together. Gillberg stresses that the introduction of a new term such as ESSENCE

should not be taken as support for lumping rather than splitting, but for the order in which those two aspects of diagnosis is approached (Gillberg, 2010).

It would not be surprising if some aspects of comorbidity do arise because our diagnostic criteria have not drawn the appropriate boundaries between disorders. That is one reason for doing research on comorbidity. Both categorical and quantitative models offer complementary approaches to the issue of nosology (Angold, et al., 1999). Overall, work in this area can be seen as having treated the diagnostic criteria as "hypotheses" to be examined and tested. In our present state of knowledge this would appear to be the right attitude to bring to psychiatric diagnoses (Angold, et al., 1999).

Insomnia and aggressiveness frequently co-occur with a diagnosis of ADHD, but are not part of the official diagnostic criteria. They are, however, in focus in the present thesis, and will be shortly described in the following paragraphs.

## 1.5 Insomnia

Sleep disturbance is increasingly recognized as an important, but understudied, mechanism in the complex and multi-factorial causation of the symptoms and functional disability associated with psychiatric disorders (A. G. Harvey, Murray, Chandler, & Soehner, 2011). People with ADHD typically struggle with maintaining structure and regulating their behavior and daytime activities. The regulatory difficulties also seem to affect the diurnal rhythm, as ADHD has been associated with various sleep problems, with insomnia being one of the most commonly reported comorbid sleep conditions (Instanes, Klungsoyr, Halmoy, Fasmer, & Haavik, 2016). Insomnia is defined as difficulties initiating or maintaining sleep, early morning awakenings or having non-restorative sleep, lasting for at least a month (American Psychiatric Association, 2000). Insomnia is one of the most frequent health concerns in the general population as well (Buysse, 2013), typically affecting 6% to 15% of the adult population (Pallesen, Sivertsen, Nordhus, & Bjorvatn, 2014). Insomnia causes irritability and fatigue as well as reduced productivity, increased absenteeism,

increased morbidity, and increased health care costs (Buysse, 2013). Most studies examining the relationship between insomnia and ADHD have been performed in children and adolescents, and the few studies addressing insomnia in adult ADHD have given conflicting results (Cohen-Zion & Ancoli-Israel, 2004; Owens, 2005). One study found that more than half of adults with probable ADHD fulfilled the criteria for insomnia (Voinescu, Szentagotai, & David, 2012). In another study, four of five adults with ADHD reported having sleep problems, irrespective of sex and subtype (Fisher et al., 2014), indicating the importance of addressing insomnia in adult ADHD.

## 1.6 Aggressiveness

Aggressiveness can be defined as any behavior directed toward an individual with the immediate intent to cause harm (Anderson & Bushman, 2002). Aggression plays an important role in evolution, both in defense and predation and is part of the normal behavioral repertoire of most, if not all, species. However, when exhibited in humans in the wrong context, aggression can lead to social maladjustment and crime. Clearly, aggression has a high cost to individuals and to society, yet there remains considerable uncertainty about the best ways to manage aggressive behavior (Asherson & Cormand, 2016). As both low and high levels of aggression can be detrimental to survival and reproduction, it has been hypothesized that aggression is under stabilizing selection, which implies that variation in aggression will show significant heritability (Asherson & Cormand, 2016).

Aggressiveness can be a serious problem, both at a societal level and individual level, causing significant (social) impairment for patients and distress for their surroundings. Violence, which is strongly related to aggressiveness, is the sixth leading cause of burden of disease for people aged 15–44 years worldwide (WHO, 2008). To date, most interventions designed to reduce violence risk typically have small effects, reflecting our limited understanding of its causes and stressing the need for further studies (McGuire, 2008; Terrie E. Moffitt, 2005).

As a complex phenomenon, aggressiveness spans across numerous facets of human behavior, ranging from emotional lability and temperamental traits (e.g., hot-tempered, short fuse, irritable) to physical violence (Lesch, Araragi, Waider, van den Hove, & Gutknecht, 2012). These traits are frequently found among youth with ADHD. Youth with ADHD often have co-existing disorders, some of which are closely related to aggressiveness and violence, such as conduct disorder (CD) and/or oppositional defiant disorder (ODD) and disorders characterized by symptoms defined within the broader term of antisocial behavior (Dalsgaard, Mortensen, Frydenberg, & Thomsen, 2002). These disorders put youth with ADHD at high risk of problems associated with aggressiveness in adulthood (Klassen, Katzman, & Chokka, 2010), especially when the aggressive behavior has an early onset (Hofvander, Ossowski, Lundstrom, & Anckarsater, 2009). This can be illustrated by the fact that around 30% of youth and 25% of adult prison inmates are found to qualify for an ADHD diagnosis (Young, Moss, Sedgwick, Fridman, & Hodgkins, 2014). Studies of childhood aggressiveness in adults can, therefore, be of great importance to improve our understanding of adult ADHD.

## 1.7 Genetics of aggressiveness in ADHD

The high heritability of neuropsychiatric disorders (46.3% as a class) (Polderman et al., 2015) is an enticing clue that genetics may provide a neurobiological framework for comprehending conditions that have eluded biological understanding for decades. Heritability refers to the proportion of phenotypic variance due to genetic factors (Gandal, Leppa, Won, Parikshak, & Geschwind, 2016). Heritability estimates indicate that inherited genetic variants contribute substantially to disease liability, often more so than early environmental influences or non-inherited, de novo mutations. However, clearly gene and environment usually contribute together (Gandal, et al., 2016). In facts, studies have found ADHD to have a particularly high heritability, estimated to be up to 88% across the lifespan (Franke et al., 2012; Larsson, Chang, D'Onofrio, & Lichtenstein, 2013).

The genetic and environmental contributions to the variation and longitudinal stability in childhood aggressive behavior has been assessed in two large twin cohorts; the Netherlands Twin Register (NTR), and the Twins Early Development Study (TEDS; United Kingdom) (Porsch et al., 2016). These studies find between 50-80% heritability of aggressive behavioral problems, and based on these longitudinal samples the authors conclude that childhood aggression is a stable trait. Further, they report that individual differences at various ages are mainly due to genetic differences between individuals. Additionally, genetic influences are also found to be the major source of stability in aggressive behavior throughout childhood. Based on the large sample size, the authors furthermore conclude that shared environmental influences are significant, especially for boys (Porsch, et al., 2016).

Much of the genomic DNA sequence differences between any two people are common (frequency >5%) single nucleotide polymorphisms (SNPs). A genome-wide association study (GWAS) is a hypothesis-free test to identify genetic variants involved in disease risk. GWAS typically targets millions of SNPs, common variants of small effect (Akutagava-Martins, Rohde, & Hutz, 2016). GWAS does not identify a gene per se, but a region that is associated with disease status. Because of localized patterns of correlation (linkage disequilibrium), a sample of 250,000 to 500,000 of these SNPs can test the hypothesis that one or more common variants explain part of the genetic risk for a disease (Cichon et al., 2009). When genome-wide significance is achieved (often defined as $P < 5 \times 10{-}8$), the effective confidence interval surrounding a 'lead' or 'index' SNP (with the lowest P-value in a given locus) is set by the surrounding region of linkage disequilibrium, which spans on average ~40 kb, but is highly variable throughout the genome. Identifying the underlying 'causal' variant(s) within a target region, and its biological effect, is typically an enormous challenge (Gandal, et al., 2016). A majority of common disease-associated genetic variation lies outside coding regions and is enriched in regulatory elements such as enhancers or promoters. Variants in these regulatory elements act to modulate the expression and splicing of distal gene targets, potentially with large effect (Gandal, et al., 2016). Although no single polymorphism reached genome-wide significance in a study of Norwegian cases and controls (Zayats et al., 2015), recent meta-analyses

using larger samples sizes from multiple populations have shown many genome wide significant findings (Demontis et al., 2017).

Given that ADHD and aggression often co-occur and that both traits are highly heritable, twin studies have noted the possibility of shared genetic etiology between ADHD and aggression. A common genetic factor has been reported among ADHD and symptoms of aggression in 9–10-year-old children (Tuvblad, Zheng, Raine, & Baker, 2009). Likewise, it has been suggested that impulsivity and aggression are genetically mediated to a similar extent (Seroczynski, Bergeman, & Coccaro, 1999).

The estimates and expressions of aggressiveness are influenced by the age of the study participants. The literature reports stability of aggressiveness between childhood and adulthood, with adolescence as a transient period with little stability in this trait (Terrie E. Moffitt, 2005). Genes seem to explain little variation in adolescent aggression, but are likely to account for individual differences in childhood and adult aggression (Lyons et al., 1995). Also, given higher levels of aggression in males and higher genetic load in males with antisocial behavior compared to females, it is an open question whether genetic propensity is of greater importance in one sex over the other (Miles & Carey, 1997; Tuvblad & Baker, 2011). Interestingly, similar considerations of age and sex effects are also present in studies of ADHD as well as when ADHD is co-morbid with aggressive behavior (Faraone, et al., 2015; Faraone, Biederman, Keenan, & Tsuang, 1991). As aggressiveness and ADHD are highly linked, aggressiveness may turn out to be an ADHD endophenotype. An endophenotype may be defined as an intermediary between a biological substrate and a disorder, one that lies in the gap between gene and disease process, so that by examining their genetic basis we would understand something about the biology of a psychiatric disease (Flint & MunafÒ, 2007). Endophenotypes may be divided into two different classes: those that simply share genetic factors with the phenotype thus being indicative of pleiotropic effects or, more importantly, those that act as mediating factors. In the latter case, the causal pathways from genetic variants to phenotype necessarily pass through the endophenotype (Akutagava-Martins, et al., 2016). An endophenotype may be not exclusive for a disorder, but may be associated

with a range of genetically related pathologies. An important caveat to mention is that several different aggression measures have been utilized to assess the genetic and environmental influences on its development (Veroude et al., 2015), reflecting that there is no consensus regarding its definition (Ramirez & Andreu, 2006).

## 1.8 Aims of the present thesis

The overall aim of the thesis was to investigate symptom domains in adults with ADHD including and beyond the ones described in the Diagnostic and Statistical Manual of Mental Disorders (DSM).

Paper I) investigated the psychometric properties and the clinical utility of self-reported childhood symptoms (WURS) versus current symptoms (ASRS) using two frequently used symptom checklists for adult ADHD.

Paper II) investigated the prevalence and clinical correlates of insomnia in adult ADHD. Using a case-control sample, we studied the importance of insomnia and the effects of symptoms of ADHD on its prevalence in both an adult ADHD sample and in random population controls.

Paper III) investigated the genetic components of aggressiveness in ADHD. Using a GWA design with international samples of youth and adults with ADHD, we investigated the genetic substrate of childhood aggressiveness in adult ADHD.

# 2. MATERIALS AND METHODS

## 2.1 Participants

This thesis is mainly based on a case-control sample of a nation wide sample of adults with ADHD and a population based control sample. Paper III represents an international collaboration adding European samples of both youth and adults with ADHD.

### 2.1.1 Patients

The aim of the collection of the main adult ADHD sample was to gather a naturalistic sample as encountered in general clinical practice. The prescription of central stimulants for adults was legally restricted in Norway until 1997. From October 1997 until May 2005, adults (≥18 years) with ADHD (or Hyperkinetic Disorder according to the ICD system which is the official diagnostic manual in use in Norway) were allowed to receive central stimulants only after a systematic and mandatory diagnostic evaluation by one of three regional diagnostic committees, i.e. the Expert Committees for Hyperkinetic Disorder/ADHD. Patients were referred to the committees by their psychiatrists, general practitioners or hospital doctors. Each of the diagnostic committees consisted of three to five clinicians (mainly psychiatrists and neuropsychologists), with special experience on diagnosing ADHD in children and adults. A few pioneering clinicians at that point also diagnosed and treated adult patients with ADHD in addition to the committees, by special permissions. The data obtained by the Expert Committees of Hyperkinetic Disorder/ADHD were not primarily designed as a patient registry, but due to the compulsory referral system for adults considered for central stimulant treatment for ADHD, it became a national cohort of adult ADHD patients. During almost eight years, the committees handled more than 5000 patient referrals, and nearly 70% were recommended for treatment (n = 3397). In May 2005, National Guidelines for Diagnosing Lifespan ADHD were implemented by the Norwegian Health Authorities. Since then the diagnosis and

treatment of adult ADHD was handled by individual specialists in psychiatry and clinical psychology without the direct involvement of the former expert committees.

### *Diagnostic assessment*

The referral procedure to the expert committees required both thorough descriptions of the patient's current symptoms and functioning and informant information about childhood behavior and functioning. Results from physical and psychiatric examinations were also required. The expert committees then reviewed the patient's records to confirm, or disprove, the diagnosis of ADHD. A formal conclusion was made recommending or not recommending treatment with central stimulants, based on a confirmed diagnosis and the absence of contra-indications for such treatment (mainly psychosis or ongoing substance abuse). The diagnostic assessment was done according to the ICD-10 research criteria for Hyperkinetic Disorder, with two modifications; allowing the inattentive subtype as sufficient for the diagnosis and allowing for the presence of comorbid psychiatric disorders as long as the criteria for ADHD were fulfilled and present before the appearance of the comorbid disorder. This diagnostic assessment strategy was chosen as a compromise between the fact that the ICD-10 was the official diagnostic system used in Norway, and the need to have an assessment comparable with the international DSM-IV standards.

Recruitment to the Norwegian adult ADHD patient sample in this thesis was based on the address lists from the Expert Committees. Patients all across Norway were invited directly by posted mail to join the project. A total of 1700 invitations were sent to patients (mainly diagnosed after the year 2000) from 2005 to 2007. By December 2007, 338 (19.9%) of the invited patients had returned completed questionnaires and were included in the study. Subsequently, clinicians (general practitioners, psychiatrists and clinical psychologists) from all over Norway were also invited to recruit patients with a verified diagnosis of adult ADHD. The inclusion criteria for these subsequently recruited patients were 1) a diagnosis of ADHD/Hyperkinetic Disorder received in adulthood confirmed by a clinician outside the project according to DSM-IV or ICD-10 criteria, and 2) age ≥18 years at the time of inclusion. There were no formal exclusion criteria.

### 2.1.2 Controls

The control sample included individuals randomly recruited from the general population in Norway having the same age range as the Norwegian adult ADHD patients. For this purpose, the Medical Birth Registry of Norway (MBRN) was used. The MBRN is based on compulsory notification of all births in Norway from 1967. During January and March 2007, 2163 invitation letters were sent out to a randomly selected sample of the Norwegian population between 18 and 40 years old, based on the MBRN. By December 2007, 417 of these (19.3%) had responded with completed questionnaires and were included in the study. Since 2008, patients and controls received reminders by mail or telephone, resulting in gradually increasing response rates. Nearly 300 patients and controls also returned symptoms score questionnaires at multiple time points (data not included in this thesis).

## 2.2 Assessment

All participants included in paper I and II filled in questionnaires for past and current ADHD symptoms, symptoms of comorbid lifetime disorders and problems, as well as sociodemographic data including educational and occupational activity. A sample of blood or saliva was collected for genetic analysis, used in paper III. The following symptom checklists were used in the papers:

### 2.2.1 WURS – Wender Utah Rating Scale (Paper I and III)

The WURS is a 25-item questionnaire used for retrospective assessment of childhood symptoms of ADHD in adults (Ward, et al., 1993). For each item, the participant was asked to evaluate if she/he as a child was (or had) a specific symptom and to rate it according to the following four response categories: “not at all/very slightly” (0), “mildly” (1), “moderately” (2), quite a bit” (3), or “very much” (4). The arithmetic sum of the responses yields a total range from 0 to 100. Internal consistency for the WURS measured by Cronbach’s alpha was .967. A principal component analysis (PCA) was run to to determine its factor structure, producing three factors: 1) Aggressiveness and Social Problems, 2) Learning and Attention Problems, and 3)

Dysthymia. The adult measure of childhood aggressiveness in the aADHD samples was derived from the highest loading items on the first factor the WURS.

### 2.2.2 ASRS – Adult ADHD Self Report Scale (Paper I and II)

The Adult ADHD Self-Rating Scale (ASRS) is the World Health Organization's (WHO) official screener for ADHD, and consists of the 18 symptoms listed in the DSM-IV criteria A (Ronald C. Kessler, et al., 2005). Nine items assess symptoms of inattention (ASRS-IA) and nine items assess hyperactive/impulsive symptoms (ASRS-HI), respectively, rated on a scale from 0 to 4 (0 = never, 1 = rarely, 2 = sometimes, 3 = often and 4 = very often), yielding a total range of 0–72. The total scores on the two subscales of IA and HI were used as continuous measures of the two main symptom domains of ADHD. Cronbach's alpha was 0.92 on the ASRS- IA subscale and 0.92 on the ASRS-HI subscale.

The ASRS version used in this study corresponds to the one used by the Expert Committees of Hyperkinetic Disorder/ADHD. It was originally translated and re-translated (by an English-native employee of the Norwegian Department of Health and Social Welfare) and has later been evaluated by four experienced psychiatrists from the adult ADHD project group.

### 2.2.3 BIS – Bergen Insomnia Scale (Paper II)

The Bergen Insomnia Scale (Pallesen et al., 2008) was constructed based on the diagnostic criteria for insomnia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1). It includes six items rated on an 8-point scale, ranging from 0 to 7 days per week during the last month. The first four assess sleep impairment (criteria A of the DSM-IV) (has it taken you more than 30 min to fall asleep after the light was switched off; have you been awake for more than 30 min between periods of sleep; have you awakened more than 30 min earlier than you wished without managing to fall asleep again; have you felt that you have not had enough rest after waking up). The last two items refer to daytime sleepiness/tiredness that has affected your participation at school or work, and your dissatisfaction with

sleep respectively (criteria B). The criteria for a DSM-IV diagnosis of insomnia are fulfilled if a respondent reports ≥3 days per week on at least one of the A-items and ≥3 days per week on at least one B item. In addition, a total composite score is calculated by adding together the scores for each item, with a possible range of 0–42. The BIS thus provides both a dichotomous score for the presence of insomnia and a dimensional symptom score. The Cronbach's alpha of the BIS scale used in the present study was 0.86.

In addition, the patients answered 31 questions concerning sociodemographic factors including educational and occupational level, past and present medical treatment and lifetime history of comorbid disorders. They were also asked about the presence of ADHD and comorbid/other disorders in first degree family members. All patients were asked to give a form to their doctor (mainly psychiatrists) with questions regarding diagnosis and medical treatment. These questionnaires were specifically designed for the adult ADHD project.

## 2.3 Statistics

A Principal Component Analysis (PCA) was run to determine the latent structure of the WURS. The PCA was run with Varimax rotation and yielded three factors with Eigen values above one. This factor structure was generated as part of paper I. The aggressiveness factor in paper III was derived from the factor explaining the greatest amount of variance in responses to the WURS (30.7%). The highest loading items (0.74–0.82) in this factor all represented prototypical elements of aggressiveness ( "temper outburst/tantrums," "angry," "hot- or short-tempered/low boiling point," "disobedient with parents/ rebellious/sassy," "losing control of myself," and "irritable").

In paper I, the following calculations were included: Sensitivity = ∑ True positive / ∑ Disorder, Specificity = ∑ True negative / ∑ No disorder, Positive Likelihood Ratio = Sensitivity / (1 – Specificity), Negative Likelihood Ratio = (1 – Sensitivity) /

Specificity, Diagnostic Odds Ratio = Positive Likelihood Ratio / Negative Likelihood Ratio.

**Table 3. Screening properties**

| | Disorder decided by "Gold Standard" | | | |
|---|---|---|---|---|
| Test result | | Disorder | No disorder | Total |
| | Positive test | A (True Positive) | B (False Positive) | T (Test positive) |
| | Negative test | C (False Negative) | D (True Negative) | T (Test negative) |
| | | T (Disorder) | T (No disorder) | (Grand) Total |

In paper I we used Receiver Operating Characteristics Area Under the Curve (AUC), Diagnostic Odds Ratio (DOR) and Likelihood Ratio (LH) to obtain statistics that were unaffected by prevalence in our study sample (rather than e.g. Positive predictive value, which is biased by the sample prevalence of the disorder).

### 2.3.1 Genome-wide association (GWA) of aggressiveness (paper III)

In the aADHD sample, single nucleotide polymorphisms (SNPs) were tested for association with the WURS-derived measure of aggressiveness in the form of linear regression carried out using post-imputation dosage data (Purcell et al., 2007). Regression models were adjusted for age and sex. Genotype data of each site were first processed individually. The results were then combined with the use of fixed-effects inverse variance meta-analysis (Willer, Li, & Abecasis, 2010). Only SNPs with minor allele frequency (MAF) equal to or above 1% and imputation INFO measure equal to or above 0.6 were included in the analyses. Genomic control, QQ

plotting, and regional plotting of top loci were applied to check the integrity of test statistics (Cuellar-Partida, Renteria, & MacGregor, 2015; Devlin & Roeder, 1999). The genomic inflation factor was calculated (Willer, et al., 2010). A genome-wide significance threshold of 5.00E-08 was adopted to correct for multiple testing.

GWA analyses of irritable and defiant/vindictive dimensions of ODD in cADHD sample was performed in PLINK software in the form of linear regression adjusted for sex and age (Purcell, et al., 2007). Details of the analyses are described elsewhere (Aebi et al., 2016).

## 2.4 Ethics

All participants filled in and signed a written informed consent form. The Adult ADHD project was approved by the Regional Committee for Medical Research Ethics of Western Norway IRB # 3 (FWA 00009490, IRB 00001872) and the Norwegian Data Inspectorate. The participants received NOK 250 for returning blood or saliva samples and questionnaires. All international samples were also ethically approved, as described in paper III.

