# Personality traits, risk factors and comorbidities in Attention-deficit/hyperactivity disorder

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Thesis for the degree of Philosophiae Doctor (PhD)
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UNIVERSITY OF BERGEN

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# Abbreviations

| | |
|---|---|
| adjOR | Adjusted odds ratio |
| ADHD | Attention-deficit/hyperactivity disorder |
| AD | Atopic dermatitis |
| ASRS | Adult ADHD Self-Report Scale |
| ASPD | Antisocial personality disorder |
| ATC | Anatomical Therapeutic Chemical (Classification System codes) |
| BMI | Body mass index |
| CI | Confidence interval |
| DSM | (American Psychiatric Association's) Diagnostic and Statistical Manual of Mental Disorders |
| MBRN | Medical Birth Registry of Norway |
| ICD | International Statistical Classification of Diseases and Related Health Problems |
| ICPC | International Classification of Primary Care |
| MDD | Major depressive disorder |
| M.I.N.I. Plus | Mini International Neuropsychiatric Interview Plus |
| MS | Multiple sclerosis |
| NorPD | Norwegian Prescription Database |
| NICE | The National Institute for Health and Care Excellence |
| NPR | Norwegian Patient Registry |
| OR | Odds ratio |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| RA | Rheumatoid arthritis |
| SLE | Systemic lupus erythematosus |
| TCI | Temperament and Character Inventory |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| UoB | University of Bergen |

## Scientific environment

The work presented in this thesis was carried out at the Department of Biomedicine and the Department of Global Public Health and Primary Care in collaboration with The Department of Medical and Biological Psychology, University of Bergen, Norway. It was initiated in 2010, when I was given the opportunity to do research one year part-time as part of my specialization in psychiatry at Haukeland University Hospital. In 2012 I received a research fellowship from the University of Bergen.

This research originated from the project "ADHD: from clinical characterisation to molecular mechanisms", being a part of the K.G. Jebsen Centre for Research on Neuropsychiatric Disorders 2011-2018. I have also been enrolled in the National research school in population based epidemiology (EPINOR).


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# Contents

# Abstract

***Background:*** Attention-deficit/hyperactivity disorder (ADHD) comprises cognitive and behavioural traits present from childhood. During lifespan, people with ADHD are more prone to develop psychiatric- and somatic comorbidities compared to those without ADHD. Knowledge about possible risk factors, personality traits and comorbidities may increase the understanding of underlying mechanisms for ADHD.

***Aims:*** The main aim of this thesis was therefore to explore clinical features and potential causal factors in ADHD: 1) Explore personality traits and their relationship to psychiatric comorbidities in adults with ADHD; 2) Investigate maternal inflammatory and immune system diseases as prenatal risk factors for offspring ADHD; 3) Explore possible sex-specific associations between ADHD and autoimmune diseases; 4) Describe the current knowledge on somatic comorbidity in adult ADHD.

***Materials and methods:*** 1) Personality traits were assessed by a self-report questionnaire and psychiatric comorbidity by an interview in a group of persons with adult ADHD and a comparison group; 2) and 3) Prenatal risk factors and comorbidity were assessed by linking data from Norwegian population-based registries such as the Medical Birth Registry and the Norwegian Prescription Database; 4) Knowledge on adult ADHD and somatic comorbidity was described in a systematic literature review.

***Results:*** 1) The personality dimensions Novelty Seeking and Harm Avoidance were highly associated with ADHD. However, these associations were dependent on common life-time psychiatric comorbidities in ADHD; 2) Maternal multiple sclerosis, rheumatoid arthritis, diabetes mellitus type 1, asthma and hypothyroidism significantly increased the risk of offspring ADHD; 3) ADHD was associated with psoriasis in both sexes, and with Crohn`s disease and ulcerative colitis in females; 4) Obesity, sleep disorders and asthma were well-documented comorbidities in adult ADHD.

***Conclusions and consequences***: Our findings add to the evidence that ADHD has many facets. Associations with immune-related diseases both as prenatal risk factors and somatic comorbidities may inform further aetiological research. Clinicians need to acknowledge personality traits and comorbidities in order to provide individuals with ADHD the best understanding and treatment.

# List of Publications

**Paper I**

Instanes, J. T., Haavik, J., & Halmoy, A. Personality traits and comorbidity in adults with ADHD. *J Atten Disord.* 2016;20(10), 845-854.