# 3. RESULTS

## 3.1 Paper I

In Paper I we found that both the WURS and the ASRS had excellent discriminatory values, with an AUC of .956 (95% CI: .946 - .965) for the WURS, and .904 (95% CI: .888 - .921) for the ASRS. The optimal cut-off balancing the trade-off between sensitivity and specificity for the respective scales may vary depending on the aims in the specific clinical or research setting. The results showed a three-factor structure of the WURS in line with previous research (Caci, Bouchez, & Baylé, 2010; McCann, Scheele, Ward, & Roy-Byrne, 2000; Stanton & Watson, 2016), with details differing somewhat at item level. We named the three WURS factors Aggressiveness and Social Problems, Learning and Attention Problems and Dysthymia, respectively. The ASRS had as expected a two-factor structure, with inattentive symptoms in the first factor and impulsivity items having the highest loadings on the second hyperactivity/impulsivity factor. The internal consistencies of the two instruments were high. Our findings fit well with previous cut-off suggestions by Ward, et al. (1993) for the WURS and Kessler, et al. (2005) on the full 18 item ASRS (table 3).

Contrary to the critique raised against the WURS for lacking content validity (i.e. diverging from the DSM symptom criteria) (Stanton & Watson, 2016), we found that it had a very high criterion validity (i.e. being highly predictive of an ADHD diagnosis). Furthermore, we found that the very items driving this discriminatory ability were part of the Learning and Attention problems factor of the WURS. The items represent developmentally important behaviors well recognized as core ADHD symptoms (WURS 1: Concentration problems, Easily distracted and WURS 7: Trouble with stick-to-it-tiveness, not following through, failing to finish things started).

## 3.2 Paper II

In Paper II we used the Bergen Insomnia Scale (BIS) to measure insomnia and the Adult ADHD Self-Report Scale (ASRS) to assess ADHD symptom domains. We found that insomnia was far more frequent among adults with ADHD (66.8%) than in the population controls (28.8%) ($P < 0.001$). Insomnia was more common in adults with the combined subtype of ADHD than in those with the inattentive subtype (79.7% and 55.6%, respectively) ($P = 0.003$). For self-reported current ADHD symptoms, inattention was strongly correlated to insomnia. Patients currently using stimulant treatment for ADHD reported a lower total insomnia score compared to patients without medication ($P < 0.05$). Regression analyses showed that the self-reported IA subscale of the ASRS significantly contributed to explain an insomnia diagnosis in the ADHD and the control group, while both the ASRS-HI and ASRS-IA subscales contributed significantly when the total BIS score was used as an outcome variable. Our findings support previous findings indicating that the severity of sleep problems are positively related to the severity of ADHD symptoms (Schredl, Alm, & Sobanski, 2007). The finding that inattentive symptoms had a higher correlated with insomnia symptoms among the controls than in the ADHD patients, suggests that a close association between inattentive symptoms and insomnia is not restricted to adults with an ADHD diagnosis. However, without any evidence of a directional relationship, inattentive symptoms may as likely be a consequence of sleep problems as the other way around.

## 3.3 Paper III

In Paper III we conducted a Genome Wide Association (GWA) study of a childhood aggressiveness phenotype in an adult ADHD sample, and compared this with GWA signals of dimensions of oppositionality (defiant/vindictive and irritable dimensions) in an adolescent sample. In total, 1,060 adult patients as well as 750 children and adolescents with ADHD were available for the analyses. The age ranges in the aADHD samples were 17–75 in the German sample, 18–57 in the Norwegian sample, and 17–60 in the Spanish sample. In the cADHD sample, the age range was 5–17.

GWA analyses revealed no genome-wide significant hits in either the aADHD sample nor in the cADHD sample, as no single polymorphism reached genome-wide significance (P<5.00E-08). No hits remained significant among protein-coding genes investigated after correcting for multiple comparisons. We did however identify a number of biologically interesting markers using less stringent significance levels. The strongest signal was noted for rs10826548 within a long non-protein coding RNA gene. Such non-protein coding RNAs play a critical role in regulation of gene expression, and have been associated with neuropsychiatric disorders, including ADHD. The second most significant loci was identified as rs35974940 in the neurotrimin gene. This is a protein-coding gene, predominantly expressed in the central nervous system. Taken together, the study identified biological markers provide targets for further genetic exploration of aggressiveness across psychiatric disorders.

# 4. DISCUSSION

## 4.1 Main findings

The studies show that ADHD patients suffer extensively, both from recognized core symptoms in the DSM, and from symptom domains often labeled as comorbidities. We found that the WURS with its broader range of symptoms identified adult ADHD patients even better than the DSM derived ASRS. Insomnia was found to be a common problem in the adult ADHD sample, with two out of three patients qualifying for a diagnosis based on the BIS. Albeit we did not find statistically significant GWAS hits, aggressiveness may be a promising endophenotype in what we today consider the ADHD landscape. Taken together, the results in the present thesis suggest that we need to broaden our approach and scope when investigating and treating patients with ADHD. We need to go beyond the classic symptom domains of inattention, hyperactivity and impulsivity, and recognize that patients qualifying for an ADHD diagnosis also have other, important impairing symptom domains. These domains, such as aggressiveness, insomnia and learning problems, need to be addressed in order to successfully help the adult ADHD patient.

The use of the word “diagnosis” in psychiatry carries an implicit and misleading connotation that stems from the use of the word in other areas of medicine, where diagnostic tests and diagnostic signs and symptoms are validated against an independent criterion for determining the presence or absence of the disorder (Wender, 1995). In the absence of well-validated and universally accepted diagnostic criteria, there is a risk for both overdiagnosis and underdiagnosis. This problem is characteristic for broader parts of medicine, not purely in the context of ADHD. However, this is of particular significance in a disorder for which controlled stimulant substances with potential for abuse are first-line treatments (McGough & Barkley, 2004). Thus, paper I is important in that it addresses the psychometric properties of two different screening instruments used in parallel on a well validated sample of clinically ascertained adult ADHD patients and a matched/randomly selected population control sample. Our findings add to the discussion as to what the defining

features of adult ADHD really are, and regardless of ongoing controversy point to the fact that clinical management of this patient group requires a broader focus than the narrow DSM criteria for ADHD alone.

## 4.2 Is there such a thing as ADHD?

ADHD is the name of a syndrome, but applying the same name to problems suffered by a group of individuals does not necessarily mean that "they have the same thing". With the inherent lack of independent criteria and biological substrates, it could be helpful if we expended less effort on trying to select the exact signs and symptoms that characterize the illness. There is no "pure" ADHD and further phenomenological redefining of symptoms chosen "to make" the diagnosis is not based on independent characteristics at a different level of discourse, meaning that the diagnosis as it is now is based upon clinical descriptions, not etiological considerations or a pathophysiological foundation (Wender, 1995).

Although issues such as lacking objective criteria for an ADHD diagnosis, as well as the problems regarding comorbidities, it is important to distinguish between validity and utility in considering psychiatric diagnoses. Diagnostic categories defined by their symptoms should be regarded as valid only if they have been shown to be discrete entities with natural boundaries that separate them from other disorders. Although most diagnostic concepts have not been shown to be valid in this sense, many possess high utility by virtue of the information about outcome, treatment response, and etiology that they convey. They are therefore helpful working concepts for clinicians (Kendell & Jablensky, 2003).

ADHD may be more an indication of a general psychopathology factor (Caspi et al., 2014; Kotov et al., 2017), an emerging view that may prove to be more harmonious than the traditional categorical entities proposed by diagnostic systems such as the DSM and ICD. In fact, recent genetic findings from genome wide association studies illustrate that most genetic liability to psychiatric disorders are shared across categorical boundaries (Cross-Disorder Group of the Psychiatric Genomics, 2013;

Cross-Disorder Group of the Psychiatric Genomics et al., 2013). One of the most consistent findings in recent psychiatric research is that of shared genetic liability, with several common factors identified across disorders. What remain to be determined are the specific factors that result in a given phenotype rather than another (Akutagava-Martins, et al., 2016). Although ADHD has been a focus of attention for clinicians for centuries with changing symptom descriptions, an issue that seems to remain constant is the dysregulation seen across several brain-based behavioral domains such as attention, impulsivity and activity.

Like most psychiatric conditions, ADHD originates from important genetic vulnerabilities and other forces. It's a far different world from half a century ago, when environmental and cultural theories were in ascendancy. But the undeniable role of biology cannot blind us to the fact that genetic tendencies unfold through interactions with a host of micro (families; schools) and macro (policy; health care) processes. Viewing ADHD as entirely biological is as misleading as it is to claim that ADHD is simply a social construction or the result of overly lax parenting (Hinshaw & Scheffler, 2014). Interestingly, a "low ADHD trait" has not been found to be significantly heritable, but rather very malleable depending on environmental factors (Greven et al., 2016).

## 4.3 Categories vs. Dimensions

The ideal of medicine is to find ever more specific biomarkers and narrow categories in the pursuit of optimizing diagnosis and treatment. However, longitudinal studies looking at discretely defined psychiatric disorders together have found these to be better explained with one higher order general psychopathology dimension. This dimension has been labeled "the p factor" as it is conceptually parallel to a familiar dimension in psychological science: the g factor of general intelligence (Caspi, et al., 2014). Higher p scores are associated with more life impairment, greater familiality, worse developmental histories, and compromised early-life brain function. The p factor explains why it is challenging to find causes, consequences, biomarkers, and treatments with specificity to individual mental disorders (Franke, 2016). As such, in

relation to existing diagnostic categories, transdiagnostic approaches may improve research (Caspi, et al., 2014).

As with autism, clinicians once thought that a person either "had" or "didn't have" this condition, but it is now well known that autistic symptoms (just like those of ADHD) are arrayed on a continuum (Posserud, Lundervold, & Gillberg, 2006). This "spectrum" notion raises the provocative idea that a large number of people without diagnosable ADHD may benefit from ADHD-linked treatments, like medication. This contention is the source of major controversy in light of the diversion of stimulants to those without a diagnosis. It also means that many people have "a bit" of ADHD (or, for that matter, of depression or autism), a truth that, when it becomes better known, could have implications for reducing stigma (Hinshaw & Scheffler, 2014).

Awareness of heterogeneity is especially crucial for understanding relations between development and psychopathology, because developmental changes and differences are so incompatible with static diagnostic categories. By contrast, hierarchical dimensional models can take account of heterogeneity, potentially important similarities, individual differences, and developmental changes in psychopathology (Achenbach, 2015). The Hierarchical Taxonomy of Psychopathology (HiTOP) is a dimensional alternative to traditional nosologies (Kotov, et al., 2017). HiTOP is a collaborative effort of nosologists from various mental health disciplines to improve the organization, description and measurement of psychopathology. Its objectives are to advance the classification of psychopathology to maximize its usefulness for research and clinical practice. The HiTOP aims to address limitations of traditional nosologies, such as the DSM-5 and ICD-10, including arbitrary boundaries between psychopathology and normality, often unclear boundaries between disorders, frequent disorder co-occurrence, heterogeneity within disorders, and diagnostic instability (https://medicine.stonybrookmedicine.edu/HITOP).

In a response to the longstanding problematic lack of biologically meaningful psychiatric diagnoses, the National Institute of Mental Health in the USA has

launched the Research Domain Criteria (RDoC) initiative (Bruce N. Cuthbert, 2014; B. N. Cuthbert & Insel, 2013; Morris & Cuthbert, 2012). Perhaps the most important point about RDoC is that its essence is to provide a broad framework for conducting research on mental disorders from a wholly new perspective. In this sense, what is most important about RDoC is not the list of constructs and the matrix per se, but the idea of freeing up investigators to pursue exciting translational research questions driven by neuroscience and behavioral science rather than by constraining sets of symptom clusters (Bruce N. Cuthbert, 2014). Disorders may be the product of shared risk factors that lead to abnormalities in intersecting drives such as motivation and reward anticipation, which can be measured and used to place people on one of several dimensions (Adam, 2013).

In applying this new model to mental health research, a key first step is to identify and systematically examine transdiagnostic symptom dimensions that are both clinically meaningful and amenable to RDoC mapping. Aggressive behavior and violence, along with related tendencies (e.g., anger, hostility), are observed in persons with various mental health problems (Verona & Bresin, 2015), and may serve as a transdiagnostic symptom dimension. Insomnia may be another meaningful transdiagnostic process, as a process that is common across diverse psychiatric disorders (Allison G. Harvey, 2008).

## 4.4 Patients have impairments, not purely symptoms

An important element to consider here is that whereas we in research generally are more concerned with symptoms, wanting pure dimensions that span from the normal range to the extreme, in reality, clinical patients are hallmarked by their functional impairment, criterion D of the ADHD diagnosis (Gordon et al., 2006). Diagnosing ADHD based primarily on symptom reports assumes that the number/frequency of symptoms is tied closely to the impairment imposed on an individual's functioning. That presumed linkage encourages diagnosis more by DSM style symptom lists than well-defined, psychometrically sound clinical assessments. In four separate, large-scale ADHD research samples the average correlation between symptoms and

impairment accounted for less than 10% of variance, and symptoms never predicted more than 25% of the variance in impairment (Gathje, Lewandowski, & Gordon, 2008; Gordon, et al., 2006). When these researchers parsed the ADHD group according to a measure of current symptoms, the sample size shrunk by 77% when a criterion-based measure of impairment was added. The partial unlinking of symptoms and impairment has implications for decisions about the diagnostic process, research criteria for participant inclusion, prevalence estimates, gender ratios, evaluation of treatment effects, service delivery, and many other issues (Gathje, et al., 2008; Gordon, et al., 2006).

Personally I wonder if not indeed impairment is part of why so many psychiatric disorders show shared genetic liability, as a final common pathway/end result, and indeed may be orthogonal to more "successful" adaptations of "extreme" ends of traits and behavioral dispositions. Such as being highly energetic, perhaps similar to an "ADHD" phenotype but not impairing to a group of highly successful people, who are able to harness this otherwise volatile energetic disposition.

## 4.5 Nature has not read the DSM

Classifications are cognitive structures imposed on data to achieve particular goals. Given the complexity of human psychology, biology, and illness, any classification in these realms is likely to be plagued by stubborn bits of data that refuse to fit neatly into uniform, well-ordered classes (Hyman, 2010). The current diagnostic framework, established with the DSM-III in 1980, has served both research and clinical practice in the decades that have elapsed since its inception (Morris & Cuthbert, 2012). It is difficult to imagine anything like the advances that have occurred over that time without having a common language and set of diagnostic referents. As diagnosis across all areas of medicine accelerates into an age of genetics and microbiology for understanding disease trajectories, the very success of the DSM/ICD approach is perhaps the major obstacle to considering substantive changes (Morris & Cuthbert, 2012). As genetic research progresses and the lines between established categories are blurred out, I expect future nosologies will look quite different than they do today

(Adam, 2013; Cross-Disorder Group of the Psychiatric Genomics, 2013; Cross-Disorder Group of the Psychiatric Genomics, et al., 2013).

Comorbidity has been found to be so extensive among DSM-IV diagnoses as to forcefully raise questions about the underlying structure and assumptions of the classification system (Hyman, 2010). The open question raised by these observations is whether individuals with comorbidity within a family of disorders are better understood as having two or more distinct DSM disorders or as having a single disorder in which complex etiological factors give rise to diverse symptom complexes that may change with time and environmental exposures (Hyman, 2010).

The reliance on biologically heterogeneous categories as the gold standard for diagnosis has clearly precluded the identification or validation of biomarkers. Although one could imagine revising the diagnostic categories to align with biological discoveries, so far the field has essentially excluded biological findings that do not map on to the current heterogeneous categories of symptom clusters (B. N. Cuthbert & Insel, 2013). The stark reality is that no one has yet agreed on how best to define and diagnose mental illnesses. DSM-5, like the two preceding editions, places disorders in discrete categories such as major-depressive disorder, bipolar disorder, schizophrenia and obsessive–compulsive disorder (OCD). These categories, which have guided psychiatry since the early 1980s, are based largely on decades-old theory and subjective symptoms (Adam, 2013).

However, introducing new nosological systems invites the creation of competing diagnostic systems, which in turn limit the comparability and generalizability of scientific research findings (McGough & Barkley, 2004). I think this is an important caveat, which may help explain why clinicians and clinical researchers may be reluctant to changing nosologies and abandon established categories. Even as science progresses, the implementation of new findings and conceptualizations in clinical practice may take time. Thus, it could be beneficial, as I have tried during the thesis, to underline the historical currents of divergent perspectives on diagnostic nosology, as a reminder that the currently supported findings do not necessarily represent an

entirely new way of thinking, but rather confirming other, and unexpected departures from what over time has become mainstream ways of thinking, and consequently diagnosing and treating patients.

The successive editions of the DSM and ICD have revised the categories and criteria in hope of better discriminating between what were assumed to be hundreds of discrete disorders. However, the once plausible goal of identifying homogeneous populations for treatment and research has resulted in narrow diagnostic categories that do not capture clinical reality, symptom heterogeneity within disorders, and significant sharing of symptoms across multiple disorders. The historical aspiration of achieving diagnostic homogeneity by progressive subtyping within disorder categories no longer seems sensible. Like most common human ills, mental disorders are heterogeneous at many levels, ranging from genetic risk factors to symptoms (American Psychiatric Association, 2013). Despite the problems posed by categorical diagnoses, the DSM-5 Task Force concluded that it was scientifically premature to propose alternative definitions for most disorders at the time when the DSM-5 was published (American Psychiatric Association, 2013). Thus, in the latest version of the DSM, the organizational structure is retained to serve as a bridge to new diagnostic approaches without disrupting clinical practice or research (American Psychiatric Association, 2013).

## 4.6 Strengths and limitations

The studies in this thesis are mainly based on an adult ADHD sample ascertained in adulthood, meaning that it is uncertain whether the patients included would have obtained a childhood diagnosis of ADHD, and showed an expected symptomatic trajectory. This is important to note, as some recent studies have put into question the idea of ADHD as a neurodevelopmental disorder, highlighting both discontinuation of childhood symptoms as well as a possible adult onset ADHD phenotype (Agnew-Blais et al., 2016; Caye, Rocha, Anselmi, & et al., 2016; T. E. Moffitt et al., 2015). However, in paper III, our findings of a genetic association with an aggressiveness phenotype was replicated in a childhood ADHD sample, with promising results. The

adult patient samples used in the three papers were clinically ascertained and are likely to represent this patient group. The Norwegian adult ADHD sample had no formal exclusion criteria, allowing for an ecologically representative group of diverse, heterogeneous patients that you would find in the clinic. However, these patients were based on their impairments, leading them to seek out treatment, and not purely their symptoms as discussed above. The population controls were randomly selected from the Medical Birth Registry of Norway, giving a representative picture of their age group. The controls were also not subject to any exclusion criteria. Thus, a strength of this study is that we find a normally distributed range of ADHD symptoms, as displayed in paper I, with some patients having a symptomatic load above what we would define as a clinical threshold. Possibly these are indeed "false negatives", i.e. people with ADHD who should have sought treatment. Or perhaps some of these individuals represent a group with a "true high ADHD symptom score", but without the clinically important aspect of impairment. This uncertainty allows for a dimensional approach, in line with modern diagnostic alternatives.

# 5. CONCLUSION

The results in the present thesis suggest that we need to broaden our approach and scope when investigating and treating patients with ADHD. We need to go beyond the classic symptom domains of inattention, hyperactivity and impulsivity, and recognize that patients qualifying for an ADHD diagnosis also have other, important impairing symptom domains. Other domains, e.g. aggressiveness, insomnia and learning problems, also need to be addressed in order to successfully help the adult ADHD patient. The complexity of impairment characterizing patients with ADHD, with executive dysfunction, emotional lability, insomnia, aggressiveness, dysthymia, and a host of other problems indicate that the narrow symptom domains defined as the core ADHD symptoms in the current DSM may in future revisions have to be broadened, expanded or changed/reconceptualized to better fit the empirical reality of the patients suffering from severe impairment.

# 6. FUTURE PERSPECTIVES

The present thesis indicates that executive dysfunction (Adler et al., 2017; Ustun et al., 2017) such as inattention, affective dysregulation (Adler, et al., 2017; Haavik, et al., 2010; Shaw, Stringaris, Nigg, & Leibenluft, 2014) exemplified by aggressiveness, and insomnia (Allison G. Harvey, 2008) are all central to the ADHD phenotype. Such evidence might point to a shifting recognition in the future diagnostic systems towards a landscape that is more complex and multifaceted than what is currently listed as core symptomatic criteria in the DSM. This is more in line with the p-factor (Caspi, et al., 2014), ESSENCE (Gillberg, 2010), HiTOP (Kotov, et al., 2017) and RDOC (Bruce N. Cuthbert, 2014) approaches, where the presence of what we now identify as ADHD may instigate the clinician towards performing a broader diagnostic evaluation in order to capture the complete picture of the patients' impairing symptomatic domains. Increasingly, a range of disorders are recognized as dysregulations of normal processes (Adam, 2013). Perhaps these features can inspire novel treatment interventions and better patient care by introducing meaningful and important perspectives. Sometime in the future we may have a new field of precision psychiatry (Fernandes et al., 2017), based on increased insight into the underpinnings of human behavior. However, an important point that is often not taken seriously enough in a present characterized by rapid advances in neuroscience, is the importance of careful theoretical and experimental distillation of behavior (Krakauer, Ghazanfar, Gomez-Marin, MacIver, & Poeppel, 2017). An example discussed earlier is the lack of a consensus regarding the definition of aggressiveness (Ramirez & Andreu, 2006). Detailed analysis of tasks and the behavior they elicit is important for discovering the component processes and their underlying algorithms. There are no short-cuts in the trajectories from psychology, cognition, perception and behavior to neurons and circuits, not to mention larger sociohistorical contexts and their influences on behaviors and brains. A correction to a reductionist bias in the neurosciences and in psychiatric research is not only welcome, but necessary if we are to better understand and treat the complex mental health challenges we are dealing with.

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# Paper I

# Comparison of the psychometric properties of the ASRS and WURS scales in discriminating between adults with and without ADHD

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**Abstract**

**Introduction:** Adult Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of inattention and hyperactivity/impulsivity. The present study investigated the psychometric properties of two commonly used screening instruments for adult ADHD; the Wender Utah Rating Scale (WURS) and the Adult ADHD Self-report Scale (ASRS).

**Methods:** The sample contained adults with clinically confirmed ADHD (n = 646) and population controls (n = 908). The 25 item WURS retrospectively assessed childhood symptoms. The ASRS assessed the 18 current defining symptoms of ADHD. Principal component analyses (PCA) examined the factor structure of the two instruments and area under the curve (AUC) analyses assessed discriminatory properties. Likelihood ratios (LH) and diagnostic odds ratios (DOR) were calculated to quantify the discriminatory abilities.

**Results:** PCA confirmed the two factors of inattention and hyperactivity/impulsivity of the DSM while PCA of the WURS yielded three factors labeled *Aggression and social problems*, *Learning and attention problems* and *Dysthymia*. AUC of both WURS (.96, 95% CI: .95-.97) and ASRS (.90, 95% CI: .89-.92) were large, and both discriminated well between adults with ADHD and controls.

**Conclusion:** Both the WURS and the ASRS had excellent properties in identifying adult ADHD, with WURS being superior to the ASRS, possibly because the WURS encompasses a broader range of symptoms than is contained by the DSM, most notably learning problems and aggressiveness.

Key-words: Adult ADHD, Screening Properties, Retrospective Self-Report, Childhood Symptoms, Persistent ADHD, Psychometric properties, ASRS, WURS

## Introduction

Adult Attention Deficit Hyperactivity Disorder (ADHD) is a persistent neurodevelopmental disorder with childhood onset, characterized by inattention, hyperactivity and impulsivity [1]. ADHD has a prevalence of about 5% in childhood [2], with about half persisting into adulthood [3]. However, because contextual demands increase with age, ADHD is often first recognized in adults [4]. Fayyad, Sampson [5] found an overall prevalence of 2.8 % of DSM-IV adult ADHD across a range of nations, spanning from 1.4% in lower income countries to 3.6% in higher income countries. Adult ADHD is associated with e.g. lower educational achievement, incarcerations, unemployment and illicit drug use [3]. Clinical assessment based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria is the gold standard for the diagnosis [6], but short screeners or symptom rating scales provide a quick and easy way of obtaining standardized information to select patients for further examination.

It is important to establish a history of childhood ADHD symptoms, as the pharmacological treatment of ADHD involves regulated substances and as several other disorders that appear in adulthood may display ADHD symptoms (e.g. affective disorders, substance use disorders and sleep disorders) [6]. To add to the complexity, these disorders may often also be comorbid with ADHD. The Wender Utah Rating Scale (WURS) was developed to retrospectively evaluate the presence and severity of childhood symptoms of ADHD in adult patients [7]. The WURS is based on the Utah criteria [8], requiring a childhood history of ADHD including both inattentive and hyperactive symptoms, with one of the following additional symptoms: behavior problems in school, impulsivity, over-excitability and temper outbursts. Secondly, it requires an adult history of persistent attention problems and motor hyperactivity with at least two of the following symptom domains: affective lability, hot temper, stress intolerance, disorganization and impulsivity [7]. The original 61 item

questionnaire was subsequently reduced to the 25 items that best distinguished an ADHD sample from control samples (i.e. healthy controls and depressed patients). Most of the final 25 items are thus not directly tapping into the core ADHD symptoms, but were chosen for their discriminative ability. A WURS-25 score of at least 36 identified 96% of adults with ADHD and 96% of healthy controls [7]. A cutoff of 46 or higher correctly identified 86% of adults with ADHD, 99% of "normal" controls, and 81% of a comparison sample with depression. Several authors have reported a 3-factor structure of the WURS under somewhat different names. McCann, Scheele [9] named the factors *Dysthymia*, *Oppositional/Defiant Behavior*, and *School Problems* while Caci, Bouchez [10] named the factors *Impulsivity/Temper*, *Inattentiveness*, and *Mood/Self-esteem*. Caci, Bouchez [10] also found moderate correlations between WURS and ASRS. Stanton and Watson [11] recently reported factors *Aggression*, *Internalizing Distress*, and *Academic Difficulties* of the WURS in a community sample.

Current symptoms of inattention and/or hyperactivity and impulsivity are also essential for the diagnosis of ADHD to be made in adulthood. The Adult ADHD Self-Report Scale (ASRS) is the official screening instrument of the World Health Organization (WHO) [12], and includes the 18 items ADHD symptoms of the DSM. It is one of the most commonly used screening instruments of current ADHD symptoms in adults. The authors/creators of the ASRS tested several variants of administering the 18 DSM symptoms of ADHD, and concluded that a 6-item version was best suited as general population screen [12, 13]. The authors based their conclusion on blind clinical ratings of DSM-IV adult ADHD in a sample of merely 154 respondents from the US National Comorbidity Survey Replication (NCS-R), oversampling those who reported childhood ADHD and adult persistence [12]. Recently, the same group [14] created an updated 6-item screen of the ASRS replacing two of the 6 items with items on

executive functioning (i.e. not part of the ADHD defining symptoms). They found this to have good psychometric properties as a general population screener. However, another small non-clinical study comparing the short screener to the full 18 items version found the lengthy version to have better psychometric properties [15]. The authors pointed out the need for a direct assessment of the utility of the ASRS in clinical samples, as there is a lack of studies examining the screening properties of the whole ASRS in an adequately large sample of adults with a clinically confirmed ADHD diagnosis and population controls.

The aims of the present study were threefold; First, to establish the validity of the Norwegian translations of the WURS and the ASRS using factor analyses. Second, to examine the psychometric properties of the WURS and the ASRS in a large clinically diagnosed adult ADHD patient sample and population controls. Third, to compare the utility of these instruments to aid the clinical ADHD diagnosis.

## Method

*Participants*

The participants were recruited as part of the "ADHD in Norwegian Adults" project launched in 2004 with the aim to improve knowledge about ADHD in adults concerning etiology, diagnosis, and treatment. The ADHD sample constitute a well-validated group, mainly recruited from a national registry of adults diagnosed in Norway from 1997 to May 2005. The diagnostic assessment was made by expert committees according to the 10$^{th}$ revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [16], with allowances for the subtypes described in the DSM-IV-TR [17]. This was mandatory at that time in Norway for adults to be considered for stimulant treatment. To increase the sample, clinicians nationwide were thereafter asked to refer adults with ADHD

according to the same procedures as the one used by the expert committees. The control sample (18-40 years old at the time of recruitment) was randomly selected from the Medical Birth Registry of Norway (MBRN). The present study included n = 646 clinically assessed adult ADHD patients and n = 908 controls, resulting in a total sample of 1,554 participants. The mean age in the control group was 29.4 (*7.8*) years and 34.0 (*10.3*) years in the ADHD group. There were 59.9% females in the control sample and 48.5% in the ADHD group. For a subset of patients, we also obtained clinician ratings on whether the patients were currently on (n = 420) or off (n = 125) pharmacological treatment for ADHD, as well as if they had been treated for ADHD as a child (n = 89) or not (n = 530). The study was approved by the regional committee for medical and health research ethics, Western Norway.

*Instruments*

The Wender Utah Rating Scale (WURS)

The 25-item version of the WURS [7] assesses childhood symptoms by asking the participants to retrospectively recall the frequency and severity of ADHD symptoms and related problems experienced in childhood. Participants responded to these items using a Likert type 5-point scale according to the following response categories: “not at all/very slightly” (0), “mildly” (1), “moderately” (2), quite a bit” (3), or “very much” (4), giving a possible range of 0-100 points.

The Adult ADHD Self-Report Scale (ASRS)

The ASRS is a brief screening instrument to identify current ADHD symptoms [12]. The scale was developed by the World Health Organization [16] and the Work Group on Adult ADHD [12]. The scale contains the 18 symptoms defining ADHD according to the DSM-IV-

TR and DSM-5 [1, 17]. The severity of the symptoms are reported on a 5-point Likert-type scale (0-4 = never, rarely, sometimes, often, to very often), with a total range of 0 to 72. The ASRS used in the present study was divided into a part A representing symptoms of inattention, and a part B representing symptoms of hyperactivity and impulsivity. The total ASRS score has shown good reliability and validity in both clinical and population samples [18, 19].

*Statistics and analytic plan*

A Principal Component Analysis (PCA) with Varimax rotation was run to determine the latent structure of the WURS and the ASRS, selecting factors with Eigenvalues above one. We calculated receiver operating curves (ROC) including Area Under the Curve (AUC) for the full WURS and ASRS, as well as for the PCA generated factors. The AUC is a preferred measure of concordance rather than Cohen's κ because AUC, unlike κ, is not influenced by prevalence [13].

The likelihood ratios for positive tests (LH+) and negative tests (LH-) and Diagnostic Odds Ratio (DOR) were calculated using formulas from Fischer, Bachmann [20]. The DOR is a measure of a diagnostic test's overall accuracy [21], and unlike positive and negative predictive values, the DOR does not depend on the prevalence of the disease, facilitating comparisons of tests for meta-analyses. A DOR value of 20 or more indicates that an instrument has useful screening properties [20].

Cronbach's alpha was calculated to measure internal consistency in the resulting factors of the WURS and ASRS. SPSS version 24.0 was used for the statistical analyses [IBM 22].

**Results**

The total scores of WURS and ASRS were strongly correlated (full sample r = .78, p < .001; ADHD group r = .36, p < . 001; Controls r = .70 , p < .001). Figure 1 shows the distributions of WURS and ASRS scores in the ADHD and control samples, including the correlation between the two. Mean scores on the ASRS were 45.0 (*12.6*) and 23.0 (*9.8*) among the ADHD group and control group (p < .001), respectively. For the WURS the mean scores were 58.2 (*17.9*) and 17.3 (*13.9*) (p < .001), respectively. The subset of adults with ADHD on current pharmacological treatment reported a significantly lower ASRS score 43.5 (*13.3*) than the off treatment group 48.1 (*10.4*) (p < .001). There was no difference between on the groups on versus off pharmacological treatment on the WURS, 58.0 (*18.3*) versus 58.6 (*17.0*), respectively. There were significant differences between the patients who had been treated for ADHD as a child compared with those who had not on both the WURS and ASRS; Patients treated in childhood scored 55.1 (*18.9*) on the WURS versus 32.5 (*25.2*) (p < .001) for those who had not received treatment in childhood. On the ASRS patients treated as children scored 41.5 (*12.7*) versus those who were not 31.4 (*14.4*) (p = .003).

Factor analyses

The Principal Component analysis generated a three-factor solution to the WURS in the full sample (Table 1) explaining 69.2% of the variance. This solution offered high item loadings on each scale, with a few exceptions. The highest loading items on the first factor were "Temper outbursts, Tantrums" and "Angry", including items of defiant behavior. The highest loading items on the second factor were "Overall a poor student, Slow learner" and "Trouble with mathematics or numbers", also including items of inattention. The items with the highest loading on the third factor were "Anxious, Worrying" and "Sad or blue, Depressed, Unhappy". We thus named the three factors *Aggressiveness and social problems*, *Learning and attention problems* and *Dysthymia*, respectively. Only the item "Unpopular with other

children […]" had ambiguous loading with factor loadings below .50 on all factors. Internal consistency measured by Cronbach's alpha was .967 for the full WURS, and .954 for *Anger and social Problems*, .919 for *Learning and attention problems* and .897 for *Dysthymia*, respectively.

A two-factor solution was generated for the ASRS in the full sample (Table 2), explaining 62.2% of the variance. The first factor included items reflecting symptoms of inattention, the second factor symptoms of hyperactivity and impulsivity. The items reflecting impulsive behavior obtained the highest loadings on the second factor.
Internal consistency measured by Cronbach's alpha was .952 for the full ASRS score, .924 for the Inattentive factor and .918 for the Hyperactivity/Impulsivity factor.

The discriminative ability of the WURS and the ASRS

Figure 2 illustrates the discriminatory values of both the WURS and the ASRS, with an AUC of .956 (95% CI: .946 - .965) for the WURS, and .904 (95% CI: .888 - .921) for the ASRS. The optimal cut-off balancing the trade-off between sensitivity and specificity for the respective scales may vary depending on the aims in the specific clinical or research setting. Table 3 provides cut-off values for 98%, 95%, 90% and 80% sensitivity and specificity, respectively, for both the WURS and the ASRS, including LHs and DORs for each cut-off. Our findings fit well with the cut-off of 36 suggested by Ward, Wender [7] and the cut-off value of 37 for the full 18 item ASRS suggested by Kessler, et al. [12]. Using sum scores from all the factors extracted from PCA, *Learning and attention problems* had the highest AUC of .95 (95% CI .94 - .96), followed by *Aggressiveness and social problems* with .93 (95% CI .92 - .94).

**Discussion**

Both the WURS and the ASRS had excellent screening and psychometric properties, with somewhat stronger properties for the WURS. The results confirmed the three-factor structure of the WURS only differing somewhat at item level [9-11]. The ASRS had the expected two-factor structure. Our findings fit well with previous cut-off suggestions by Ward, Wender [7] for the WURS and by Kessler, et al. [12] on the full 18 item ASRS (Table 3). Contrary to the critique raised against the WURS for lacking content validity (i.e. diverging from the DSM symptom criteria) [11], we found a very high criterion validity of WURS (i.e. being highly predictive of an ADHD diagnosis). Furthermore, the very items driving this discriminatory ability were part of the *Learning and attention problems* factor of the WURS. The items represent behaviours well recognized as core ADHD symptoms (WURS 1*: Concentration problems, Easily distracted* and WURS 7: *Trouble with stick-to-it-tiveness, not following through, failing to finish things started*).

The delineation of disorder versus normality is a universal problem when a diagnosis is based on symptoms that are dimensional and normally distributed, but it is of particular concern in a disorder for which controlled stimulant substances with potential for abuse are first-line treatments [23]. Thus, our study is important in that it addresses the psychometric properties of two commonly used screening instruments employed in parallel on a well-validated sample including both clinically ascertained adult ADHD patients and a population control sample. Our findings add to the ongoing controversy of what the optimal defining features of adult ADHD are. Adler, Faraone [24] suggested that executive dysfunction is as central as the DSM-5 symptoms to adult ADHD, while emotional dysregulation has been suggested to be more distinct but nevertheless part of the combined presentation of adult ADHD [6, 25]. In the present study, the WURS had better discriminatory properties than the ASRS. This is

noteworthy as our patients were diagnosed as adults based on a comprehensive clinical evaluation following the ICD/DSM criteria. Thus, even strictly defined adult ADHD patients are more easily distinguished from controls with a broader childhood symptom array than the current DSM core symptoms. This fits well with the well-established finding that ADHD is characterized by symptoms within domains of executive problems and emotional dysregulation. Although traditionally viewed as comorbid problems, these symptoms may rather be characteristic of having ADHD itself. The broader aspect covered by the WURS may reflect the broader picture that is essentially characteristic of persistent ADHD.

Possibly the retrospective focus of the WURS evoking a developmental frame and spanning over a longer period of time may elicit responses that separate better between adult patients with ADHD and controls. Another possible explanation for the better screening properties of the WURS could be that some of the patients have ADHD in partial remission (and thus a low ASRS score). However, we found that adult ADHD patients on current pharmacological (mainly stimulant) treatment reported less current symptoms of ADHD compared to those who were not on medication, but no differences on the WURS. Furthermore, patients treated for ADHD in childhood reported more symptoms than those who had not been treated in childhood on both the WURS and the ASRS, indicating a more severe and persistent phenotype [26].

*Strengths and limitations*

These findings should be viewed in light of some limitations. There are obvious problems related to the use of self-report measures. Measures that employ a retrospective approach might be affected by memory biases and lack of recall. McGough and Barkley [23] argued that ”a major obstacle to retrospective diagnosis is that it is significantly biased by current

functioning". However, our findings show that the retrospective WURS did better than reports of current ADHD symptoms in differentiating adult ADHD patients from controls. This is in line with previous studies on the WURS by e.g. Fossati, Di Ceglie [27] showing excellent short-term retest reliability. Both Fossati, Di Ceglie [27] and Grogan and Bramham [28] found that current mood symptoms do not affect the accuracy of retrospective self-ratings of childhood ADHD symptoms. The ASRS on the other hand may be more affected by short term confounders such as affective fluctuations [29], time of day [30] and sleep problems [31, 32]. We did not attempt to control for comorbidities, as ADHD is more often comorbid than not (e.g. Singh [33], Sobanski [34]).

We used a clinically validated patient sample and a representative population control sample, which strengthens the clinical utility of our findings. Our control sample was randomly recruited from the Norwegian Medical Birth Registry, without any formal exclusion criteria, so there is a potential for some undiagnosed cases of ADHD in this group.

*Conclusion*

Diagnosing ADHD in adults requires information about childhood symptoms in addition to current symptoms, impairments and functioning. Although the WURS differs from the ASRS, both had excellent psychometric properties. Including symptoms beyond the core ADHD symptoms, the WURS has been criticized for lacking validity. However, the WURS was not only highly accurate in separating ADHD patients from controls, but had even better screening properties than the ASRS. This in spite of our sample being clinically assessed in adulthood. The findings support a broader conceptualization of ADHD in line with the Utah tradition, as the three factors of the WURS picked up dimensions that were highly relevant to identify adult ADHD in our sample. With their different temporal focus and clinically

relevant symptom domains, we recommend using the ASRS and the WURS jointly in screening for adult ADHD.

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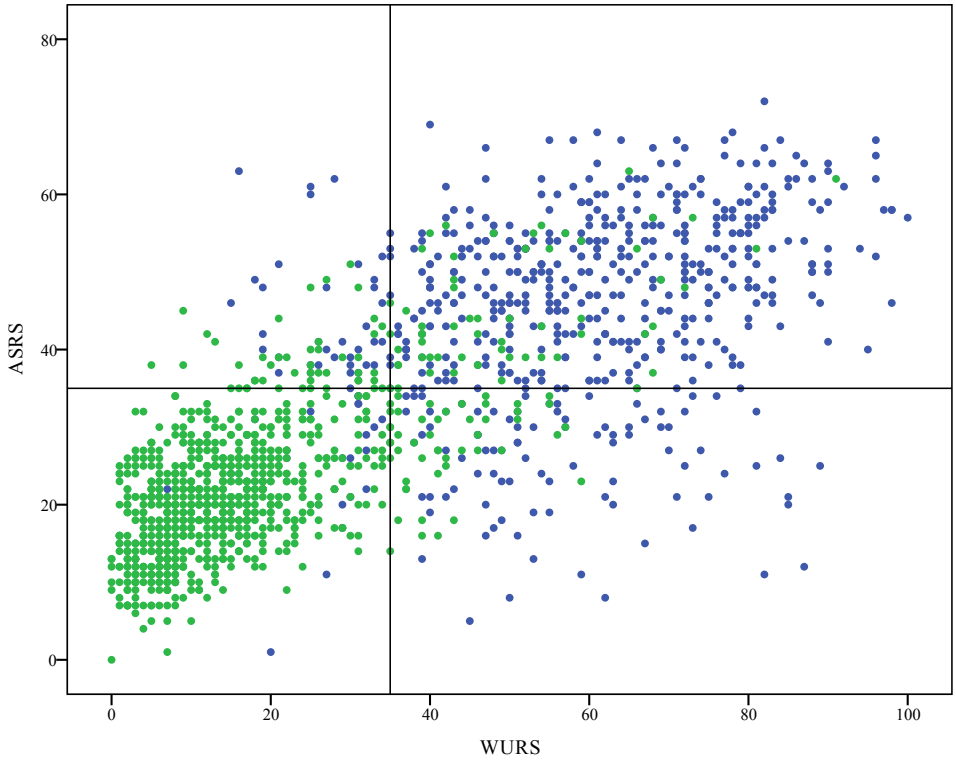
Figure 1: Distribution of WURS and ASRS scores in the ADHD and control samples.

Top left: Distribution of ASRS scores. Bottom left: Distribution of WURS scores. Right: Overlap between scores on the WURS and ASRS. Controls are green. ADHD patients are blue. Lines represent a cut-off score of 35; vertical line for WURS, horizontal line for ASRS. This gives a sensitivity of .90 and specificity of .88 for the WURS, and a sensitivity of .80 and specificity of .88 for the ASRS.

Figure 2: Receiving operator curve illustrating the psychometric properties of the WURS and the ASRS in predicting adult ADHD status.

Blue line represents the WURS. Green line represents the ASRS. A steeper curve indicates better discriminatory properties.


80
60
40
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ASRS
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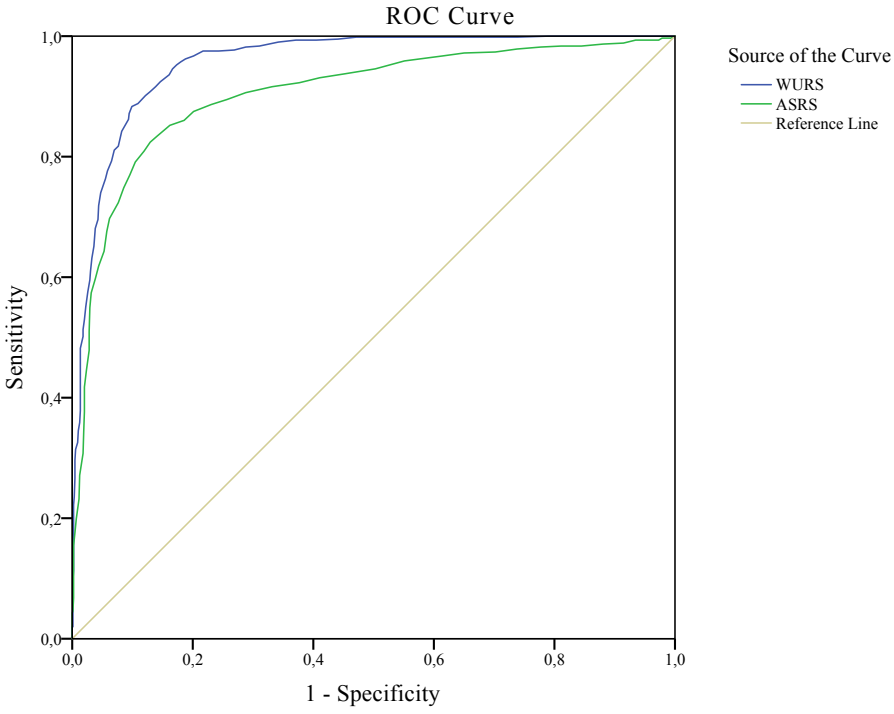
WURS




Diagonal segments are produced by ties.