**Paper II**

Instanes, J. T., Halmoy, A., Engeland, A., Haavik, J., Furu, K., & Klungsoyr, K. Attention-deficit/hyperactivity disorder in offspring of mothers with inflammatory and immune system diseases. *Biol Psychiatry.* 2017;81(5), 452-459.

**Paper III**

Hegvik, TA., Instanes, J. T., Haavik, J., Klungsøyr, K., & Engeland, A. Associations between attention-deficit/hyperactivity disorder and autoimmune diseases are modified by sex: a population-based cross-sectional study. *Eur Child Adolesc Psychiatry.* 2018;27(5), 663-675.

**Paper IV**

Instanes, J. T., Klungsoyr, K., Halmoy, A., Fasmer, O. B., & Haavik, J. Adult ADHD and comorbid somatic disease: A systematic literature review. *J Atten Disord.* 2018;22(3), 203-228.

*Paper I reprinted in accordance with SAGE Journal guidelines. Papers II, III and IV are open access articles.*

# 1. Introduction

## 1.1 Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is a disorder characterised by symptoms of hyperactivity-impulsivity and/or inattention interfering with a person's normal development or functioning. The clinical presentation of ADHD is varied and may seriously affect life quality. The diagnosis is associated with social impairment, poor academic performance, low occupational status, less job stability and increased mortality rates[1,2]. Further, ADHD patients often suffer from psychiatric and somatic comorbidities[1]. The aetiology behind the disorder is diverse and complex, and specific underlying pathophysiological pathways are yet to be identified[3].

### 1.1.1 **ADHD diagnostic criteria**

The core symptoms comprising ADHD have been described in the literature throughout history, portraying people with restless and impulsive behaviour[4-6]. Throughout the 19th and 20th centuries the modern conceptualization of ADHD developed, describing such behaviour in a medical context. The term ADHD was introduced in 1987 in the revision of the third American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM)[7]. In DSM-IV (1994), three subtypes were specified: predominantly Inattentive, predominantly Hyperactive-Impulsive, and Combined[8]. According to these criteria the symptoms have to be present since before the age of 7. ADHD was until the end of the 20th century mainly viewed as a condition in children and in Norway, adults with ADHD were not allowed to receive specific pharmacological treatment for this disorder before 1997[9].

Published in 2013, DSM-5 is used as an international standard for defining ADHD in research worldwide[10]. ADHD is here categorized as a neurodevelopmental disorder[10], characterised by impairment in neurological functioning affecting behaviour, cognition and motor skills[11]. According to DSM-5, six of nine symptoms from either symptom dimension (inattention or hyperactivity-impulsivity) have to be present prior to 12 years of age. For those 17 years or more, five symptoms have to be present. The specific

criteria are listed in Appendix I. Three clinical presentations are specified, corresponding to the sub-types in DSM-IV. DSM-5 also describes associated features common in ADHD which may dominate the clinical appearance of ADHD, such as mood lability and emotional dysregulation.

In Norway, the present official diagnostic system is the World Health Organization's International Statistical Classification of Diseases ICD 10th revision (ICD-10), published in 1992[12]. The diagnostic group corresponding to ADHD in ICD-10 is termed Hyperkinetic disorders[13]. The Hyperkinetic disorders share the same core symptoms as ADHD, but the impairment criteria of daily life function are stricter. As opposed to DSM, ICD-10 requires symptoms of both inattention and hyperactivity/impulsivity to be present and impairing on several life domains before 7 years of age. Nevertheless, and as described in the Norwegian national guidelines, the term ADHD, as well as the criteria from DSM, are commonly used when diagnosing the disorder[13].

The diagnosis is based solely on the clinical presentation of symptoms, and impairment as a direct consequence of these symptoms. Thus, ADHD can be a challenge to assess, both due to the lack of pathognomonic symptoms, the heterogeneity of symptom presentation, including the associated features and comorbid disorders that often co-occur. To diagnose ADHD, symptoms also have to interfere with or reduce the quality of daily life functioning. This judgement can be difficult since the distinction from normal behaviour is not always clear. Social and cultural factors may also influence to which extent the symptoms lead to impairment[14].

Another obstacle when diagnosing ADHD, is that the symptoms of ADHD and other psychiatric diagnoses overlap[15,16]. One example is ADHD and borderline personality disorder, sharing clinical features such as impulsivity and emotional dysregulation[16,17]. Further, symptoms of mood disorders such as restlessness, concentration problems and irritability can also be present in ADHD[16,18]. Clinicians' experience may also influence the diagnostic process. If for example a clinician is more familiar with diagnosing and

treating patients with depression, an ADHD patient with depressive symptoms may end up being diagnosed with depression, and the ADHD not recognized[18].