Tables:
Table 1: Rotated Factor Component Matrix for the WURS
Table 2. Rotated Factor Component Matrix for the ASRS
Table 3. Predictive validity of the WURS and the ASRS.

Table 1: Rotated Factor Component Matrix for the WURS

| | Component | | |
|---|---|---|---|
| As a child I was (or had): | *1* | *2* | *3* |
| **Aggressiveness and Social Problems** (*30.7% of the variance*) | .817 | .204 | .235 |
| WURS 6: Temper outbursts, Tantrums | | | |
| WURS 14: Angry | .811 | .172 | .318 |
| WURS 5: Hot- or short-tempered, Low boiling point | .785 | .242 | .261 |
| WURS 10: Disobedient with parents, Rebellious, Sassy | .746 | .214 | .137 |
| WURS 19: Losing control of myself | .740 | .342 | .328 |
| WURS 12: Irritable | .738 | .247 | .401 |
| WURS 8: Stubborn, Strong-willed | .673 | .242 | .475 |
| WURS 13: Moody, Ups and downs | .672 | .403 | .336 |
| WURS 20: Tendency to be or act irrational | .662 | .154 | .090 |
| WURS 15: Trouble seeing things from someone else's point of view | .652 | .390 | .115 |
| WURS 22: Trouble with authorities, trouble with school, visits to principal's office | .635 | .374 | .230 |
| WURS 16: Acting without thinking, Impulsive | .621 | .559 | .234 |
| WURS 21: Unpopular with other children, didn't keep friends for long, didn't get along with other children | .467 | .349 | .433 |
| **Learning and Attention Problems** (*19.5% of the variance*) | .229 | .783 | .195 |
| WURS 23: Overall a poor student, slow learner | | | |
| WURS 24: Trouble with mathematics or numbers | .147 | .757 | .209 |
| WURS 25: Not achieving up to potential | .312 | .730 | .370 |
| WURS 1: Concentration problems, Easily distracted | .459 | .694 | .310 |
| WURS 7: Trouble with stick-to-it-tiveness, not following through, failing to finish things started | .369 | .595 | .427 |
| WURS 4: Inattentive, Daydreaming | .519 | .587 | .330 |
| WURS 17: Tendency to be immature | .432 | .542 | .308 |
| **Dysthymia** (*19.0% of the variance*) | .200 | .240 | .814 |
| WURS 2: Anxious, worrying | | | |
| WURS 9: Sad or blue, depressed, unhappy | .313 | .151 | .799 |
| WURS 11: Low opinion of myself | .166 | .265 | .754 |
| WURS 18: Guilty feelings, regretful | .230 | .280 | .728 |
| WURS 3: Nervous, fidgety | .334 | .377 | .684 |

PCA with Varimax rotation on the WURS in the full sample.

Items sorted by factor loadings. Total variance explained by the three factor solution: 69.2%

Table 2. Rotated Factor Component Matrix for the ASRS

| Circle the number that best describes how you have felt and conducted yourself over the past 6 months | *Component* 1 | 2 |
|---|---|---|
| **Inattentive** (*34.0% of the variance*) | | |
| ASRS5 How often do you have difficulty getting things in order when you have to do a task that requires organization? | .794 | .263 |
| ASRS2 How often do you have difficulty keeping your attention when you are doing boring or repetitive work? | .753 | .373 |
| ASRS6 When you have a task that requires a lot of thought, how often do you avoid or delay getting started? | .739 | .291 |
| ASRS1 How often do you make careless mistakes when you have to work on a boring or difficult project? | .735 | .327 |
| ASRS4 How often do you have trouble wrapping up the fine details of a project, once the challenging parts have been done? | .721 | .394 |
| ASRS3 How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly? | .679 | .413 |
| ASRS7 How often do you misplace or have difficulty finding things at home or at work? | .662 | .230 |
| ASRS9 How often do you have problems remembering appointments or obligations? | .655 | .264 |
| ASRS8 How often are you distracted by activity or noise around you? | .654 | .437 |
| **Hyperactive/Impulsive** (*28.2% of the variance*) | | |
| ASRS15 How often do you find yourself talking too much when you are in a social situation? | .209 | .761 |
| ASRS16 When you're in a conversation, how often do you find yourself finishing the sentences of the people that you are talking to, before they can finish them themselves? | .236 | .749 |
| ASRS17 How often do you have difficulty waiting your turn in situations when turn-taking is required? | .371 | .740 |
| ASRS18 How often do you interrupt others when they are busy? | .305 | .731 |
| ASRS14 How often do you feel overly active and compelled to do things, like you were driven by a motor? | .394 | .684 |
| ASRS12 How often do you feel restless or fidgety? | .579 | .595 |
| ASRS11 How often do you leave your seat in meetings or other situations in which you are expected to remain seated? | .502 | .577 |
| ASRS13 How often do you have difficulty unwinding and relaxing when you have time to yourself? | .478 | .574 |
| ASRS10 How often do you fidget or squirm with your hands or your feet when you have to sit down for a long time? | .514 | .567 |

PCA with Varimax rotation on the ASRS in the full sample.
62.2% Variance explained in the full sample rotated factor solution. Items sorted by factor loadings.

Table 3. Predictive validity of the WURS and the ASRS.

| WURS | | | | | | ASRS | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Sensitivity | | (Specificity) | LH+ | LH- | DOR | | (Specificity) | LH+ | LH- | DOR |
| .98 | 21 | (.71) | 3.38 | 0.03 | 135.5 | 16 | (.22) | 1.26 | 0.09 | 14.6 |
| .95 | 29 | (.83) | 5.59 | 0.06 | 95.6 | 21 | (.45) | 1.73 | 0.11 | 18.0 |
| .90 | 35 | (.88) | 7.50 | 0.11 | 64.7 | 27 | (.71) | 3.10 | 0.14 | 23.6 |
| .80 | 42 | (.93) | 11.43 | 0.22 | 56.1 | 35 | (.88) | 6.67 | 0.23 | 30.8 |
| Specificity | | (Sensitivity) | | | | | (Sensitivity) | | | |
| .98 | 56 | (.55) | 27.5 | 0.46 | 53.4 | 49 | (.45) | 22.5 | 0.56 | 34.0 |
| .95 | 46 | (.75) | 15 | 0.26 | 54.5 | 42 | (.64) | 12.8 | 0.38 | 32.7 |
| .90 | 36 | (.89) | 8.9 | 0.12 | 63.5 | 36 | (.79) | 7.9 | 0.23 | 32.0 |
| .80 | 26 | (.97) | 4.85 | 0.04 | 117.3 | 30 | (.88) | 4.4 | 0.15 | 27.8 |

Complimentary Specificity/Sensitivity given in parenthesis.

WURS = Wender Utah Rating Scale
ASRS = Adult ADHD Self-Report Scale

LH+ = Likelihood ratio positive test
LH- = Likelihood ratio negative test
DOR = Diagnostic Odds Ratio

# Paper II

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*ACTA PSYCHIATRICA SCANDINAVICA*

# Prevalence and clinical correlates of insomnia in adults with attention-deficit hyperactivity disorder

Brevik EJ, Lundervold AJ, Halmøy A, Posserud MB, Instanes JT, Bjorvatn B, Haavik J. Prevalence and clinical correlates of insomnia in adults with attention-deficit hyperactivity disorder

**Objective:** To investigate the prevalence of insomnia in adults with Attention-deficit hyperactivity disorder (ADHD) and its association with clinical subtypes, current ADHD symptoms, and stimulant treatment.
**Method:** We obtained diagnostic information, symptom rating scales and treatment history from clinically ascertained adult ADHD patients diagnosed according to DSM-IV criteria ($n$ = 268, mean age 38.1 years) and randomly selected population controls ($n$ = 202, mean age 36.5 years). The Bergen Insomnia Scale (BIS) was used to measure insomnia. ADHD symptom domains were self-rated using the Adult ADHD Self-Rating Scale.
**Results:** Insomnia was far more frequent among adults with ADHD (66.8%) than in the population controls (28.8%) ($P < 0.001$). Insomnia was more common in adults with the combined subtype than in those with the inattentive subtype (79.7% and 55.6%, respectively) ($P = 0.003$). For self-reported current ADHD symptoms, inattention was strongly correlated to insomnia. Patients currently using stimulant treatment for ADHD reported a lower total insomnia score compared to patients without medication ($P < 0.05$).
**Conclusion:** Insomnia was highly prevalent among adults with ADHD. The lower insomnia score in patients on current stimulant treatment suggests that stimulant treatment is not associated with worsening of insomnia symptoms in adult ADHD patients.

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Key words: attention-deficit hyperactivity disorder; sleep; psychostimulants; clinical aspects; neuropsychiatry

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**Significant Outcomes**

- Insomnia is highly relevant in adult ADHD, with a fivefold increased risk compared with controls
- Stimulant treatment of ADHD in adults is not associated with worsening of insomnia, and may potentially even be helpful in alleviating insomnia symptoms
- Insomnia was more common in the combined and hyperactive/impulsive subtypes than in the inattentive subtype

**Limitations**

- Insomnia symptoms were based on self-reports, which may be unreliable and lead to an overestimation
- We do not include other sleep variables which may be of interest
- This study employed a cross-sectional, survey design, limiting the possibility of making causal conclusions.

## Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of inattention and/or hyperactivity/impulsivity. Based on these symptom domains, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV/DSM-5) differentiate between inattentive (IA), hyperactive/impulsive (HI), and combined subtypes/presentations (1). It is estimated that 2–3% of the adult population suffer from ADHD (2). People with ADHD typically struggle with maintaining structure and regulating their behaviour and daytime activities. The regulatory difficulties also seem to affect the diurnal rhythm, as ADHD has been associated with various sleep problems, with insomnia being one of the most commonly reported comorbid conditions (3). Insomnia is defined as difficulties initiating or maintaining sleep, early morning awakenings or having non-restorative sleep, lasting for at least a month (1). Insomnia is one of the most frequent health concerns in the general population as well (4), typically affecting 6% to 15% of the adult population (5). Insomnia causes irritability and fatigue as well as reduced productivity, increased absenteeism, increased morbidity, and increased health care costs (4). Most studies examining the relationship between insomnia and ADHD have been performed in children and adolescents, and the few studies addressing insomnia in adult ADHD have given conflicting results (6, 7). One study found that more than half of adults with probable ADHD fulfilled the criteria for insomnia (8). In another study, four of five adults with ADHD reported having sleep problems, irrespective of sex and subtype (9), indicating the importance of addressing insomnia in adult ADHD.

It is well established that ADHD is associated with impairment in cognitive functions such as attention, vigilance and working memory, as well as long-term memory, and decision-making (10). Considering that insomnia also affects cognitive functioning (9), insomnia in addition to ADHD may lead to a vicious cycle where impairments are exacerbated. Studies have shown that sleep problems in general are associated with inattention, whereas some specific sleep problems have been associated with the different ADHD subtypes (3). According to Gau and Kessler (11), HI has been associated with decreased sleep duration, whereas IA has been associated with disturbed sleep, delayed circadian rhythm, and greater sleep need (8, 11–14). Meanwhile, the ADHD combined subtype is characterized by an overall higher symptom burden and severity compared with the other subtypes (15), which may also affect the rate of insomnia. Conversely, the severity of sleep problems is associated with the severity levels of self-reported ADHD symptoms, both among ADHD patients and in the general population (11, 16, 17). Among ADHD patients, this association held when comorbidity and medication were taken into account (17). Of the above cited studies, only three studies (14, 16, 17) used samples with clinically ascertained ADHD patients, the remaining used questionnaires to assign ADHD status.

The relationship between sleep problems and pharmacological treatment for adults with ADHD is not settled. One study reported that nearly four of five non-medicated ADHD participants suffered from sleep-onset insomnia (18), while other studies have found insomnia to be a side-effect of treatment with both stimulants (19) and atomoxetine (20). There is, however, substantial individual variation in whether these medications cause insomnia or not, and sleep problems seem to decrease as the medication is titrated and ADHD symptoms improve (21). Usually, insomnia as a side-effect of stimulant treatment attenuates after 1–2 months treatment (22) and ADHD patients on methylphenidate treatment have even been found to self-report an improvement in sleep quality (23).

Thus, although several studies on the relationship between adult ADHD and insomnia have been published, many of these are of modest quality, with few participants, unclear inclusion criteria, and lack of validated diagnostic protocols. Studies using large samples of clinically ascertained adult ADHD patients and validated measures of insomnia are therefore needed to clarify the relationship between insomnia, clinical subtypes, and symptoms of ADHD and their relationship to stimulant treatment (3).

### Aims of study

The aim of the current study was to determine the prevalence of insomnia in a large Norwegian sample of adults with Attention-deficit hyperactivity disorder (ADHD) compared with population controls. Based on previous findings, we expected adults with ADHD to experience higher levels of insomnia than control subjects. We first compared the prevalence of insomnia in the patient group with the control group, then in subtypes of ADHD, and in groups of patients on and off current stimulant treatment. Finally, we calculated the odds ratio of insomnia based on self-reported symptoms of ADHD.

## Method

### Sample

This cross-sectional study is part of an ongoing project on adults with ADHD in Norway (http://www.uib.no/kgj-npd). The data included in the present study were collected between 2011 and 2016. The sample included adult ADHD patients ($n = 268$), clinically diagnosed by psychiatrists and psychologists according to the DSM-IV criteria (1). All patients were born in Norway of Norwegian parents. The first patients were recruited from regional expert committees on ADHD, subsequent patients were recruited from clinical psychologists and psychiatrists in outpatient clinics nationwide. Controls ($n = 202$) were randomly selected and invited to participate in the study directly from the Medical Birth Registry of Norway. This registry includes all persons born in Norway from January 1st 1967 (approx. 2.5 million persons at the time of recruitment). To allow for comorbidities no formal exclusion criteria were used in either sample. This allowed for considerable comorbidities, most noticeably in the adult ADHD group (Table S1). All participants ($n = 470$) completed a questionnaire including the six Bergen Insomnia Scale (BIS) items, the 18 item Adult ADHD Self-Rating Scale (ASRS) and questions about life-time comorbid disorders (e.g., have you ever had severe anxiety and/or depression). For half of the patients ($n = 135/50.4\%$) clinician reported information was available on the patients' ADHD subtype and pharmacological treatment. The ADHD subtypes were IA ($n = 54$), HI ($n = 6$) or Combined ($n = 75$). As the HI group was very small, the HI group was analyzed together with the Combined group for ease of interpretation. Pharmacological treatment data included whether the patients were on ($n = 94$) or off ($n = 36$) current pharmacological treatment with methylphenidate ($n = 69$), amphetamines ($n = 12$), atomoxetine ($n = 3$), or a combination of these ($n = 7$). Three patients had missing data on use of pharmacological treatment. The patients on atomoxetine are included in the group on current stimulant treatment in this paper, as analyzing the data without these patients did not alter the results. The differences in distribution of sex and age between the ADHD subtypes and between the stimulant treatment groups were all non-significant. As no interaction was found between medication use and ADHD subtypes, we used the greatest sample sizes available when performing the respective analyses. All participants signed a written informed consent, and the study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics, RECWest (IRB #3 (FWA00009490, IRB00001872)).

### The Bergen Insomnia Scale

The Bergen Insomnia Scale (24) was constructed based on the diagnostic criteria for insomnia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1). It includes six items rated on an 8-point scale, ranging from 0 to 7 days per week during the last month. The first four assess sleep impairment (criteria A of the DSM-IV) (has it taken you more than 30 min to fall asleep after the light was switched off; have you been awake for more than 30 min between periods of sleep; have you awakened more than 30 min earlier than you wished without managing to fall asleep again; have you felt that you have not had enough rest after waking up). The last two items refer to daytime sleepiness/tiredness that has affected your participation at school or work, and your dissatisfaction with sleep respectively (criteria *B*). The criteria for a DSM-IV diagnosis of insomnia are fulfilled if a respondent reports ≥3 days per week on at least one of the A-items and ≥3 days per week on at least one *B* item. In addition, a total composite score is calculated by adding together the scores for each item, with a possible range of 0–42. The BIS thus provides both a dichotomous score for the presence of insomnia and a dimensional symptom score. The Cronbach's alpha of the BIS scale used in the present study was 0.86.

### The Adult ADHD Self-Rating Scale

The Adult ADHD Self-Rating Scale (ASRS) is the World Health Organization's (WHO) official

screener for ADHD, and consists of the 18 symptoms listed in the DSM-IV criteria A (25). Nine items assess symptoms of inattention (ASRS-IA) and nine items assess hyperactive/impulsive symptoms (ASRS-HI), respectively, rated on a scale from 0 to 4 (0 = never, 1 = rarely, 2 = sometimes, 3 = often and 4 = very often), yielding a total range of 0–72. The total scores on the two subscales of IA and HI were used as continuous measures of the two main symptom domains of ADHD. Cronbach's alpha was 0.92 on the ASRS-IA subscale and 0.92 on the ASRS-HI subscale.

### Statistics and analytical plan

Data were analyzed using SPSS v-23 (26). Independent samples *t*-tests were used to compare pairs of groups on continuous variables and chi-square tests for categorical variables. Logistic regression analysis with insomnia (yes/no) as the output variable was used to investigate the association between self-reported current ADHD symptom scores and the insomnia diagnosis. A final linear regression model, with the BIS score as the output variable, was included to investigate the association between self-reported symptoms of inattention and hyperactivity-impulsivity and the severity level of insomnia symptoms. These two regression models were run separately for the ADHD and the control group. Adjusted models are controlled for age, sex and self-reported comorbid anxiety/depression. Significance levels were set at the 0.05 level on two-tailed tests, unless otherwise indicated.

## Results

The differences in mean age and sex distribution between the ADHD patients and the controls were non-significant (age range from 18 to 74 in the ADHD sample and 19–73 in the controls, for more details see Table 1). The BIS total sum score was significantly higher in the ADHD group compared to the control group ($t$ (457.7) = 11.5, P < 0.001). In the clinician defined subgroups, the Combined subtype had higher scores than the IA subtype ($t$ (131) = 2.1, $P$ = 0.036). Furthermore, ADHD patients currently using ADHD medication had lower insomnia scores than patients without stimulant treatment ($t$ (126) = −2.4, $P$ = 0.017) (Table 2).

As shown in Table 2, the ADHD group had higher scores on all six BIS items than the control group. Overall, the prevalence of adults with ADHD fulfilling the criteria for an insomnia diagnosis was 66.8%, which was significantly higher than the prevalence of 28.8% in the control group ($\chi^2$ = 65.2, P < 0.001). The ADHD subtypes also differed in prevalence of insomnia ($\chi^2$ = 8.9, $P$ = 0.003), with the Combined subtype having a higher prevalence of insomnia than the IA subtype (79.7% and 55.6% respectively). There was no significant difference in prevalence of insomnia between the groups on and off stimulant treatment, 66.3% and 72.2% respectively) (Table 2). However, the treatment group reported a significantly lower insomnia symptom score than the group not currently on stimulant treatment.

As expected, the ADHD group had significantly higher ASRS scores than the control group ($P$ < 0.001) (Table 3). Of note, the group off medication reported higher ASRS scores than the subgroup on current stimulant treatment on both the ASRS-IA ($t$(87.4) = 3.7, $P$ < 0.001) and the ASRS-HI subscales ($t$(127) = 2.6, $P$ = 0.011). A logistic regression analysis showed that having ADHD was associated with a five-fold increased odds-ratio for insomnia in the full sample [OR: 5.0 (95% CI: 3.3–7.4)]. Further analyses included the ASRS subscales as predictors (Table 4). Logistic regression analysis showed that both ASRS subscales were significantly associated with insomnia in the full sample, but that only ASRS-IA remained a significant predictor when adjusting for sex, age and comorbid anxiety/depression. Of note, the anxiety/depression variable was dichotomous, whereas the ASRS consisted of two scales. The odds of self-reported insomnia thus increased by 0.091 (OR = 1.091) per increased score of ASRS-IA in the full sample. When analyzed separately, anxiety/depression was the only significant predictor of insomnia in

Table 1. Age and sex distributions in the control sample and the ADHD sample

| | Controls | Total ADHD | ADHD Subtypes | | On current stimulant treatment | |
|---|---|---|---|---|---|---|
| | | | Combined | Inattentive | Yes | No |
| | $n$ = 202 | $n$ = 268 | $n$ = 81 | $n$ = 54 | $n$ = 94 | $n$ = 36 |
| Age (SD) | 36.5 (8.0) | 38.1 (11.4) | 33.2 (9.5) | 35.9 (10.0) | 34.1 (10.4) | 36.7 (8.6) |
| Female (%) | 62.9 | 59.7 | 70.4 | 55.6 | 66.0 | 63.9 |

SD, Standard deviation.

Table 2. Scores on the Bergen Insomnia Scale (BIS)

| | | Controls | Total | ADHD Subtypes | | On current stimulant treatment | |
|---|---|---|---|---|---|---|---|
| | During the past month, how many days a week | $n = 202$ | $n = 268$ | Combined $n = 81$ | Inattentive $n = 54$ | Yes $n = 94$ | No $n = 36$ |
| BIS1 | Has it taken you more than 30 min to fall asleep after the light was switched off? | 1.4 (1.8) | 3.4 (2.5)** | 3.9 (2.4) | 3.2 (2.6) | 3.5 (2.5) | 3.9 (2.4) |
| BIS2 | Have you been awake for more than 30 min between periods of sleep? | 1.0 (1.7) | 2.2 (2.2)** | 2.4 (2.4) | 1.9 (2.1) | 2.0 (2.2) | 2.8 (2.3) |
| BIS3 | Have you awakened more than 30 min earlier than you wished without managing to fall asleep again? | 0.8 (1.3) | 2.2 (2.3)** | 2.1 (2.5) | 1.7 (1.9) | 1.7 (2.1) | 2.8 (2.4)* |
| BIS4 | Have you felt that you have not had enough rest after waking up? | 2.7 (2.0) | 4.4 (2.3)** | 4.9 (1.9) | 4.0 (2.3)* | 4.3 (2.1) | 4.9 (2.3) |
| BIS5 | Have you been so sleepy/tired that it has affected you at school/work or in your private life? | 1.0 (1.5) | 2.5 (2.2)** | 2.9 (2.1) | 2.5 (2.1) | 2.4 (2.0) | 3.3 (2.1)* |
| BIS6 | Have you been dissatisfied with your sleep? | 1.9 (2.0) | 3.7 (2.4)** | 4.3 (2.1) | 3.3 (2.4)* | 3.6 (2.2) | 4.5 (2.5) |
| | BIS Sum (SD) | 8.9 (7.4) | 18.3 (10.1)** | 20.6 (10.0) | 16.8 (10.3)* | 17.5 (9.5) | 22.2 (10.6)* |
| | BIS Insomnia (%) | 28.8 | 66.8** | 79.7 | 55.6** | 66.3 | 72.2 |

*$P < 0.05$
**$P < 0.01$

Table 3. Scores on the Adult ADHD Self-Rating Scale (ASRS)

| | Controls | Total ADHD | ADHD Subtypes | | On current stimulant treatment | |
|---|---|---|---|---|---|---|
| | $n = 202$ | $n = 268$ | Combined $n = 81$ | Inattentive $n = 54$ | Yes $n = 94$ | No $n = 36$ |
| ASRS SUM (SD) | 21.5 (9.6) | 42.7 (13.0)** | 46.0 (12.0) | 37.0 (13.9)** | 40.2 (14.5) | 47.8 (9.6)** |
| Inattention (SD) | 11.8 (5.0) | 22.5 (6.5)** | 23.8 (6.2) | 20.7 (7.5)** | 21.1 (7.1) | 25.4 (5.2)** |
| Hyperactivity/Impulsivity (SD) | 9.7 (5.6) | 19.9 (7.3)** | 22.2 (6.6) | 16.4 (7.3)** | 18.8 (7.6) | 22.4 (6.1)* |

*$P < 0.05$
**$P < 0.01$

the control sample, whereas ASRS-IA was the only significant predictor in the ADHD sample.

The BIS sum score was included as an outcome variable in a linear regression analysis (Table 5), showing that 31% of its variance was explained by the two ASRS-subscales in the full sample. Each subscale contributed significantly, and they continued to do so even when controlled for sex, age and comorbid anxiety/depression. When analyzed separately within the ADHD and control groups, significant contribution was restricted to the ASRS-HI subscale, with a somewhat stronger overall explained variance in the ADHD group (16.1%) than in the control group (9.7%). The ASRS-HI scale remained significant in the adjusted models, with sex and anxiety/depression as added significant predictors in the control sample and ASRS-IA and anxiety/depression as added significant predictors in the ADHD sample.

## Discussion

The present study showed that insomnia was far more frequent among adults with ADHD (66.8%) than in the population controls (28.8%), with the highest prevalence in the Combined subtype (79.7%). There was no significant difference in the prevalence of insomnia between the ADHD subgroups on and off medication. The total BIS scores of the un-medicated patients were, however, significantly higher than for patients receiving stimulant treatment, as were the BIS scores of the Combined compared to the IA subtype. Regression analyses showed that the self-reported IA subscale of the ASRS significantly contributed to explain an insomnia diagnosis in the ADHD and the control group, while both the ASRS-HI and ASRS-IA subscales contributed significantly when the total BIS score was used as an outcome variable.

Attention-deficit hyperactivity disorder and sleep problems, including insomnia, are bi-directionally related and mutually exacerbating conditions (9, 27). As ADHD is a heterogeneous developmental disorder, there are likely to be variations in the relationship between ADHD and insomnia. We explored this by examining differences in insomnia for subtypes of ADHD as rated by the clinicians referring the patients, and by including information about self-reported ADHD symptoms. We found that the ADHD Combined subtype had a higher

Table 4. Odds Ratios for Insomnia for the different ASRS ADHD symptom domains

| Predictor | Crude OR | 95% CI | *P* | Adjusted OR | 95% CI | *P* |
|---|---|---|---|---|---|---|
| Full sample | | | | | | |
| Inattention | 1.092 | 1.045–1.140 | <0.001 | 1.091 | 1.043–1.141 | <0.001 |
| Hyperactivity/Impulsivity | 1.050 | 1.008–1.093 | 0.019 | 1.036 | 0.994–1.080 | 0.095 |
| Sex | | | | 0.697 | 0.453–1.072 | 0.100 |
| Age | | | | 0.982 | 0.962–1.003 | 0.096 |
| Anxiety/Depression | | | | 1.858 | 1.179–2.929 | 0.008 |
| Controls | | | | | | |
| Inattention | 1.095 | 1.007–1.191 | 0.035 | 1.087 | 0.995–1.188 | 0.065 |
| Hyperactivity/Impulsivity | 1.036 | 0.963–1.116 | 0.341 | 1.032 | 0.956–1.113 | 0.420 |
| Sex | | | | 0.558 | 0.271–1.149 | 0.114 |
| Age | | | | 0.984 | 0.945–1.025 | 0.443 |
| Anxiety/Depression | | | | 2.504 | 1.098–5.711 | 0.029 |
| ADHD | | | | | | |
| Inattention | 1.062 | 1.005–1.123 | 0.034 | 1.068 | 1.009–1.131 | 0.022 |
| Hyperactivity/Impulsivity | 1.044 | 0.993–1.097 | 0.091 | 1.033 | 0.982–1.088 | 0.208 |
| Sex | | | | 0.732 | 0.417–1.284 | 0.277 |
| Age | | | | 0.983 | 0.960–1.008 | 0.179 |
| Anxiety/Depression | | | | 1.324 | 0.738–2.374 | 0.346 |

OR, Odds ratio; CI, Confidence interval. Adjusted ORs have been controlled for age, sex, and comorbid anxiety/depression.

Table 5. Multiple Regression analyses for the effect of ASRS ADHD symptom domains on the BIS sum score

| | Crude | | | | | Adjusted | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Predictor | *B* | SE *B* | β | *P* | 95% CI for *B* | *B* | SE *B* | β | *P* | 95% CI for *B* |
| Full sample | | | | | | | | | | |
| Inattention | 0.327 | 0.084 | 0.255 | <0.001 | 0.163–0.491 | 0.291 | 0.083 | 0.227 | 0.001 | 0.127–0.454 |
| Hyperactivity/Impulsivity | 0.406 | 0.079 | 0.334 | <0.001 | 0.250–0.562 | 0.338 | 0.079 | 0.278 | <0.001 | 0.183–0.492 |
| Sex | | | | | | 1.704 | 0.796 | 0.082 | 0.033 | 0.140–3.268 |
| Age | | | | | | −0.061 | 0.039 | −0.061 | 0.113 | −0.137–0.014 |
| Anxiety/Depression | | | | | | −3.672 | 0.880 | −0.180 | <0.001 | −5.401 to −1.943 |
| Model | *F*: | 103.949 | | AdjR$^2$ | 0.310 | *F*: | 49.207 | | AdjR$^2$ | 0.345 |
| Controls | | | | | | | | | | |
| Inattention | 0.230 | 0.134 | 0.156 | 0.087 | −0.033 to 0.493 | 0.186 | 0.131 | 0.128 | 0.158 | −0.072 to 0.443 |
| Hyperactivity/Impulsivity | 0.265 | 0.120 | 0.201 | 0.028 | 0.029–0.501 | 0.238 | 0.114 | 0.185 | 0.038 | 0.014–0.463 |
| Sex | | | | | | 2.065 | 1.000 | 0.138 | 0.040 | 0.094–4.037 |
| Age | | | | | | −0.112 | 0.060 | −0.125 | 0.063 | −0.229 to 0.006 |
| Anxiety/Depression | | | | | | −3.578 | 1.337 | −0.187 | 0.008 | −6.215 to −0.941 |
| Model | *F*: | 11.572 | | AdjR$^2$ | 0.097 | *F*: | 8.009 | | AdjR$^2$ | 0.152 |
| ADHD | | | | | | | | | | |
| Inattention | 0.229 | 0.119 | 0.148 | 0.056 | −0.006 to 0.464 | 0.237 | 0.119 | 0.153 | 0.047 | 0.003–0.471 |
| Hyperactivity/Impulsivity | 0.411 | 0.107 | 0.295 | <0.001 | 0.200–0.622 | 0.350 | 0.108 | 0.251 | 0.001 | 0.136–0.563 |
| Sex | | | | | | 1.598 | 1.194 | 0.078 | 0.182 | −0.754 to 3.949 |
| Age | | | | | | −0.036 | 0.051 | −0.040 | 0.480 | −0.136 to 0.064 |
| Anxiety/Depression | | | | | | −2.923 | 1.242 | −0.137 | 0.019 | −5.368 to −0.478 |
| Model | *F*: | 25.910 | | AdjR$^2$ | 0.161 | *F*: | 12.246 | | AdjR$^2$ | 0.178 |

*B*, Beta; SE, Standard Error; β, Standardized Beta; CI, Confidence interval; AdjR$^2$, Adjusted R$^2$. Adjusted models have been controlled for age, sex, and comorbid anxiety/depression.

prevalence of insomnia than the IA subtype. When including information about symptom domains, reported at the same time as the insomnia symptoms, inattention was found to be most closely associated with a diagnosis of insomnia. Since the inattention score was substantially higher in the ADHD-Combined subtype than the other subtypes (see Table 3), both findings support the interpretation that overall ADHD severity is a main predictor of insomnia. Our findings thus support previous reports of the severity of sleep problems being positively related to the severity of ADHD symptoms (17).

The finding that inattentive symptoms were more strongly correlated to insomnia symptoms in the control group than in the ADHD group, suggests that a close association between inattentive symptoms and insomnia is not restricted to adults with an ADHD diagnosis. Without any information about causal relationship, inattentive symptoms may as likely be a consequence of sleep problems than the other way around. It is well known that in itself, insomnia may mimic and cause symptoms resembling ADHD and may also exacerbate underlying ADHD symptoms (7), creating a vicious cycle. This may be detrimental to,

for example, learning outcomes, both through lack of attentional resources and through lack of consolidation through sleep (10). The bidirectionality of this relationship indicates that adequate treatment of ADHD may also be important in improving insomnia. One may be hesitant to use stimulant medication late in the afternoon/evening as insomnia has been associated with stimulant treatment. Our findings however do not support the advice to abstain from medication for fear of causing or exacerbate insomnia in ADHD. The prevalence of insomnia was so high that it should rather be viewed as a problem intrinsic to ADHD. Second, we found no support of an exacerbating effect of stimulant treatment. In fact, and in line with studies suggesting a beneficial effect of ADHD medication in adults with ADHD (21, 23), we found that adult ADHD patients who were currently on stimulant treatment obtained a *lower* BIS sum score compared to those who were not on stimulant treatment, although the prevalence of insomnia was similar across the two groups. Generally, our findings fit well with and extend previous studies on ADHD and insomnia in children and adolescents (28, 29). According to the present knowledge and the present study, the best clinical practice seems to be active pharmacological management of ADHD, combined with a close monitoring of sleep problems in all patients with ADHD regardless of medication. The high overall prevalence of insomnia in ADHD found in the present study, and indications that ADHD patients with the most severe symptoms are also the ones with the most severe insomnia, make it imperative to provide adequate treatment targeting insomnia in the clinical management of ADHD, alongside other problems associated with ADHD symptoms (30, 31). If insomnia is detected, it should be specifically targeted in addition to the ADHD itself, but not preclude stimulant treatment.

### Limitations

This study employed a cross-sectional, survey design, limiting the possibility of making causal conclusions. Our definition of insomnia may be inadequate to differentiate patients suffering from delayed sleep phase disorder (DSPD), which is not easily distinguishable from sleep-onset insomnia (32). The use of stimulant treatment was clinician reported, not based on, for example, blood samples, thus not objectively measured. Particularly in the ADHD group, a large fraction of the participants reported present and/or life-time occurring comorbid conditions, such as anxiety/depression, bipolar disorder, dyslexia or substance use disorders (Table S1) (33). While no formal exclusion criteria were used to ensure more clinically valid phenotypes, such comorbidities may have added to the general symptom load, and also influenced the associations with insomnia. The design of the present study precludes strong conclusions, as insomnia as a side-effect from medication may be the cause for cessation. Further studies with experimental designs are needed to clarify this association. One way to assess the relationship between sleep problems and ADHD would be to systematically screen for insomnia before starting stimulant treatment of ADHD, thus enabling the clinical evaluation of insomnia symptoms associated with stimulant treatment (21).

Strengths of the study include the use of a large, clinically validated sample of adult ADHD patients and representative population controls, as well as validated screening tools for insomnia and ADHD symptoms. The BIS has high external and internal validity and worked well in the present study. Its brevity and free availability thus makes it well suited to screen for and detect insomnia in ADHD patients in clinical practice.

To conclude, insomnia is an important health problem that needs to be addressed in adult ADHD patients. Compared to population-based controls, ADHD patients had a five-fold increased odds ratio of having insomnia. Patients with the Combined subtype of ADHD reported a significantly higher prevalence of insomnia than the Inattentive subtype. Patients currently using ADHD medication reported significantly lower insomnia scores than patients not using ADHD medication. Our results indicate that stimulant treatment of ADHD, as used in practice and over time, is not associated with worsening of the severe difficulties with insomnia that are found to be a commonly associated condition of ADHD.

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## Declaration of interests

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1**. Prevalence of self-reported psychiatric comorbidities in the control sample and the ADHD sample.

Supplementary Table 1. Prevalence of self-reported psychiatric comorbidities in the control sample and the ADHD sample.

| Life-time prevalence % (n) | Controls (n = 202) | ADHD Full (n = 268) | *p* | Combined subtype (n = 81) | Inattentive subtype (n = 54) | *p* | On ADHD meds (n = 94) | Off ADHD meds (n = 36) | *p* |
|---|---|---|---|---|---|---|---|---|---|
| Anxiety/Depression | 16.9% (34) | 66.3% (177) | <.001 | 72.5% (58) | 70.4% (38) | .788 | 67.7% (63) | 69.4% (25) | .852 |
| Bipolar | 0.5% (1) | 12.1% (32) | <.001 | 13.8% (11) | 13.0% (7) | .896 | 15.1% (14) | 13.9% (5) | .867 |
| Dyslexia | 6.9% (14) | 45.5% (121) | <.001 | 41.3% (33) | 44.4% (24) | .714 | 41.9% (39) | 41.7% (15) | .978 |
| Alcohol problems | 1.0% (2) | 13.2% (35) | <.001 | 8.8% (7) | 11.1% (6) | .651 | 9.7% (9) | 5.6% (2) | .452 |
| Problems with other drugs | 0.5% (1) | 13.6% (36) | <.001 | 11.4% (9) | 15.1% (8) | .534 | 13.2% (12) | 16.7% (6) | .612 |
| Treatment for psychiatric disorder other than ADHD | 6.0% (12) | 31.3% (82) | <.001 | 32.5% (26) | 38.9% (21) | .447 | 50.5% (47) | 42.9% (15) | .438 |

Groups are compared using Chi square.

The Combined subtype includes the 6 patients with the Hyperactive/Impulsive subtype.

# Paper III

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART B
Neuropsychiatric Genetics

# Genome-Wide Analyses of Aggressiveness in Attention-Deficit Hyperactivity Disorder

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**Aggressiveness is a behavioral trait that has the potential to be harmful to individuals and society. With an estimated heritability of about 40%, genetics is important in its development. We performed an exploratory genome-wide association (GWA) analysis of childhood aggressiveness in attention deficit hyperactivity disorder (ADHD) to gain insight into the underlying biological processes associated with this trait. Our primary sample consisted of 1,060 adult ADHD patients (aADHD). To further explore the genetic architecture of childhood aggressiveness, we performed enrichment analyses of suggestive genome-wide associations observed in aADHD among GWA signals of dimensions of oppositionality (defiant/vindictive and irritable dimensions) in childhood ADHD (cADHD). No single polymorphism reached genome-wide significance ($P < 5.00E-08$). The strongest signal in aADHD was observed at rs10826548, within a long noncoding RNA gene (beta = −1.66, standard error (SE) = 0.34, $P = 1.07E-06$), closely followed by rs35974940 in the neurotrimin gene (beta = 3.23, SE = 0.67, $P = 1.26E-06$). The top GWA SNPs observed in aADHD showed significant enrichment of signals from both the defiant/vindictive dimension (Fisher's $P$-value = 2.28E-06) and the irritable dimension in cADHD (Fisher's $P$-value = 0.0061). In sum, our results identify a number of biologically interesting markers possibly underlying childhood aggressiveness and provide targets for further genetic exploration of aggressiveness across psychiatric disorders.** © 2016 Wiley Periodicals, Inc.

**Key words: ADHD; aggression; GWAS**

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## INTRODUCTION

Aggressiveness can be defined as any behavior directed toward an individual with the immediate intent to cause harm [Anderson and Bushman, 2002]. Violence, which is strongly related to aggressiveness, is the sixth leading cause of burden of disease for people aged 15–44 years worldwide [WHO, 2008]. To date, most interventions designed to reduce violence risk typically have small effects, reflecting our limited understanding of its causes and stressing the need for further studies [Moffitt, 2005; McGuire, 2008].

As a complex phenomenon, aggressiveness spans across numerous facets of human behavior, ranging from emotional lability and temperamental traits (e.g., hot-tempered, short fuse, irritable) to physical violence [Lesch et al., 2012]. These traits are frequently found among youth with attention deficit hyperactivity disorder (ADHD), a common child and adolescent psychiatric disorder with a prevalence of about 5% and a rate of persistence into adulthood of about 50% [Faraone et al., 2015]. ADHD is defined by symptoms of inattention and hyperactivity/impulsivity, and youth with ADHD often have co-existing disorders, some of which are closely related to aggressiveness and violence, such as conduct disorder (CD) and/or oppositional defiant disorder (ODD) and disorders characterized by symptoms defined within the broader term of antisocial behavior [Dalsgaard et al., 2002]. These disorders put youth with ADHD at high risk of problems associated with aggressiveness in adulthood [Klassen et al., 2010], especially when the aggressive behavior has an early onset [Hofvander et al., 2009]. This can be illustrated by the fact that around 30% of youth and 25% of adult prison inmates are found to qualify for an ADHD diagnosis [Young et al., 2014]. Studies of childhood aggressiveness in adults can, therefore, be of great importance to improve our understanding of adult ADHD.

The etiology of ADHD as well as traits of aggressiveness is complex, with genetics playing an important role. The heritability of ADHD has been estimated to be up to 88% across the lifespan [Larsson et al., 2013], whereas the estimates of genetic influence on aggression vary across studies, collectively reaching about 40–50% [Brendgen et al., 2006; Tuvblad and Baker, 2011]. Such diversity in the estimation of aggression heritability may result from inconsistency in measures across studies. Several different aggression measures have been utilized to assess the genetic and environmental influences on its development [Veroude et al., 2015], reflecting that there is no consensus regarding its definition [Ramirez and Andreu, 2006]. Furthermore, the estimates of aggressiveness are influenced by the age of the study participants. The literature reports stability of aggressiveness between childhood and adulthood, with adolescence as a transient period with little stability in this trait [Moffitt, 2005]. Genes seem to explain little variation in adolescent aggression, but are likely to account for individual differences in childhood and adult aggression [Lyons et al., 1995]. Also, given higher levels of aggression in males and higher genetic load in males with antisocial behavior compared to females, it is an open question whether genetic propensity is of greater importance in one sex over the other [Miles and Carey, 1997; Tuvblad and Baker, 2011]. Interestingly, similar considerations of age and sex effects are also present in studies of ADHD as well as when ADHD is co-morbid with aggressive behavior [Faraone et al., 1991, 2015].

Given that ADHD and aggression often co-occur and that both traits are heritable, twin studies have noted the possibility of shared genetic etiology between ADHD and aggression. A common genetic factor has been reported among ADHD and symptoms of aggression in 9–10-year-old children [Tuvblad et al., 2009]. Likewise, it has been suggested that impulsivity and aggression are genetically mediated to a similar extent [Seroczynski et al., 1999].

Influenced by major theories on neuronal circuits, genetic association studies of ADHD and/or aggression have been dominated by candidate gene studies, focusing on the regulation of

monoaminergic transmission [Faraone et al., 2015; Veroude et al., 2015]. In line with twin studies, these candidate gene analyses have provided further support toward a shared genetic component between ADHD and aggression. Many genes associated with ADHD point toward the same biological mechanisms as those associated with aggressive behavior, including genes that are involved in the synthesis, binding, transport and degradation of neurotransmitters, especially dopamine and serotonin [Faraone et al., 2015; Veroude et al., 2015]. It has been reported, for example, that the genes *MAOA*, *DRD2*, *DRD4*, *COMT*, *SLC6A4*, *TPH1*, and *TPH2* may contribute to the development of ADHD as well as aggressive behaviors [Gizer et al., 2009; Vassos et al., 2014]. However, these candidate gene studies suffer from the lack of replication in independent samples (where available) and small effect sizes suggest that some of these genes play a more limited role in the susceptibility to ADHD and/or aggressive behavior, or that their involvement may be limited to rare familial cases [McKinney et al., 2008; Halmoy et al., 2010; Tiihonen et al., 2014]. Thus, the overall genetic architecture of ADHD and/or aggression remains largely unknown and warrants studies using a hypothesis-free approach [Vassos et al., 2014].