### 1.1.2 Prevalence, sex distribution and treatment

The world-wide pooled prevalence estimates of childhood ADHD vary from 3.4%-7.2%, reported in meta-analyses[19,20]. The prevalence of diagnosed ADHD in children has increased the last decades, in the US from 6.1% in 1997-1998 to 10.2% in 2015-2016[21]. However, this seemingly increase in prevalence may not be true when standardized diagnostic procedures are followed[22]. The estimated prevalence in adults (mainly up to 45 years) ranges from 1.4%-3.6%[23,24] across studies. The reported prevalence is higher in high-income countries compared to low-income countries[24].

The ADHD prevalence also varies by sex. Among children, 2-3 times more boys than girls are diagnosed with ADHD[25,26]. In adults, the distribution is less skewed, with a male/female ratio approaching 1:1[23].

The National Institute for Health and Care Excellence (NICE) guideline for ADHD emphasizes the importance of a multimodal and broad approach when treating ADHD[27]. This may involve a range of different psychological and pharmacological treatments, psychoeducation and psycho-social interventions[13].

In Norway, pharmacological treatment of ADHD is strictly regulated and only prescribed after thorough diagnostic assessment in specialist health services[28(p.14)]. The pharmacological treatment is generally divided into two groups, psychostimulant and non-stimulant medication. Psychostimulants include methylphenidate and different formulations of amphetamines, and such treatment is the first pharmacological choice in both children and adults[13,27,29,30]. Psychostimulants are essentially used only in ADHD treatment, except also for the sleep disorder narcolepsy. However, stimulants used for narcolepsy comprises only about 0.1% of all prescribed stimulants in Norway[31]. Non-stimulant treatment is usually offered when psychostimulants are contraindicated, the side-effects intolerable or the effect not satisfactory[27,28(p.18)], and comprises about 7% of the total amount of prescribed ADHD medication[32].

## 1.2 Aetiology and risk factors

### 1.2.1 **Genes, environement and their interactions**

Although several risk factors contributing to ADHD have been established, the definite causes remain unknown[33]. The aetiology behind ADHD is considered to be multifactorial, with both genetic and non-genetic factors contributing to altered neurodevelopment[1]. Heritability is a term used to describe the proportion of variance in a specific trait that is attributable to genetic factors at a population level[34]. Twin studies of ADHD have consistently yielded high heritability estimates at about 74%[35]. The heritability is mainly due to the combination of many gene variants, each having small effects, and where, in most cases, none of these variants are considered sufficient or necessary to cause ADHD. An exception is ADHD in individuals with specific syndromes such as Klinefelter syndrome and velo-cardio-facial syndrome[35]. Numerous environmental factors have been associated with ADHD. These are often classified by their time of influence as pre, peri- and postnatal (i.e. during intrauterine life, the immediate time around birth and during infancy and childhood, respectively). Examples of prenatal risk factors are maternal smoking, alcohol consumption, thyroid levels and urinary tract infections during pregnancy[49-55], while maternal epilepsy can influence the foetus by prenatal exposure to medication, hypoxia during maternal seizures and/or genetic factors[36]. Examples of perinatal factors are low birth weight and prematurity[37-39], while traumatic brain injury and emotional trauma during childhood[40-43] are examples of postnatal factors. Psychosocial factors, e.g. young maternal age, low family income, parental education and beginning school at an early age have also repeatedly been associated with ADHD[38,44-47]. The heritability estimates in twin studies being less than 100% supports the fact that the environment also plays a role in ADHD aetiology[35]. It may, however, be difficult to disentangle the potential genetic and/or environmental mechanisms, and also causal versus non-causal associations underlying these primarily environmentally termed risk factors[1]. Instead of trying to separate genetic from environmental mechanisms, they can be seen as complementary explanations[48]. Gene−environment interactions may account for a substantial part of the ADHD aetiology[35]. The environmental risk factors may interact

with genetic factors through epigenetic mechanisms[49]. Epigenetic mechanisms refer to changes in the gene expression that are not caused by alterations in the genetic code itself, but rather by modifications of the gene expression[50]. Further, genetic or other factors shared within families may account for the observed association between the environmental risk factor and ADHD, so-called familial confounding[51]. Familial confounding will be discussed in section 5.3.2.

### 1.2.2 Maternal immune activation

There is a growing recognition that maternal immune activation during pregnancy impacts foetal brain development, and this is suggested to play a role in the development of neurodevelopmental disorders[52,53]. Such maternal immune activation may be due to maternal infection or other causes of inflammation such as autoimmune disease or allergy[53]. The immune activation may weaken the foetal blood-brain barrier, making the foetal brain vulnerable to influence by immune components from outside the central nervous system[54]. The precise mechanisms of how this immune activation alters brain development in the foetus is not known. Complex pathways involving the release of interleukins, signalling molecules generated during immune activation, have been proposed, based on findings from rodent models[55,56]. A hypothetical model showing how maternal immune activation can impact the foetal brain development is shown in Figure 1[55]. This model was originally made to explain altered brain development in autism, but the principal ideas can be used as a model also in other neurodevelopmental disorders such as ADHD. Maternal immune activation increases the level of interleukin-6, leading to the activation of T helper 17 cells. These produce interleukin-17 (IL-17) to be present in the mother´s blood. By passing the placenta barrier, IL-17 can alter the *in utero* environment leading to increased expression of the IL-17 receptor and further to increased IL-17 signalling in the foetal brain. Exact how the altered level of IL-17 influences foetal brain development is, however, unknown.

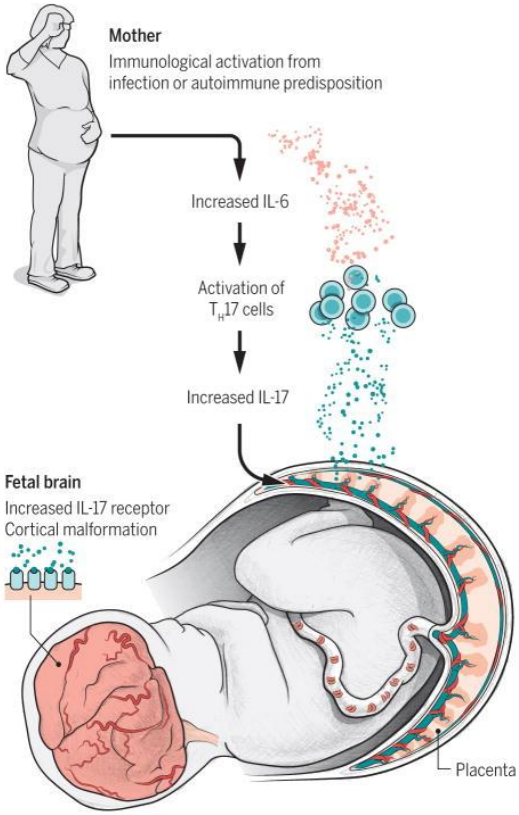
Mechanisms including glial activation may also play a role in the altered brain development[54]. Glial cells are immunocompetent cells in the central nervous system. In addition to responding to injury and inflammation, they are involved in synaptic pruning and neuronal phagocytosis. Hence, glial cells are important in the development

of brain neuronal networks[54]. Interestingly, rodent models have shown that sex hormones impact the function of the glial cells, thus glial cells are involved in the sexual differentiation of the brain[57,58].

Based on the existing knowledge concerning maternal immune activation and foetal brain development when Paper II was planned, we hypothesized that chronic maternal inflammatory and immune system diseases could be prenatal risk factors for offspring ADHD. Investigating such risk factors is important both to inform research on ADHD aetiology and also to improve ADHD treatment[35,48].

**Figure 1.** Hypothetical model showing how maternal immune activation can impact foetal brain development.

IL, Interleukin. $T_h17$, T helper 17 cells.




From *Estes ML, McAllister AK. IMMUNOLOGY. Maternal TH17 cells take a toll on baby's brain*[55]. Reprinted with permission from American Association for the Advancement of Science. License Number 4521840973540.

## 1.3 Personality and personality traits

### 1.3.1 **The trait theory of personality**

Personality can be described as the total sum of mental and behavioural characteristics unique to an individual[59]. There are different theories on personality. The psychodynamic theory developed by S. Freud emphasizes unconscious thoughts, memories and feelings as important factors to understand human behaviour[60(p.544)]. Another personality theory, the behavioural theory, emphasizes that personality is developed through interaction between the individual and the environment[61].