Genome-wide association (GWA) studies allow interrogation of the entire genome to generate new hypotheses. To date, few GWA studies have been performed for ADHD and/or aggressiveness, with no finding passing the stringent Bonferroni-corrected genome-wide significance level ($P < 5.00E-08$) for either phenotype [Dick et al., 2011; Tielbeek et al., 2012; Mick et al., 2014; Salvatore et al., 2015]. Nonetheless, as these studies were generally underpowered, some understanding of biological processes behind ADHD and/or aggressiveness may emerge from the convergence of identified nominally significant loci. Previous GWA studies on aggressive behaviors in ADHD have noted a number of suggestive association signals, generating biological hypotheses regarding the etiology of ADHD and/or aggression [Anney et al., 2008; Aebi et al., 2015]. In addition, a recent GWA study revealed a positive linear correlation between ADHD polygenic scores and comorbid aggression scores, indicating that the presence of aggressive symptoms in ADHD is likely to index a greater genetic load [Hamshere et al., 2013]. Similarly hypothesis-free, genome-wide linkage analyses have also reported evidence of significant co-segregation between ADHD and disruptive behavior [Jain et al., 2007].

The lack of robust genetic association signals may be explained by the modest sample sizes and the complex nature of both ADHD and aggressiveness, where genetic factors are intertwined with environmental influences [Brendgen et al., 2006]. In addition, heterogeneity in genetic susceptibility, phenotypic manifestation, and operationalization of aggressiveness may depress association signals [Cross-Disorder Group of the Psychiatric Genomics et al., 2013]. The phenotypic heterogeneity in ADHD may potentially be exacerbated by its high rates of comorbidity with not only aggressive behaviors, but also mood and anxiety disorders [Biederman et al., 1992]. Another possible reason behind the lack of replicable genetic findings is the limited annotation of the human genome. The annotation has mostly been focused on protein-coding genes that represent only ~1% of our genome, making it difficult to evaluate possible biological pathways involved in ADHD and/or aggressiveness, as the majority of GWA findings tend to reside outside the traditional protein-coding regions [Dick et al., 2011; Schizophrenia Working Group of the Psychiatric Genomics, 2014].

In the present study, we aimed to perform exploratory genome-wide association tests to shed light on the genetic susceptibility loci and biological processes possibly involved in the etiology of childhood aggressiveness in ADHD. We utilized the GWA method to analyze childhood aggressiveness in adults with ADHD gathered in studies across Europe. To minimize phenotypic heterogeneity between samples, we derived our measure of childhood aggressiveness in adult ADHD (aADHD) from the Wender Utah Rating Scale (WURS). This questionnaire was used as part of the assessment procedure at all sites. As the WURS reflects childhood recollections, we also explored a possible genetic overlap of association signals observed in aADHD with those of irritable and defiant/vindictive dimensions of ODD in youth with ADHD (cADHD) [Aebi et al., 2015]. Finally, we performed an examination of non-protein coding genes in order to obtain a better understanding of the biological processes underlying childhood aggressiveness in aADHD.

## MATERIALS AND METHODS

### Subjects

***aADHD samples.*** Recruitment of adult ADHD patients was conducted at three sites within an international multicenter persistent ADHD collaboration (IMpACT, http://www.impactadhdgenomics.com): Germany, Norway, and Spain. All individuals were of Caucasian ancestry. Only participants who gave written informed consent were enrolled in the studies, which complied with the Declaration of Helsinki.

***German sample.*** Patients with a diagnosis of aADHD were recruited by experienced psychiatrists at the University of Würzburg (Würzburg, Germany). Unrelated in- and outpatients of self-reported central-European descent completed a semi-structured clinical interview according to DSM-IV. Inclusion criteria were onset before the age of 7 years, lifelong persistence, current diagnosis and age of recruitment between 18 and 65 years. Exclusion criteria were the appearance of symptoms restricted to the duration of any other Axis I disorder; current diagnosis of active alcohol or other drug abuse or dependence; lifetime diagnosis of bipolar I disorder, schizophrenia, or any other psychotic disorder; and an IQ score below 80. For a more detailed sample description, please confer previous publications [Reif et al., 2009; Franke et al., 2010]. The study was approved by the Ethic Committee of the University of Würzburg (Würzburg, Germany).

***Norwegian sample.*** Participants were recruited at the University of Bergen (UiB, Bergen, Norway) as described elsewhere [Halmoy et al., 2009]. In short, adult patients with ADHD were recruited through a Norwegian national medical registry as well as by psychologists and psychiatrists working at outpatient clinics. All patients had been previously diagnosed with ADHD using either DSM-IV or ICD-10. The ICD-10 criteria were adapted to the DSM-IV criteria by allowing the inattentive subtype as sufficient for the ADHD diagnosis. Individuals with other neuropsychiatric disorders were not excluded as long as the ADHD criteria were fulfilled.

Individuals with IQ below 70 were excluded from the study. All participants provided either blood or saliva samples for DNA extraction. The study was approved by the regional committee for medical and health research ethics, western Norway.

***Spanish sample.*** Participants were recruited at the Department of Psychiatry from the Hospital Universitari Vall d'Hebron (HUVH, Barcelona, Spain) as described elsewhere [Sanchez-Mora et al., 2015]. Patients were adults of Caucasian origin and met Diagnostic and Statistical Manual for Mental Disorders-IV (DSM-IV) criteria for ADHD. The diagnosis of ADHD was evaluated with the Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID-I and SCID-II) and the Conner's Adult ADHD Diagnostic Interview for DSM-IV (CAADID Parts I and II). Consensus eligibility criteria for the current study were a diagnosis of ADHD according to the diagnostic criteria of DSM-IV, onset before the age of 7 years via retrospective diagnosis (which was confirmed by a family member, wherever possible), lifelong persistence and current diagnosis. DNA was extracted from either peripheral blood or saliva samples. The study was approved by the ethics committee of the institution.

***cADHD sample.*** Youth with ADHD were participants in the International Multicentre ADHD Genetics (IMAGE) study, recruited in 12 children and adolescent psychiatry clinics representing eight countries across Europe. Approval was obtained by the Institutional Review Board of SUNY Upstate Medical University and from ethical review boards within each country. A detailed description of the study design and assessment procedures has been provided in previous publications [Muller et al., 2011a,b]. In short, entry criteria for probands were a clinical diagnosis of ADHD according to DSM-IV-based structured interviews and access to one or both biological parents and one or more full siblings for DNA collection and clinical assessment. Exclusion criteria included autism, epilepsy, IQ $< 70$, brain disorders, and any genetic or medical disorder associated with externalizing behaviors that might mimic ADHD.

## Measures of Aggressiveness

***aADHD samples.*** The adult measure of childhood aggressiveness in the aADHD samples was derived from the Wender Utah Rating Scale (WURS) [Ward et al., 1993]. The WURS is a questionnaire used for retrospective assessment of childhood symptoms of ADHD in adults. An exploratory factor analysis (EFA) was run to determine the latent structure of the WURS. The EFA consisted of a principal component analysis with Varimax rotation and yielded three factors with Eigen values above one. From the main factor explaining the greatest amount of variance in responses to the WURS (30.7%), the top six items with the highest loadings (0.74–0.82) all represented prototypical elements of aggressiveness: "temper outburst/tantrums," "angry," "hot- or short-tempered/low boiling point," "disobedient with parents/rebellious/sassy," "losing control of myself," and "irritable," For each item, the participant was asked to evaluate if she/he as a child was (or had) a specific symptom and to rate it according to the following four response categories: "not at all/very slightly" (0), "mildly" (1), "moderately" (2), quite a bit" (3), or "very much" (4). The arithmetic sum of the responses of the aforementioned items was adopted as a continuous measure of aggressiveness, ranging from 0 to 24. Supplementary Figure S1 shows the distribution of this measure across genders in the three aADHD datasets.

***cADHD sample.*** The dimensions of oppositionality were assessed using the long form of the revised Conners Parent Rating Scale (CPRS-R:L) [Conners et al., 1998]. The defiant/vindictive and irritable dimensions of ODD were defined on theoretical grounds as described elsewhere [Aebi et al., 2015], and reflect two previously described dimensions of ODD [Stringaris et al., 2012; Aebi et al., 2013].

## Genotype Data

Genotyping of each sample was performed by each of the four participating groups, individually. To maximize available genetic information among examined datasets, genetic imputation was carried out independently at each site.

## aADHD Samples

***German sample.*** Genotyping of participants was performed on Illumina's PsychChip array (Illumina, San Diego, CA) at the Broad Institute (Cambridge, MA) using the PsychChip 15048346 B manifest. Genotypes were assigned in Illumina's GenomeStudio v2010.3, using the calling algorithm/genotyping module version 1.8.4. Quality control procedures were performed as described previously, with lightly modified exclusion criteria (SNPs exhibiting missingness above 98%; minor allele frequency below 5%; failing Hardy–Weinberg equilibrium test [$P < 10^{-4}$]) [Zayats et al., 2015]. Genotype imputation was performed with SHAPEIT/IMPUTE2 pipeline as described elsewhere, using 1000 Genomes Phase 3 data as a reference [Marchini et al., 2007; Howie et al., 2009; Cross-Disorder Group of the Psychiatric Genomics, 2013].

***Norwegian sample.*** Participants were genotyped on Human OmniExpress-12v1-1_B (Illumina, San Diego, CA) platform at the deCODE Genetics facility (Reykjavik, Iceland). Genotyping and quality control procedures are described elsewhere [Zayats et al., 2015]. Imputation was performed utilizing IMPUTE software as previously detailed [Marchini et al., 2007; Howie et al., 2009; Cross-Disorder Group of the Psychiatric Genomics, 2013].

***Spanish sample.*** Genome-wide genotyping was performed with the Illumina HumanOmni1-Quad BeadChip platform. Quality control was implemented at the individual and SNP level using PLINK and included filtering subjects with low call rate ($<$98%) or gender discrepancy followed by filtering SNPs with minor allele frequency (MAF) $< 0.01$, Hardy–Weinberg equilibrium test $P$-values $<$ 1e-06 or call rate $< 0.99$ in either cases or controls. Imputation was performed using BEAGLE software [Browning and Browning, 2007].

***cADHD sample.*** Sample collection and DNA isolation has been described previously [Brookes et al., 2006]. Genome-wide genotyping and quality control was performed as part of the GAIN study using the Perlegen 600 K genotyping platform, as previously described [Neale et al., 2008]. The imputation was performed using MACH and the Hapmap 2 (Release 22 Build 36) reference data set [Li et al., 2010]. Quality control was performed on the imputed data, and SNPs with imputation quality scores lower than 0.30, a

minor allele frequency lower than 0.01, and those failing the Hardy–Weinberg equilibrium test at a threshold of $P \leq 10^{-5}$ were excluded. SNPs and subjects with missingness rates higher than 0.05 were removed from the data.

## Statistical Analyses

The age and gender distributions between the aADHD and cADHD samples were assessed using $\chi^2$ for gender and ANOVA for age.

***Genome-wide association (GWA) of aggressiveness.*** In the aADHD sample, single nucleotide polymorphisms (SNPs) were tested for association with the WURS-derived measure of aggressiveness in the form of linear regression carried out in PLINK using post-imputation dosage data [Purcell et al., 2007]. Regression models were adjusted for age and sex. Genotype data of each site were first processed individually. The results were then combined with the use of fixed-effects inverse variance meta-analysis in METAL [Willer et al., 2010]. Only SNPs with minor allele frequency (MAF) equal to or above 1% and imputation INFO measure equal to or above 0.6 were included in the analyses. Genomic control, QQ plotting, and regional plotting of top loci were applied to check the integrity of test statistics [Devlin and Roeder, 1999; Cuellar-Partida et al., 2015]. The genomic inflation factor was calculated using METAL [Willer et al., 2010]. A genome-wide significance threshold of 5.00E-08 was adopted to correct for multiple testing.

GWA analyses of irritable and defiant/vindictive dimensions of ODD in cADHD sample was performed in PLINK software in the form of linear regression adjusted for sex and age [Purcell et al., 2007]. Details of the analyses are described elsewhere [Aebi et al., 2015].

***Gene-based and Gene-set association of aggressiveness in the aADHD meta-analyzed sample.*** Gene-based and gene-set pathway analysis were performed in the aADHD sample carried out in MAGMA software [de Leeuw et al., 2015]. First, a degree of association was calculated for each gene based on METAL-derived individual SNPs' *P*-values, using 1000 Genomes CEU dataset as a reference panel to correct for linkage disequilibrium (LD) [Genomes Project et al., 2012]. To evaluate each gene's contribution to examined gene-sets (gene-set pathway analysis), the *P*-value of each gene was converted to a *Z*-value and used as an outcome variable in a regression model with gene-set membership as a predictor. Gene size and gene-sets' gene density were added as covariates to adjust for possible confounding effects and prevent spurious association.

For gene-based tests, we assessed the association with both protein and non-protein-coding genes. The protein-coding gene list was curated from the catalog of known genes downloaded from the Genome Browser of the University of California Santa Cruz (UCSC, CA). The non-protein-coding genes were examined in the form of long non-coding RNA (lncRNA) genes detailed in the aforementioned catalog. For gene-set pathway analysis, we examined structural categories of gene ontology (GO, http://geneontology.org), with respect to cellular function, biological process and cellular compartments. To achieve meaningful statistics and interpretation of the results, we restricted our pathway analysis to those GO terms that contained SNPs in at least 10 genes per term in our aADHD data.

***Genome-wide enrichment analyses between GWA results in aADHD and cADHD samples.*** Prior to performing enrichment analyses, the genetic data in both aADHD and cADHD samples were pruned to remove correlated loci in linkage disequilibrium (LD) with each other. A pairwise correlation coefficient ($r^2$) threshold of 0.2 and the 1000 Genomes CEU reference dataset were used to identify independent SNPs, as previously described [Lindgren et al., 2009; Genomes Project et al., 2012].

Enrichment was examined by means of Fisher's test performed in the R software, assessing the difference in proportion of SNPs revealing association *P*-values below 0.05 in the cADHD sample according to suggestive association in the aADHD sample (*P*-value below or equal to 1.00E-03 versus *P*-value above 1.00E-03) [Rahmioglu et al., 2015]. Consistency in directionality of SNP effects with indication of enrichment between aADHD and cADHD samples was tested as linear regression on the effect (beta) of each SNP for aADHD as an outcome and for cADHD (either irritable or defiant/vindictive dimensions of ODD, respectively) as predictor variables [Do et al., 2013].

***Examination of previously reported aggressiveness-related candidate GWA loci.*** We assembled a list of previously reported candidate GWA loci associated with aggressive behavior by systematic literature search the catalog of published genome-wide association studies provided by National Human Genome Research Institute (NHGRI) (https://www.genome.gov/26525384), using key words of "aggression," "anger," "violence," as well as "conduct disorder" and "antisocial personality disorder." Each identified candidate GWA locus was then looked up in meta-analyzed aADHD sample.

# RESULTS

## Subjects, Measure of Aggressiveness, and GWA Analyses

In total, 1,060 adult patients as well as 750 children and adolescents with ADHD were available for the analyses. The age ranges in the aADHD samples were 17–75 in the German sample, 18–57 in the Norwegian sample, and 17–60 in the Spanish sample. In the cADHD sample, the age range was 5–17. Details of the final samples are summarized in Table I. Supplementary Figure S1 presents the distribution of the selected measure of aggressiveness in each aADHD dataset.

After quality control of imputed SNPs in the adult samples, 9.301.568 SNPs were available for the analyses in the German sample, 8.910.491 SNPs in the Norwegian sample, and 6.683.176 SNPs in the Spanish sample. Among these three datasets, 7.576.458 autosomal SNPs were present in at least two and, thus, were meta-analyzed to assess genetic architecture of childhood aggressiveness in aADHD. In cADHD sample, 1.871.025 autosomal SNPs were available for the analyses.

Individual GWA analyses revealed no genome-wide significant hits ($P \leq 5.00E-08$) in either aADHD sample (not shown) nor in the cADHD sample (Supplementary Table SI and Fig. S2). None of the variants in the meta-analysis reached the Bonferroni-corrected genome-wide significance level ($P \leq 5.00E-08$) either. The strongest signal was observed at rs10826548 on chromosome 10 located within the transcript of a long noncoding RNA (lncRNA) (beta $= -1.66$,

TABLE I. Details of the ADHD Patient Samples

| aADHD samples | | | | |
|---|---|---|---|---|
| IMpACT site | Number of participants | Females (%) | Age (mean ± SD) | Aggressiveness score (mean ± SD) |
| Germany | 368 | 53.0 | 35.18 ± 10.53 | 11.33 ± 5.17 |
| Norway | 293 | 52.6 | 32.61 ± 11.00 | 12.10 ± 6.39 |
| Spain | 399 | 32.3 | 31.31 ± 12.39 | 10.19 ± 6.15 |
| Total | 1,060 | 45.1 | 33.01 ± 11.51 | 11.11 ± 5.94 |

| cADHD sample | | | | | |
|---|---|---|---|---|---|
| | | | | ODD scores (mean ± SD) | |
| | Number of participants | Females[a] (%) | Age[b] (mean ± SD) | Irritable | Defiant/vindictive |
| IMAGE | 750 | 12.3 | 10.67 ± 2.77 | 7.75 ± 3.06 | 8.95 ± 4.18 |

SD, standard deviation.
Aggressiveness score was derived from WURS in the aADHD sample. In the cADHD sample, dimensions of oppositionality (irritable and defiant/vindictive dimensions) were examined [Aebi et al., 2015].
[a]Difference in the proportion of females between the aADHD and cADHD samples: $P < 2.2E\text{-}16$ ($\chi^2$ test).
[b]Difference in age between the aADHD and cADHD samples: $P < 2.2E\text{-}16$ (ANOVA).

standard error (SE) = 0.34, *P*-value = 1.07E-06) (Fig. 1), closely followed by rs35974940 in the neurotrimin (*NTM*) gene (beta = 3.23, SE = 0.67, *P*-value = 1.26E-06) (Fig. 2). Top associated markers ($P \leq 1.00E\text{-}05$) are summarized in Supplementary Table SII. The genomic inflation factor was close to one for all individual and meta-GWA analyses in aADHD. QQ plots of GWA analyses in aADHD are presented in Supplementary Figure S3.

## Gene-Based and Gene-Set Association of Aggressiveness in the aADHD Meta-Analyzed Sample

Among annotated protein-coding genes, 17.595 had more than one SNP present in the aADHD data. The strongest signal was noted for the WD repeat domain 62 (*WDR62*) gene (*P*-value = 4.84E-05). Supplementary Table SIII summarizes the top protein-coding genes ($P \leq 1.00E\text{-}03$) observed in aADHD sample. None of the protein-coding gene-based tests survived the correction for multiple testing.

Among lncRNA genes, 22.696 had more than one SNP present in our aADHD data. The strongest association was observed for ENST00000427806 (*P*-value = 3.04E-05). The top lncRNA genes ($P \leq 1.00E\text{-}03$) detected in this study are reported in Supplementary Table SIV. None of the non-protein-coding gene-based tests survived the correction for multiple testing.

Among GO pathways, 1.945 terms contained SNPs in at least 10 genes per term in the aADHD data. The most prominent association was observed for negative regulation of I-kappaB kinase/NF-kappaB signaling pathway (GO:0043124 term, *P*-value = 7.26E-04). Supplementary Table SV reports top GO terms ($P \leq 0.01$) recognized in this study. None of the GO pathways survived the correction for multiple testing.

## Genome-Wide Enrichment Analyses Between GWA Results in aADHD and cADHD Samples

To assess potential genome-wide overlap of association signals between measures of childhood aggressiveness in aADHD and cADHD, we investigated the independent ($r^2 < 0.2$) GWA signals of suggestive significance ($P \leq 1.00E\text{-}03$) in aADHD for enrichment in GWA signals of either defiant/vindictive or irritable dimensions in cADHD. Given our modest sample size, only those SNPs were considered in cADHD results that revealed a *P*-value below or equal to 0.05 to avoid the examination of effects with a wide confidence interval. The top GWA SNPs of WURS-derived childhood aggressiveness in aADHD showed significant enrichment of signals from both the defiant/vindictive dimension (Fisher's *P*-value = 2.28E-06) and the irritable dimension in cADHD GWA analysis (Fisher's *P*-value = 0.0061; Fig. 3A).

Next, we examined the directionality of effects of variants with association signals in both aADHD and cADHD samples ($P \leq 1.00$ E-03 in aADHD and $P < 0.05$ in cADHD). Significant correlation between betas was observed in assessment of both oppositional dimensions in cADHD and childhood aggressiveness in aADHD ($P = 0.0053$ and 0.0045 for defiant/vindictive and irritable dimensions respectively), but the direction of the relationship was negative (Fig. 3B and C). Supplementary Table SVII summarizes the top hits ($P \leq 1\text{-}00E\text{-}05$) observed in GWA meta-analysis of childhood aggressiveness in aADHD and their corresponding statistics observed in cADHD.