Today, one major theory for explaining personality is the trait theory[62]. According to this theory, it is the combination of personality traits that forms each individual´s personality[62]. B. Roberts has described personality traits as *"the relatively enduring patterns of thoughts, feelings, and behaviors that reflect the tendency to respond in certain ways under certain circumstances"*[63]. Trait theory emphasizes the ability to describe and measure personality traits, focusing on differences between individuals[62]. In the trait theory, personality traits are quantitatively assessed[64(p.160)] and are regarded as continuously, not categorically, distributed[65]. This means that a specific personality trait is not a quality that an individual has or has not, but rather has more or less, expressed somewhere along the line between the extremities of that trait. Assessment of personality traits is useful to predict a person´s behaviour and function[66]. As personality traits can be overthrown by strong factors in a specific situation, they are most useful to predict long-term behaviour patterns[60(p.533)]. In addition, investigating personality traits may be beneficial to increase our understanding of the structure, behaviour, heterogeneity and development of a disorder[67-69].

A number of models based on the trait theory have been developed, with different definitions and names of personality traits. One way to develop a trait model was based on English words used to describe personality in lay people, applying statistical analyses to find underlying clusters or factors of traits by doing factor analyses. This model was the basis for developing the Five-Factor model, the most dominating trait model today. In this model, five basic traits of personality interact to form the

individual personality[70]. The version of P. Costa's and R. McCrae's is presently the best-known and most frequently used[60(p.529)]. This model was developed to describe traits in normal life, with no aetiological or neurobiological assumptions behind[70,71]. Now widely accepted used to describe the structure of both normal and abnormal personality, it has also proven useful in addressing psychiatric disorders[72-74]. The five traits comprising this model are called Openness, Conscientiousness, Extroversion, Agreeableness and Neuroticism[75,76(p.6-7)]. The different traits reflect the individual´s tendency to be curious, creative and appreciate variation in experiences (Openness); to be self-disciplined, responsible and work towards a goal (Conscientiousness); to be optimistic, energetic, sociable and talkative (Extraversion); to be cooperative, trustworthy and compassionate towards others (Agreeableness); and to be anxious, angry, depressed and emotional unstable (Neuroticism).

### 1.3.2 **A psychobiological model of temperament and character**

The Five-Factor model has been criticized for not being based on any underlying personality theory, and for not capturing all traits of personality, such as aspects of maturity, traditional moral values, individual autonomy and religiosity[71,77]. The psychobiological model of temperament and character developed by C.R. Cloninger, one of the most commonly used personality models in ADHD research, aims also to cover these issues[67,71]. As opposed to the Five-Factor model, it is based on seven personality dimensions and emphasises the difference between temperament and character. For the purpose of this thesis, the psychobiological model of temperament and character will be named "the psychobiological model".

#### *Temperament and character*

According to the psychobiological model, personality can be divided into two different domains; "temperament" and "character"[78]. Temperament can be perceived as the innate tendency to behave or react to the environment in a particular way, such as quality and lability of mood, attitudes and coping strategies[78-80]. These response patterns are considered to be moderately heritable and relatively consistent throughout life[81(p.9)]. Character relates to the self-regulation of attention and emotions in order to achieve intentional goals and values in a rational process[82,83]. The character influences

the voluntary choices of an individual and moderates the influence of the temperament [71,84]. On the other hand, character is largely influenced by temperament traits, sociocultural environment and life events[78,85]. As opposed to temperament traits, character traits develop and mature by age[78].

### *The seven personality dimensions*

The psychobiological model consists of seven different putatively independent personality dimensions, four dimensions of temperament and three dimensions of character. The temperament dimensions are called Harm Avoidance, Novelty Seeking, Reward Dependence and Persistence. The character dimensions are named Self-Directedness, Cooperativeness and Self-Transcendence. Each dimension is further divided into 3-5 subscales. (The subscales will not be specifically described in this thesis, as they are not a part of the results in Paper I). Characterisations of individuals with high and low scores on the temperament and character scales are described in Table 1[85]. The dimensions are measured by the Temperament and Character Inventory (TCI). See sections 3.2.1 and 5.2.1 for description and discussion of strengths and limitations of the TCI.

The specific emotional style of a person as described by the temperament dimensions is not either socially desirable or undesirable. Having high or low scores on the temperament dimensions are associated with both advantages and disadvantages[83]. Taking Harm Avoidance as an example, individuals with high Harm Avoidance tend to be cautious, nervous and pessimistic[81(p.20)]. This can be a disadvantage in social situations, but an advantage in dangerous situations were caution is needed[83]. Contrary, persons with low Harm Avoidance tend to be relaxed, optimistic, risk-taking and confident when facing danger, but can also behave foolhardily[81(p.20)].