## Examination of Previously Reported Aggressiveness-Related Candidate Genes and GWA Loci

Among previously reported aggressiveness-related GWA loci, several SNPs noted to be associated with anger, conduct disorder and adult anti-social personality disorder revealed *P*-values below 0.05 in our study (Supplementary Table SVIII). The strongest signal in the GWA analysis of childhood aggressiveness in aADHD among the aforementioned loci was observed for rs4889240 in the *PKD1L2* (polycystic kidney disease 1-like 2) gene (beta = −0.73, SE = 0.25, *P*-value = 0.0039), previously

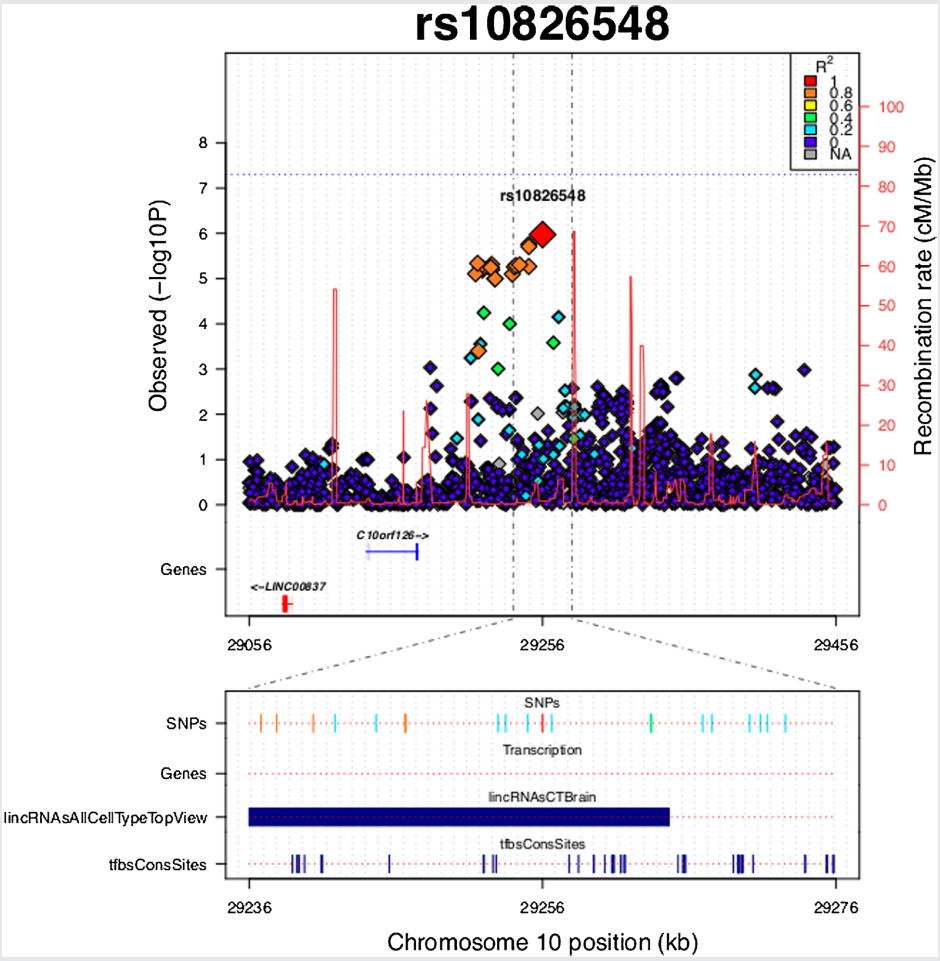


**FIG. 1. Plot of the locus surrounding rs10826548. SNPs are plotted by position on chromosome 10 against GWA *P*-values for aggressive behavior measure in aADHD. Estimated recombination rates from HapMap are plotted in bright red to reflect local LD structure. The SNPs surrounding rs10826548 are color-coded to reflect their LD with it (according to pair-wise $r^2$ values from the HapMap CEU database). SNPs with LD $r^2 \geq 0.2$ are plotted at the bottom of the graph with LD color-coding specified in the top right corner. "Genes" refers to protein-coding genes in the presented region. "lincRNAsAllCellTypeTopView" reflects the data from lncRNA USCS track in brain tissue. "tfbsConsSites" reflects the TFBS UCSC track. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb].**

reported to be associated with CD symptom count in ADHD patients. The same SNP also revealed nominally significant association in the same direction with the defiant/vindictive dimension (beta = −0.54, SE = 0.21, *P*-value = 0.0094), but not with the irritable dimension in cADHD. In this result, one should keep in mind that the cADHD described here is a subsample of the sample in which the original finding for rs4889240 was described [Aebi et al., 2015]. Full results of our literature search are presented in Supplementary Table SVIII.

## DISCUSSION

In this study, we performed a genome-wide exploration of childhood aggressiveness as reported retrospectively by adult patients with ADHD (aADHD), examining both conventional protein-coding and lncRNA genes. We also explored the overlap with parent-reported oppositional behavior in youth with ADHD (cADHD) and evaluated previously reported aggression-related GWA loci. Given our modest sample size (1060 aADHD patients)

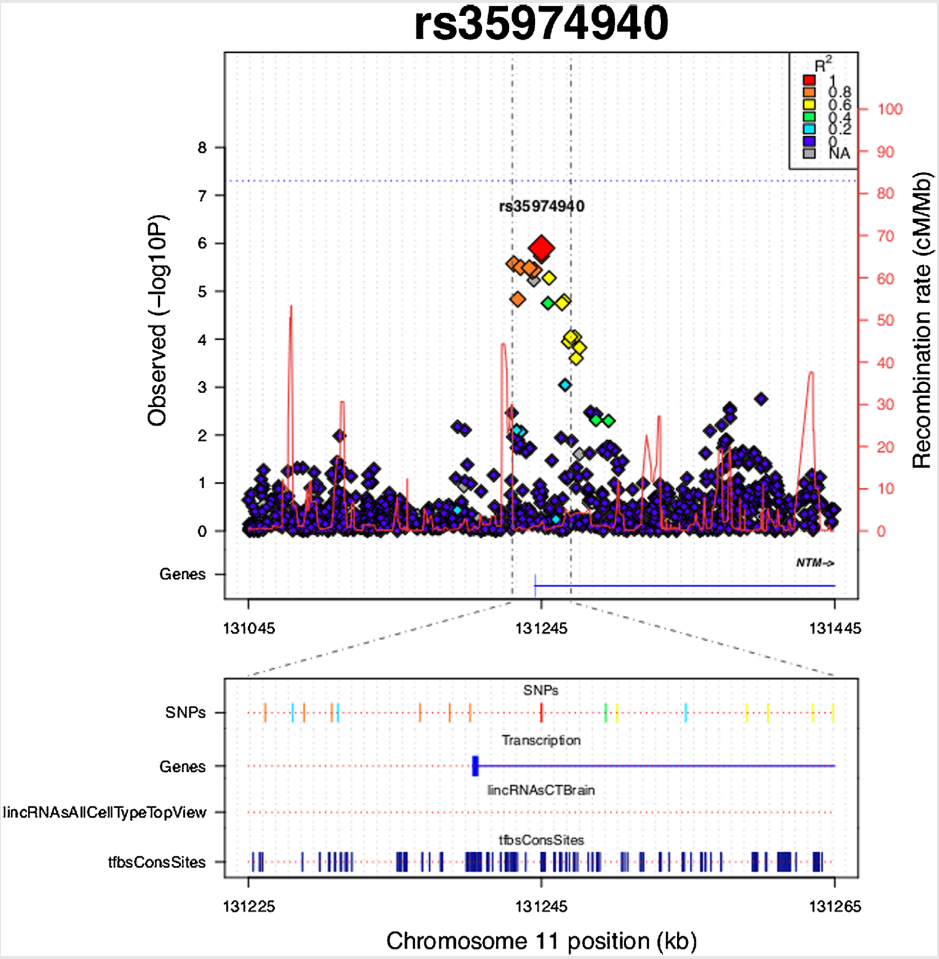


**FIG. 2. Plot of the locus surrounding rs35974940. SNPs are plotted by position on chromosome 11 against GWA *P*-values for aggressive behavior measure in aADHD. Estimated recombination rates from HapMap are plotted in bright red to reflect local LD structure. The SNPs surrounding rs35974940 are color-coded to reflect their LD with it [according to pair-wise $r^2$ values from the HapMap CEU database). SNPs with LD $r^2 \geq 0.2$ are plotted at the bottom of the graph with LD color-coding specified in the top right corner. "Genes" refers to protein-coding genes in the presented region. "lincRNAsAllCellTypeTopView" reflects the data from lncRNA USCS track in brain tissue. "tfbsConsSites" reflects the TFBS UCSC track. [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmgb].**

and the anticipated small effect of common polymorphisms in complex traits, it is not surprising that we did not observe any genome-wide significant SNPs ($P < 5.00E-08$). Nonetheless, we were able to identify several nominally significant variants ($P \leq 1.00E-05$) in biologically interesting genes for follow-up studies of aggressiveness in ADHD, a feature of the disorder that has received little attention so far.

The strongest signal in the performed single-point GWA tests of childhood aggressiveness in aADHD was noted for rs10826548 (beta = −1.16, SE = 0.34, $P = 1.07E-06$, Supplementary Table SI). This variant resides in the transcript of a lncRNA with uncertain coding potential (TCONS_00018147) (Fig. 1). Non-protein coding RNAs play a critical role in the regulation of gene expression and have been previously associated with neuropsychiatric disorders, including ADHD [Perkins et al., 2005; Gonzalez-Giraldo et al., 2015; Zayats et al., 2015]. In addition, it has recently been observed that SNPs previously associated with neurological and psychiatric conditions may be highly

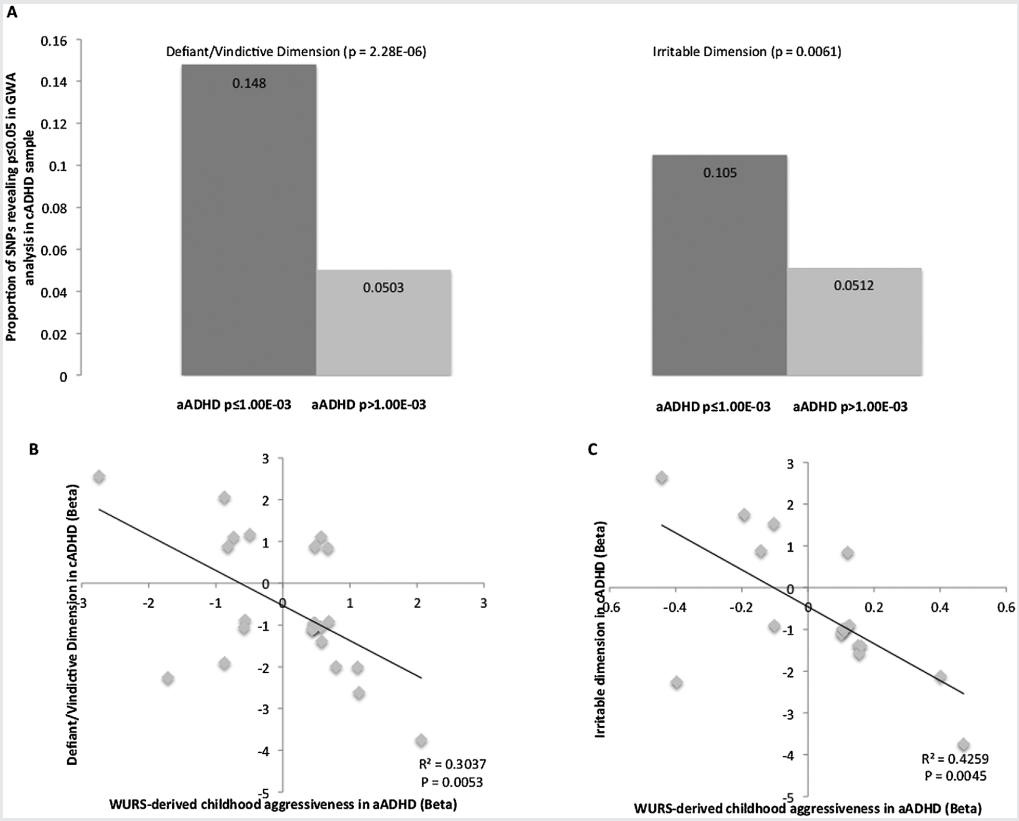


**FIG. 3. Enrichment and direction of effect among GWA signals of oppositional dimensions in cADHD and WURS-derived childhood aggressiveness in aADHD. Part A reflects the proportion of SNPs nominally associated ($P < 0.05$) with each examined oppositional dimension in cADHD (defiant/vindictive and irritable) among suggestive signals ($P \leq 1.00E-03$) of association with childhood aggressiveness in aADHD. Reported *P*-values are those of Fisher's exact test. Parts B and C reflect directions of effect of 24 independent nominally significant loci in GWA analyses of defiant/vindictive dimension in cADHD and childhood aggressiveness in aADHD (part B) as well as 17 independent nominally significant loci in GWA analyses of irritable dimension in cADHD and childhood aggressiveness in aADHD (part C). Linear regression $r^2$ measures and *P*-values are shown.**

concentrated in the regions of long non-protein coding RNA genes [Ning et al., 2014].

The second most significant locus identified in this study is located within the neurotrimin (*NTM*) gene (intronic rs35974940, $P = 1.26E-06$, Supplementary Table SI and Fig. S2). *NTM* is a protein-coding gene, encoding a member of glycosylphosphatidylinositol (GPI)-anchored cell adhesion molecules, containing immunoglobulin (Ig) domain. These proteins are predominantly expressed in the central nervous system (CNS) [Struyk et al., 1995].

Among the association signals observed in *NTM* gene, several have the potential to alter its expression. As determined in the TRANSFAC database implemented in the SNPinfo server of the National Institute of Environmental Health Sciences (http://snpinfo.niehs.nih.gov), rs34588147 and rs35665773 (GWA *P*-values of 3.59E-06 and 3.25E-06, respectively, Supplementary Table SI) are transcription factor binding sites (TFBS) (Fig. 2). Moreover, two other SNPs in high linkage disequilibrium with the aforementioned ones (rs12804059 and rs7119590, $r^2 = 1$ in CEU population) also represent TFBS. Notably, differential expression of *NTM* between two major brain regions linked to aggression subtypes—prefrontal cortex and amygdala—was observed in early prenatal stage of human brain development ($P = 0.015$, http://www.brainspan.org).

Gene expression regulation during neuronal development as one of the possible mechanisms behind aggressiveness in aADHD was further affirmed by our top associated lncRNA gene—ENST00000427806 ($P = 3.04E-05$, Supplementary Table SIV). The target gene of this lncRNA has been predicted to be the protein-coding ST6

(alpha-N-acetyl-neuraminyl-2,3-beta-galactosyl-1,3)-N-acetylgalactosaminide alpha-2,6-sialyltransferase 5 (*ST6GALNAC5*) gene [Vucicevic et al., 2015]. The protein encoded by *ST6GALNAC5* is a member of sialyltransferases, with reported function in cell adhesion through cell–cell and cell–extracellular matrix interactions [Tsuchida et al., 2003]. Intriguingly, *ST6GALNAC5*, similarly to *NTM*, also revealed differential expression in the aggression-related structures of prefrontal cortex and amygdala in early prenatal stages of human brain development ($P = 0.013$; http://www.brainspan.org).

As the adult measure of aggressiveness was derived from self-reported experiences in childhood, we examined the possibility of overlap of its GWA signals with those from GWA analyses of two oppositional dimensions in a cADHD sample. We observed a slight enrichment of association signals between the nominally associated loci in aADHD and those observed in the GWA of both the defiant/vindictive and the irritable ODD dimensions examined in cADHD (Fig. 3). However, it is noteworthy that the aADHD and cADHD samples were imputed using different reference panels with disparate genomic coverage.

Surprisingly, the correlation between the direction of effects of the aforementioned SNPs was negative (Fig. 3B and C). Such an inverse relationship in effect directionality between parent-reported ODD dimensions and adult retrospective report of childhood aggressiveness is most likely a chance finding due to our study being under-powered. It might also be related to phenotypic and genetic heterogeneity of the examined samples. There were considerable differences in the percentage of females between the aADHD and the cADHD samples (Table I), which could indicate such mechanisms. It has been shown that both age and sex are important factors in genetic influences in ADHD and aggression [Lyons et al., 1995; Miles and Carey, 1997; Tuvblad and Baker, 2011; Faraone et al., 2015]. In addition, the aggressiveness in the cADHD sample was determined by parent-report, whereas in the aADHD sample, it was based on retrospective self-report. The correlation between parent-report and self-report has been shown to be generally poor [Achenbach et al., 1987], as also discussed in a recent study that found little overlap between samples of cADHD and aADHD [Moffitt et al., 2015]. Hence, the measures of aggressiveness in the cADHD and the aADHD samples are different. Furthermore, the youth and adult ADHD samples may also be heterogeneous because childhood ADHD does not always persist into adulthood [Faraone et al., 2006; Moffitt et al., 2015]. Thus, to gain better understanding of the genetic overlap between childhood aggression in aADHD and oppositional dimensions in cADHD, this relationship should be examined in larger sample using more rigorous statistical methods, such as those developed to test specifically for genetic correlation among various traits [Yang et al., 2011; Bulik-Sullivan et al., 2015a,b]. This was not possible to implement in the current study due to our modest sample size.

Examination of previously reported aggressiveness-related GWA loci revealed modest commonality in genetic architecture between the childhood measures of aggressiveness in both cADHD and aADHD, as well as in CD and anti-social personality disorder (Supplementary Table SVIII). This observation may be in line with formerly reported phenotypic overlap between these conditions, although to which extent this overlap can be transmitted to various subtypes of aggressiveness remains to be determined [Storebo and Simonsen, 2013].

This study should be viewed in light of its limitations. One explanation for not observing any genome-wide significant loci ($P < 5.00E-08$) could be our relatively modest sample size and examination of common variants only (MAF > 1%). This study had 63% power to detect common variants with small effect size of explaining 0.5% of variability under an additive model and an alpha level of 0.05 (http://genome.sph.umich.edu/wiki/Power_Calculations: Quantitative_Traits). This may also be observed in the distribution of the QQ plots (Supplementary Fig. S3).

Another explanation for the lack of significant findings may lay in phenotypic variability. Clinical heterogeneity may weaken true association signals due to the use of different assessment protocols or real genetic heterogeneity among subtypes of ADHD [McClellan and King, 2010]. There are several methodological caveats to assessing aggressiveness [Moffitt et al., 2015]. As our samples consist of outpatients, we investigate a broader and perhaps "softer" aspect of aggressiveness than say, for example, if we were to study prison inmates and/or juvenile offenders. However, this approach provides us with access to the vast majority of aggressive behaviors, which may not come to be written in official records [Moffitt, 2005]. Furthermore, we lack assessment of different subtypes of aggressive behavior that may be related to different genotypes.

Considering the different direction of effects and different measures of aggression in the cADHD and the aADHD samples, analyzing the adult samples and the youth sample together could potentially have obscured the genetic association signal. This is why we refrained from performing meta-analysis across all samples. Nonetheless, the WURS includes a host of symptoms related to various elements of aggressiveness, which, based on our factor analysis as well as previous research [Ward et al., 1993] seem to be of key importance to the phenotype of aADHD, and the ODD measures have also been validated in previous studies of cADHD [Stringaris et al., 2012; Aebi et al., 2013]. Our approach may add to the discussion of the Negative Valence System in the Research Domain Criteria (RDoC) of the National Institute of Mental Health (NIMH) of how to conceptualize and operationalize aggressiveness as a dimension across different samples and disorders [Verona and Bresin, 2015; Veroude et al., 2015].

We lacked information on current substance abuse in our aADHD sample. Substance abuse is known to be frequently comorbid with ADHD and may confound the relationship between ADHD and current aggressiveness. However, we utilized a retrospective measure of childhood aggressiveness that is likely to reflect behavior over a longer period of time and should, thus, be less affected by volatile environmental influences [Gulberg-Kjär and Johansson, 2009].

Finally, since the genome-wide genotyping arrays consist of SNPs only, we were not able to assess the contribution of previously reported variable tandem repeats (e.g., those in MAOA) that were noted to be associated with aggressive behaviors and/or ADHD.

Taken together with evidence from previous studies, our results implicate mechanisms of cell adhesion as well as regulation of gene expression in the etiology of childhood aggressiveness in ADHD. As there is a substantial degree of overlap in aggressiveness among neuropsychiatric disorders, it could be beneficial to analyze

conditions where aggression is present together in order to pinpoint biological processes in dysfunctional forms of aggressiveness. Further studies including samples of both children, adolescents and adults, adopting multimodal measures and longitudinal designs are warranted. Such studies may help our understanding as to which extent various subtypes of aggression are mediated by different mechanisms.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

# Appendix

## SPØRRESKJEMA FOR PASIENT

*August 2011*

Navn: _____

Personnummer: _____

**Er du tvilling?**

☐ Ja ☐ Nei

**Utdanning**

☐ Universitet/høyskole
☐ Videregående skole
☐ Ungdomsskole

**Yrkesstatus**

☐ I arbeid
☐ Sykmeldt
☐ Uføretrygdet
☐ Arbeidsavklaringspenger
☐ Arbeidsledig
☐ Annet

Evt. hva: _____

**Etnisk bakgrunn**

☐ Begge foreldre norske

Evt. annen opprinnelse:

_____

_____

| | | |
|---|---|---|
| Hadde du som barn diagnostisert hyperkinetisk lidelse/ADHD? | ja ☐ | nei ☐ |
| Tror du selv at du som barn hadde ADHD? | ja ☐ | nei ☐ |
| Ble du som barn behandlet med Ritalin eller amfetamin? | ja ☐ | nei ☐ |
| Hvis ja, hvor lenge fikk du slik behandling? _____ | | |
| Har du eller har du hatt lese- eller skrivevansker? | ja ☐ | nei ☐ |
| Har du eller har du hatt epilepsi? | ja ☐ | nei ☐ |
| Har du eller har du hatt migrene? | ja ☐ | nei ☐ |
| Har du eller har du hatt astma? | ja ☐ | nei ☐ |
| Har du eller har du hatt betydelig angst eller depresjon? | ja ☐ | nei ☐ |
| Har du eller har du hatt autisme, tics, Tourettes eller Aspergers syndrom? | ja ☐ | nei ☐ |
| Har du eller har du hatt psykisk utviklingshemming? | ja ☐ | nei ☐ |
| Har du bipolar eller manisk depressiv lidelse? | ja ☐ | nei ☐ |
| Har du eller har du hatt problem med alkohol? | ja ☐ | nei ☐ |
| Har du prøvd andre rusmidler? | ja ☐ | nei ☐ |
| Har du eller har du hatt problem med andre rusmidler? | ja ☐ | nei ☐ |
| Har du eller har du hatt annen psykisk lidelse? | ja ☐ | nei ☐ |
| Har du fått behandling for annen psykisk lidelse enn ADHD? | ja ☐ | nei ☐ |
| Har du eller har hatt spiseforstyrrelse (bulimi, anorexia nervosa)? | ja ☐ | nei ☐ |

**Er det noen blant dine foreldre, søsken eller barn som har eller har hatt:**

| | | | |
|---|---|---|---|
| hyperkinetisk lidelse/ADHD? | ja ☐ | nei ☐ | usikker ☐ |
| lese- eller skrivevansker? | ja ☐ | nei ☐ | usikker ☐ |
| epilepsi? | ja ☐ | nei ☐ | usikker ☐ |
| migrene? | ja ☐ | nei ☐ | usikker ☐ |
| astma? | ja ☐ | nei ☐ | usikker ☐ |
| betydelig angst eller depresjon? | ja ☐ | nei ☐ | usikker ☐ |
| autisme, tics, Tourettes eller Aspergers syndrom? | ja ☐ | nei ☐ | usikker ☐ |
| psykisk utviklingshemming? | ja ☐ | nei ☐ | usikker ☐ |
| bipolar (manisk depressiv) lidelse? | ja ☐ | nei ☐ | usikker ☐ |
| problem med alkohol? | ja ☐ | nei ☐ | usikker ☐ |
| problem med andre rusmidler? | ja ☐ | nei ☐ | usikker ☐ |
| annen psykisk lidelse? | ja ☐ | nei ☐ | usikker ☐ |

**Sett ring rundt det tallet som best mulig beskriver din atferd i løpet av de siste 6 måneder**

| | | Aldri | Sjelden | Av og til | Ofte | Veldig ofte |
|---|---|---|---|---|---|---|
| **1.** | Hvor ofte gjør du ubetenksomme feil når du må arbeide med en kjedelig eller vanskelig oppgave? | 0 | 1 | 2 | 3 | 4 |
| **2.** | Hvor ofte har du vansker med å opprettholde oppmerksomheten når du utfører kjedelig arbeid eller arbeid som innebærer gjentakelser? | 0 | 1 | 2 | 3 | 4 |
| **3.** | Hvor ofte har du vansker med å konsentrere deg om hva andre sier til deg, selv om de snakker direkte til deg? | 0 | 1 | 2 | 3 | 4 |
| **4.** | Hvor ofte har du vansker med å få gjort ferdig de siste detaljer av en oppgave, når den utfordrende delen er gjennomført? | 0 | 1 | 2 | 3 | 4 |
| **5.** | Hvor ofte har du vansker med å få plassert saker i riktig rekkefølge når du arbeider med oppgaver som krever organisering? | 0 | 1 | 2 | 3 | 4 |
| **6.** | Når du har en oppgave som krever mye gjennom-tenkning, hvor ofte unngår eller utsetter du å begynne med den? | 0 | 1 | 2 | 3 | 4 |
| **7.** | Hvor ofte har du forlagt eller har vansker med å finne igjen ting hjemme eller på jobben? | 0 | 1 | 2 | 3 | 4 |
| **8.** | Hvor ofte distraheres du av aktiviteter og støy rundt deg? | 0 | 1 | 2 | 3 | 4 |
| **9.** | Hvor ofte har du vanskeligheter med å huske avtaler eller forpliktelser? | 0 | 1 | 2 | 3 | 4 |
| **10.** | Når du må sitte stille over en lengre tid, hvor ofte beveger du hender eller føtter på en urolig eller rastløs måte? | 0 | 1 | 2 | 3 | 4 |
| **11.** | Hvor ofte må du forlate din plass i møter eller andre situasjoner, hvor det forventes at du blir sittende? | 0 | 1 | 2 | 3 | 4 |
| **12.** | Hvor ofte føler du deg rastløs eller urolig? | 0 | 1 | 2 | 3 | 4 |
| **13.** | Hvor ofte har du vansker med å koble ut og slappe av når du har tid til deg selv? | 0 | 1 | 2 | 3 | 4 |
| **14.** | Hvor ofte føler du deg overaktiv og tvunget til å gjøre ting, som om du var drevet av en motor? | 0 | 1 | 2 | 3 | 4 |
| **15.** | Hvor ofte opplever du at du snakker for mye i sosiale situasjoner? | 0 | 1 | 2 | 3 | 4 |
| **16.** | Når du deltar i en samtale, hvor ofte fullfører du andres setninger før de selv kan gjøre det? | 0 | 1 | 2 | 3 | 4 |
| **17.** | Hvor ofte har du vansker med å vente på at det er din tur i situasjoner hvor det forventes at man venter på tur? | 0 | 1 | 2 | 3 | 4 |
| **18.** | Hvor ofte forstyrrer du andre når de er opptatt? | 0 | 1 | 2 | 3 | 4 |

**Som barn var jeg/hadde jeg (sett ring rundt det tallet som passer best):**

| | | Ikke i det hele tatt el. bare litt | Av og til | En del | Nokså mye | Veldig mye |
|---|---|---|---|---|---|---|
| **1.** | Konsentrasjonsproblemer, lett å distrahere | 0 | 1 | 2 | 3 | 4 |
| **2.** | Engstelig, bekymret | 0 | 1 | 2 | 3 | 4 |
| **3.** | Nervøs, urolig | 0 | 1 | 2 | 3 | 4 |
| **4.** | Uoppmerksom, dagdrømmende | 0 | 1 | 2 | 3 | 4 |
| **5.** | Hissig temperament, ble lett sint | 0 | 1 | 2 | 3 | 4 |
| **6.** | Raserianfall | 0 | 1 | 2 | 3 | 4 |
| **7.** | Problemer med å holde seg til en aktivitet, fullførte ikke det en hadde begynt på | 0 | 1 | 2 | 3 | 4 |
| **8.** | Sta, sterk viljestyrke | 0 | 1 | 2 | 3 | 4 |
| **9.** | Trist, deprimert, ikke glad | 0 | 1 | 2 | 3 | 4 |
| **10.** | Ulydig, uforskammet, frekk | 0 | 1 | 2 | 3 | 4 |
| **11.** | Dårlig selvbilde | 0 | 1 | 2 | 3 | 4 |
| **12.** | Irritabel | 0 | 1 | 2 | 3 | 4 |
| **13.** | Humørsyk, humøret svingte ofte | 0 | 1 | 2 | 3 | 4 |
| **14.** | Sint | 0 | 1 | 2 | 3 | 4 |
| **15.** | Vanskelig for å se ting fra andres synsvinkel | 0 | 1 | 2 | 3 | 4 |
| **16.** | Handlet uten å tenke, var impulsiv | 0 | 1 | 2 | 3 | 4 |
| **17.** | Tendens til å være umoden | 0 | 1 | 2 | 3 | 4 |
| **18.** | Plaget av skyldfølelse og anger | 0 | 1 | 2 | 3 | 4 |
| **19.** | Lett for å miste kontrollen over meg selv | 0 | 1 | 2 | 3 | 4 |
| **20.** | Tendens til å være, eller oppføre meg irrasjonelt | 0 | 1 | 2 | 3 | 4 |
| **21.** | Upopulær blant andre barn, hadde bare venner for en kort stund, kom dårlig overens med andre barn | 0 | 1 | 2 | 3 | 4 |
| **22.** | Trøbbel med autoriteter, problemer på skolen, ble sendt til rektor | 0 | 1 | 2 | 3 | 4 |
| **23.** | Lite flink, lærte sent | 0 | 1 | 2 | 3 | 4 |
| **24.** | Problemer med matematikk eller tall | 0 | 1 | 2 | 3 | 4 |
| **25.** | Fikk aldri vist hva jeg kunne klare | 0 | 1 | 2 | 3 | 4 |

## Søvn og søvnproblemer

1. Har du i løpet av livet hatt en periode på en måned eller mer der du har hatt søvnproblemer? ☐ Ja ☐ Nei

2. Har du noen gang benyttet reseptbelagt(e) sovemedisin(er)? ☐ Ja ☐ Nei

3. Hvor ofte har du i løpet av de siste 4 ukene sovnet uten at du ville det eller måtte kjempe for å holde deg våken på dagtid?

☐ Aldri ☐ Noen ganger ☐ Vanligvis (mesteparten av tiden) ☐ Alltid (hele tiden)

4. Hvor ofte har du i løpet av de siste 4 ukene hatt urolige eller maurende følelser i beina om kvelden eller natten, og som ble bedre av bevegelse?

☐ Aldri ☐ Noen ganger ☐ Vanligvis (mesteparten av tiden) ☐ Alltid (hele tiden)

5. Kjenner du til (eventuelt gjennom andre) om du i løpet av de siste 4 ukene har hatt gjentatte rykninger eller bevegelser i beina i søvne?

☐ Aldri ☐ Noen ganger ☐ Vanligvis (mesteparten av tiden) ☐ Alltid (hele tiden)

6. Kjenner du til (eventuelt gjennom andre) om du i løpet av de siste 4 ukene har snorket høyt?

☐ Aldri ☐ Noen ganger ☐ Vanligvis (mesteparten av tiden) ☐ Alltid (hele tiden)

7. Kjenner du til (eventuelt gjennom andre) om du i løpet av de siste 4 ukene har hatt pustepauser eller stoppet å puste i søvne?

☐ Aldri ☐ Noen ganger ☐ Vanligvis (mesteparten av tiden) ☐ Alltid (hele tiden)

8. Hvor ofte har du i løpet av de siste 4 ukene opplevd plutselig tap av muskelkraft (f.eks. knekk i knærne) ved følelsesmessige reaksjoner som f.eks. latter, sinne eller frykt?

☐ Aldri ☐ Noen ganger ☐ Vanligvis (mesteparten av tiden) ☐ Alltid (hele tiden)

9. Er du morgen- eller kveldsmenneske?

☐ Utpreget morgenmenneske
☐ Mer morgen- enn kveldsmenneske
☐ Verken eller
☐ Mer kvelds- enn morgenmenneske
☐ Utpreget kveldsmenneske

Sett ring rundt det alternativet (antall dager pr. uke) som passer best for deg.
0 er ingen dager i løpet av en uke, 7 er alle dager i løpet av en uke. Sett ring rundt ett tall for hvert spørsmål.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 10. I løpet av den siste måneden, hvor mange dager pr. uke har du brukt mer enn 30 minutter for å sovne etter at lysene ble slukket? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 11. I løpet av den siste måneden, hvor mange dager pr. uke har du vært våken mer enn 30 minutter innimellom søvnen? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 12. I løpet av den siste måneden, hvor mange dager pr. uke har du våknet mer enn 30 minutter tidligere enn du har ønsket uten å få sove igjen? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 13. I løpet av den siste måneden hvor mange dager pr. uke har du følt deg for lite uthvilt etter å ha sovet? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 14. I løpet av den siste måneden, hvor mange dager pr. uke har du vært så søvnig/trett at det har gått ut over skole/jobb eller privatlivet? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 15. I løpet av den siste måneden, hvor mange dager pr. uke har du vært misfornøyd med søvnen din? | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

16. Hvor mye søvn får du gjennomsnittlig per døgn? ____ timer ____ minutter

17. Hvordan synes du at du sover totalt sett? (Sett strek under)
Veldig bra Ganske bra Hverken bra eller dårlig Ganske dårlig Veldig dårlig

18. Har det vært spesielle forhold (livssituasjon, helse m.m.) som har påvirket søvnen din siste 4 uker?
Ja ☐ Nei ☐ Usikker ☐
Og i så fall hvilke? (Fritekst svar)

# Doctoral Theses at The Faculty of Psychology, University of Bergen

| | | |
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| **1980** | Allen, H.M., Dr. philos. | Parent-offspring interactions in willow grouse (Lagopus L. Lagopus). |
| **1981** | Myhrer, T., Dr. philos. | Behavioral Studies after selective disruption of hippocampal inputs in albino rats. |
| **1982** | Svebak, S., Dr. philos. | The significance of motivation for task-induced tonic physiological changes. |
| **1983** | Myhre, G., Dr. philos. | The Biopsychology of behavior in captive Willow ptarmigan. |
| | Eide, R., Dr. philos. | PSYCHOSOCIAL FACTORS AND INDICES OF HEALTH RISKS. The relationship of psychosocial conditions to subjective complaints, arterial blood pressure, serum cholesterol, serum triglycerides and urinary catecholamines in middle aged populations in Western Norway. |
| | Værnes, R.J., Dr. philos. | Neuropsychological effects of diving. |
| **1984** | Kolstad, A., Dr. philos. | Til diskusjonen om sammenhengen mellom sosiale forhold og psykiske strukturer. En epidemiologisk undersøkelse blant barn og unge. |
| | Løberg, T., Dr. philos. | Neuropsychological assessment in alcohol dependence. |
| **1985** | Hellesnes, T., Dr. philos. | Læring og problemløsning. En studie av den perseptuelle analysens betydning for verbal læring. |
| | Håland, W., Dr. philos. | Psykoterapi: relasjon, utviklingsprosess og effekt. |
| **1986** | Hagtvet, K.A., Dr. philos. | The construct of test anxiety: Conceptual and methodological issues. |
| | Jellestad, F.K., Dr. philos. | Effects of neuron specific amygdala lesions on fear-motivated behavior in rats. |
| **1987** | Aarø, L.E., Dr. philos. | Health behaviour and sosioeconomic Status. A survey among the adult population in Norway. |
| | Underlid, K., Dr. philos. | Arbeidsløyse i psykososialt perspektiv. |
| | Laberg, J.C., Dr. philos. | Expectancy and classical conditioning in alcoholics' craving. |
| | Vollmer, F.C., Dr. philos. | Essays on explanation in psychology. |
| | Ellertsen, B., Dr. philos. | Migraine and tension headache: Psychophysiology, personality and therapy. |
| **1988** | Kaufmann, A., Dr. philos. | Antisosial atferd hos ungdom. En studie av psykologiske determinanter. |

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| | Mykletun, R.J., Dr. philos. | Teacher stress: personality, work-load and health. |
| | Havik, O.E., Dr. philos. | After the myocardial infarction: A medical and psychological study with special emphasis on perceived illness. |
| **1989** | Bråten, S., Dr. philos. | Menneskedyaden. En teoretisk tese om sinnets dialogiske natur med informasjons- og utviklingspsykologiske implikasjoner sammenholdt med utvalgte spedbarnsstudier. |
| | Wold, B., Dr. psychol. | Lifestyles and physical activity. A theoretical and empirical analysis of socialization among children and adolescents. |
| **1990** | Flaten, M.A., Dr. psychol. | The role of habituation and learning in reflex modification. |
| **1991** | Alsaker, F.D., Dr. philos. | Global negative self-evaluations in early adolescence. |
| | Kraft, P., Dr. philos. | AIDS prevention in Norway. Empirical studies on diffusion of knowledge, public opinion, and sexual behaviour. |
| | Endresen, I.M., Dr. philos. | Psychoimmuniological stress markers in working life. |
| | Faleide, A.O., Dr. philos. | Asthma and allergy in childhood. Psychosocial and psychotherapeutic problems. |
| **1992** | Dalen, K., Dr. philos. | Hemispheric asymmetry and the Dual-Task Paradigm: An experimental approach. |
| | Bø, I.B., Dr. philos. | Ungdoms sosiale økologi. En undersøkelse av 14-16 åringers sosiale nettverk. |
| | Nivison, M.E., Dr. philos. | The relationship between noise as an experimental and environmental stressor, physiological changes and psychological factors. |
| | Torgersen, A.M., Dr. philos. | Genetic and environmental influence on temperamental behaviour. A longitudinal study of twins from infancy to adolescence. |
| **1993** | Larsen, S., Dr. philos. | Cultural background and problem drinking. |
| | Nordhus, I.H., Dr. philos. | Family caregiving. A community psychological study with special emphasis on clinical interventions. |
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| | Solheim, R., Dr. philos. | Spesifikke lærevansker. Diskrepanskriteriet anvendt i seleksjonsmetodikk. |
| | Johnsen, B.H., Dr. psychol. | Brain assymetry and facial emotional expressions: Conditioning experiments. |
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| | Kvale, G., Dr. psychol. | Psychological factors in anticipatory nausea and vomiting in cancer chemotherapy. |

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| | Bru, E., Dr. philos. | The role of psychological factors in neck, shoulder and low back pain among female hospitale staff. |
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| | Larsen, Torill M. B. , PhD | Evaluating principals` and teachers` implementation of Second Step. A case study of four Norwegian primary schools. |
| | Bancila, Delia, PhD | Psychosocial stress and distress among Romanian adolescents and adults. |
| **2006 V** | Hillestad, Torgeir Martin, Dr. philos. | Normalitet og avvik. Forutsetninger for et objektivt psykopatologisk avviksbegrep. En psykologisk, sosial, erkjennelsesteoretisk og teorihistorisk framstilling. |

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| | Nordanger, Dag Øystein, Dr. psychol. | Psychosocial discourses and responses to political violence in post-war Tigray, Ethiopia. |
| | Rimol, Lars Morten, PhD | Behavioral and fMRI studies of auditory laterality and speech sound processing. |
| | Krumsvik, Rune Johan, Dr. philos. | ICT in the school. ICT-initiated school development in lower secondary school. |
| | Norman, Elisabeth, Dr. psychol. | Gut feelings and unconscious thought:<br>An exploration of fringe consiousness in implicit cognition. |
| | Israel, K Pravin, Dr. psychol. | Parent involvement in the mental health care of children and adolescents. Emperical studies from clinical care setting. |
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| | Knutsen, Ketil, Dr. philos. | HISTORIER UNGDOM LEVER – En studie av hvordan ungdommer bruker historie for å gjøre livet meningsfullt. |
| | Matthiesen, Stig Berge, PhD | Bullying at work. Antecedents and outcomes. |
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| | Hetland, Jørn, Dr. psychol. | The nature of subjective health complaints in adolescence: Dimensionality, stability, and psychosocial predictors |
| | Kakoko, Deodatus Conatus Vitalis, PhD | Voluntary HIV counselling and testing service uptake among primary school teachers in Mwanza, Tanzania: assessment of socio-demographic, psychosocial and socio-cognitive aspects |
| | Mykletun, Arnstein, Dr. psychol. | Mortality and work-related disability as long-term consequences of anxiety and depression: Historical cohort designs based on the HUNT-2 study |
| | Sivertsen, Børge, PhD | Insomnia in older adults. Consequences, assessment and treatment. |
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| | Janvin, Carmen Ani Cristea, PhD | Cognitive impairment in patients with Parkinson's disease: profiles and implications for prognosis |
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| | Tveito, Torill Helene, PhD | Sick Leave and Subjective Health Complaints |

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| | Magnussen, Liv Heide, PhD | Returning disability pensioners with back pain to work |
| | Thuen, Elin Marie, Dr.philos. | Learning environment, students' coping styles and emotional and behavioural problems. A study of Norwegian secondary school students. |
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| | Øverland, Simon Nygaard, PhD | Mental health and impairment in disability benefits. Studies applying linkages between health surveys and administrative registries. |
| | Eichele, Tom, PhD | Electrophysiological and Hemodynamic Correlates of Expectancy in Target Processing |
| | Børhaug, Kjetil, Dr.philos. | Oppseding til demokrati. Ein studie av politisk oppseding i norsk skule. |
| | Eikeland, Thorleif, Dr.philos. | Om å vokse opp på barnehjem og på sykehus. En undersøkelse av barnehjemsbarns opplevelser på barnehjem sammenholdt med sanatoriebarns beskrivelse av langvarige sykehusopphold – og et forsøk på forklaring. |
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| | Carvalhosa, Susana Fonseca, PhD | Prevention of bullying in schools: an ecological model |
| **2008 H** | Brønnick, Kolbjørn Selvåg | Attentional dysfunction in dementia associated with Parkinson's disease. |
| | Posserud, Maj-Britt Rocio | Epidemiology of autism spectrum disorders |
| | Haug, Ellen | Multilevel correlates of physical activity in the school setting |
| | Skjerve, Arvid | Assessing mild dementia – a study of brief cognitive tests. |

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| | Wehling, Eike | Cognitive and olfactory changes in aging |
| | Wangberg, Silje C. | Internet based interventions to support health behaviours: The role of self-efficacy. |
| | Nielsen, Morten B. | Methodological issues in research on workplace bullying. Operationalisations, measurements and samples. |
| | Sandu, Anca Larisa | MRI measures of brain volume and cortical complexity in clinical groups and during development. |
| | Guribye, Eugene | Refugees and mental health interventions |
| | Sørensen, Lin | Emotional problems in inattentive children – effects on cognitive control functions. |
| | Tjomsland, Hege E. | Health promotion with teachers. Evaluation of the Norwegian Network of Health Promoting Schools: Quantitative and qualitative analyses of predisposing, reinforcing and enabling conditions related to teacher participation and program sustainability. |
| | Helleve, Ingrid | Productive interactions in ICT supported communities of learners |
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| | Stang, Ingun | Being in the same boat: An empowerment intervention in breast cancer self-help groups |
| | Sequeira, Sarah Dorothee Dos Santos | The effects of background noise on asymmetrical speech perception |
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| | Wageningen, Heidi Karin van | The role of glutamate on brain function |

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| | Andersson, Martin | A study of attention control in children and elderly using a forced-attention dichotic listening paradigm |
| | Almås, Aslaug Grov | Teachers in the Digital Network Society: Visions and Realities. A study of teachers' experiences with the use of ICT in teaching and learning. |
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| | Schanche, Elisabeth | From self-criticism to self-compassion. An empirical investigation of hypothesized change prosesses in the Affect Phobia Treatment Model of short-term dynamic psychotherapy for patients with Cluster C personality disorders. |
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| | Aasland, Merethe Schanke | Destructive leadership: Conceptualization, measurement, prevalence and outcomes |
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| | Vangsnes, Vigdis | The Dramaturgy and Didactics of Computer Gaming. A Study of a Medium in the Educational Context of Kindergartens. |

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| | Chimhutu, Victor | Results-Based Financing (RBF) in the health sector of a low-income country. From agenda setting to implementation: The case of Tanzania |
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