As opposed to the temperament dimensions scores, high scores on the character dimensions are more socially advantageous compared to low scores[83]. This can be illustrated by using Self-Directedness as an example. Individuals with low scores on Self-Directedness are often described as immature by clinicians, and tend to be unreliable, blaming and destructive. Persons with high scores on Self-Directedness

**Table 1.** Description of the Temperament and Character dimensions, showing personality traits in individuals with high and low scores on the specific dimensions.

| **I. Temperament scales** | **High scorer** | **Low scorer** |
|---|---|---|
| Harm Avoidance | | |
| Worry and pessimism | Pessimistic | Optimistic |
| Fear of uncertainty | Fearful | Daring |
| Shyness | Shy | Outgoing |
| Fatigability | Fatigable | Energetic |
| | | |
| Novelty Seeking | | |
| Exploratory excitability | Exploratory | Reserved |
| Impulsiveness | Impulsive | Deliberate |
| Extravagance | Extravagant | Thrifty |
| Disorderliness | Irritable | Stoical |
| | | |
| Reward Dependence | | |
| Sentimentality | Sentimental | Detached |
| Openness to communication | Open | Reserved |
| Attachment | Warm | Cold |
| Dependence | Appreciative | Independent |
| | | |
| Persistence | | |
| Eagerness of effort | Industrious | Inert |
| Work hardened | Determined | Spoiled |
| Ambitiousness | Enthusiastic | Underachiever |
| Perfectionism | Perfectionistic | Pragmatic |
| | | |
| **II. Character scales and subscales** | **High scorer** | **Low scorer** |
| Self-Directedness | | |
| Responsibility | Responsible | Blaming |
| Purposefulness | Purposeful | Aimless |
| Resourcefulness | Resourceful | Inept |
| Self-acceptance | Self-accepted | Vain |
| Congruent second nature | Disciplined | Undisciplined |
| | | |
| Cooperativeness | | |
| Social acceptance | Tenderhearted | Intolerant |
| Empathy | Empathic | Insensitive |
| Helpfulness | Helpful | Hostile |
| Compassion | Compassionate | Revengeful |
| Purehearted | Principled | Opportunistic |
| | | |
| Self-transcendence | | |
| Self-forgetful | Intuitive | Contrived |
| Transpersonal identification | Acquiescent | Controlling |
| Spiritual acceptance | Spiritual | Materialistic |

From Svrakic DM, Draganic S, Hill K, Bayon C, Przybeck TR, Cloninger CR. Temperament, character, and personality disorders: etiologic, diagnostic, treatment issues[85]. Content reused with permission from John Wiley and Sons. License Number 4527231176918.

have high self-esteem, are responsible, mature and reliable. They have the ability to adapt their behaviour to achieve their own individual chosen goals[81(p.24)].

### *Strengths and limitations*

The psychobiological model has been used across countries and in different cultures worldwide[86-88]. A study by Miettunen et al. (2008) pooled results from 16 papers with information on the temperament dimensions from non-clinical populations with sample sizes of at least 100 individuals[89]. This study supported the validity and reliability of the psychobiological model across countries, i.e. the model actually captures what is meant to be measured and findings are reproducible[90,91(p.57)]. However, the studies included mainly European and East Asian samples[89]. Thus, the external validity, i.e. whether the model is valid in other parts of the world, is limited. A more detailed explanation of the terms validity and reliability will follow in section 5.1.1.

The notion of seven dimensions was corroborated in the previously described study by Miettunen et al.[89]. The correlations between the temperament dimensions were small, with the exception of a negative correlation between Harm Avoidance and Novelty Seeking. However, a Swedish community-based study by Maitland et al. (2009), failed to confirm these seven factors in a confirmatory factor analysis[92].

A study by Josefsson et al. (2013) investigating ~1500 individuals from a Finnish population-based sample with 4-10 years follow-up time, showed that character traits changed more by age compared to temperament traits[93]. This is in line with the notion that character traits, as opposed to temperament traits, mature through life.

As opposed to the Five-Factor model, the psychobiological model was based on a synthesis of information from neurobehavioural and neuropharmacological studies, and family- and twin studies to investigate genetics, and psychometric dimensions of personality in individuals and twin pairs[71]. The model assumptions have partially been corroborated with findings from factor-analyses. Contrary to the Five-Factor model, the psychobiological model was developed for the assessment of psychopathology[94]. Further, it emphasised the neurobiological basis of personality traits[85]. Originally, Cloninger suggested that independent neurobiological systems underlay each

temperament traits. However, this model has been criticized to be simple and reductionistic, as the function of neurotransmitters is very complex and affect different brain functions[95]. Another critique towards the model is that the distinction between temperament and character may not be valid, as research has shown that heritability is important not only to explain the variability in temperament traits, but also in character traits[96-99]. Cloninger has recently acknowledged these limitations, and although he and his co-authors still argue for the distinction between temperament and character, they accept the complex biopsychological structures with different molecular mechanisms underlying temperament versus character[100].

The psychobiological model has shown to overlap considerably with the Five-Factor Model in both clinical and non-clinical samples[101-105]. To give an example replicated in several studies, Harm Avoidance has been shown to be positively correlated with Neuroticism and negatively correlated with Extraversion. This makes sense, as being anxious and pessimistic are traits common in both Harm Avoidance and Neuroticism. Further, the opposite of the trait Extraversion is introversion – a feature related to "shyness" of Harm Avoidance.

### *Temperament and character dimensions associated with ADHD and comorbid psychiatric disorders*

Distinct psychiatric disorders have been associated with specific personality traits as measured by the TCI[84,106-109]. In a meta-analysis by Gomez et al. (2017) including 20 studies (clinical and community based, children and adults) on the relation between ADHD and personality dimensions, ADHD or ADHD symptoms were associated with high scores on Harm Avoidance and Novelty Seeking, and low scores on the other dimensions. The exception was Self-Transcendence, which showed no significant association[84]. The associations between high Harm Avoidance and Novelty Seeking with ADHD or ADHD symptoms are corroborated by results from other clinical and community based samples[110-112]. Albeit representing a broad base of investigation, due to their cross-sectional design they are not suitable to investigate potential causality.

Similar to ADHD, depressive- and anxiety disorders have been associated with high Harm Avoidance and low Self-Directedness[107-109]. For antisocial personality disorder

(ASPD), personality dimensions as measured by the TCI appear to be little studied. However, in a small Turkish case-control study by Basoglu et al. (2011), ASPD was associated with high scores on Harm Avoidance and Novelty Seeking, and with low scores on Self-Directedness[106]. According to these findings, high Harm Avoidance and low Self-Directedness are associated with several psychiatric disorders.

This exemplifies that one personality trait can be common in different psychiatric disorders. Such information can be used to elucidate patterns of comorbidity between the disorders[113]. Whether personality traits associated with ADHD are also associated with personality traits in common comorbidities in ADHD, is poorly studied.

## 1.4 Comorbidity

Comorbidity may be defined as *"any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study"* ( A. Feinstein)[114,(cited in 115)]. The index condition is the condition which is the subject of the study, and comorbidities are diseases coexisting in the participant(s) in addition to the index condition[116]. However, synchronous occurrence of the conditions is not always the case, and it is also of interest to study conditions which occur at different time periods[115]. Whether the term 'comorbid conditions' should be used only for diseases that are causally related to each other, has been discussed, without any consensus[115,117,118].

For the purpose of this thesis, a comorbid disorder is understood as a disorder or disease occurring during the lifetime of a person once diagnosed with ADHD, where ADHD is the index disorder. None of the diagnoses are given priority, and a causal relationship is not required. For some purposes, as in Paper III, a disorder can be regarded as a comorbid disorder to ADHD even if the person no longer meets the ADHD criteria (e.g. psoriasis in an adult diagnosed with ADHD in childhood, but who no longer fulfils the ADHD criteria). Further, the specific terms psychiatric comorbidity and somatic comorbidity are used when a person with ADHD suffers from another psychiatric disorder or somatic/ physical disease, respectively.

To study comorbidity is important for many reasons, such as to gain knowledge of common risk factors and aetiological factors underlying both the index and the comorbid disorders, understand the impact comorbidity may have on the clinical course of the index disorder and contribute to holistic care of this disorder[114,119-122].

### 1.4.1 Psychiatric comorbidity in ADHD

Psychiatric comorbidity in ADHD is common in all age groups. Results from both population-based and clinical studies on children and adolescents show that 52%-66%[123,124] of those with ADHD suffer from comorbid psychiatric disorders. For adults, about 50%-85% have had at least one lifetime psychiatric comorbidity[31,125-128], indicating that the risk of comorbidity increases by age. Thus, psychiatric comorbidity is an important clinical dimension of ADHD heterogeneity[29].

The comorbidity profile alters throughout life[3]. In childhood, the most frequent psychiatric comorbidities are behavioural problems such as conduct disorder and oppositional defiant disorder; neurodevelopmental disorders such as autism spectrum disorders, learning disability, intellectual disability and tic disorder; and depression and anxiety disorders[10,33,123,124,129]. In adolescence substance use disorders become more common, continuing into adulthood[1,130]. Major depressive disorder (MDD) is highly comorbid in adults with ADHD, 25%-65% experience this disorder during their lifetime[125-128]. Other common comorbidities are bipolar, - anxiety, - eating, - and personality disorders (in particular antisocial and borderline personality disorders)[31,125,126,130-133].

### 1.4.2 Somatic comorbidity in ADHD

Compared to psychiatric comorbidity, somatic comorbidity in ADHD has been investigated to a lesser degree, and mainly focused on children. At the time when paper IV was written, there was a need for a systematic review to describe what was known about somatic comorbidity in adults with ADHD, not only to get an overview over the current knowledge, but to gather information about fields warranting further attention. Since then, the importance of somatic comorbidity in adults with ADHD has been increasingly recognized. A recent study by Dornquast et al. (2017), has shown that

somatic diseases are poorly documented in psychiatric journals, indicating that information on somatic comorbidity currently is lacking in psychiatric care[134]. Studies on somatic comorbidity in ADHD have now documented increased risk of eczema, asthma, obesity, sleep disorders, migraine, epilepsy and enuresis[119,121,135-146]. Similarly to psychiatric comorbidities, the pattern of somatic comorbidities changes throughout life, such as obesity normally appearing later than enuresis[3]. This underscores the importance of studying comorbid somatic diseases both in children and adults.

Immune system diseases are of special interest, as activation of the immune system can be involved in triggering psychiatric disorders[147]. One example is the possible disruption of neuronal "pruning" in schizophrenia, involving brain-based immune cells called microglia[148]. Pruning is the process of shearing away unwanted or non-effective connections between neurons[149]. The immune system also plays a role in brain development, indicating that brain-immune interactions may be causally related to psychopathology in children (see section 1.2.2.)[52].

One particular focus of interest has been the relation between psychiatric disorders and autoimmune diseases. Autoimmune diseases are a heterogeneous group of conditions, their common feature being an immune-mediated attack on the body's own tissues or products of own tissues[150,151]. Today, studies have reported ADHD to be associated with different autoimmune diseases such as autoimmune thyroiditis, celiac disease, type 1 diabetes mellitus (T1DM), juvenile arthritis and psoriasis[152-155]. Genetic correlations have been found between ADHD and rheumatoid arthritis (RA) and psoriasis, possibly implying an inherited immune abnormality behind both ADHD and the autoimmune diseases[156,157]. Moreover, stress related to having ADHD may trigger outbreak of autoimmune disease, such as the role of stress in triggering psoriasis[158,159].

However, at the time when Paper III was written, a possible increased risk for autoimmune diseases in ADHD had hardly been studied. Immune related diseases and ADHD was therefore an understudied area of significant interest, both as possible risk factors for the exposed foetus whose mother has immune related diseases, and as comorbid diseases with ADHD in both sexes.

### 1.4.3 Sex differences in ADHD comorbidity

The ADHD prevalence differs by sex (see section 1.1.2), and this pattern is also present in the prevalence of ADHD comorbidities. In persons with ADHD, both anxiety, bulimia, depression and asthma have been shown to be more prevalent during lifetime in women than in males, whereas substance use disorder, ASPD and hypertension were most prevalent in males[31,131,160]. Knowledge of sex differences in risk of comorbid diseases in individuals with ADHD is important for early and correct diagnosis and for deciding treatment and prevention strategies[31,161]. Such knowledge is also important to inform further research on aetiological pathways, which may differ by sex. There is a large knowledge gap with regards to sex differences in ADHD and comorbid diseases, especially for somatic comorbidity. This was the rationale for planning our third study, where we aimed at studying sex differences in the associations between ADHD and autoimmune diseases. Autoimmune diseases include diseases with evident sex differences, where most of these diseases are more common in females. Thus, studying sex differences in the association with ADHD was highly relevant.

*The literature search was finished March 23, 2020.*

# 2. Aims

The overall aims of this thesis were to explore clinical features and potential causal factors in ADHD.

More specifically, our aims were as follows:

I) To assess personality traits in adult ADHD patients and a comparison group, and explore how these traits are associated with anxiety, depression and antisocial personality disorder.

II) To investigate chronic maternal inflammatory and immune system diseases as prenatal risk factors for offspring ADHD.

III) To compare the prevalence of autoimmune diseases in individuals with and without ADHD, and evaluate whether possible associations vary by sex.

IV) To summarise the current knowledge regarding associations between ADHD and somatic diseases in adults by doing a systematic literature review.

# 3. Material and methods

An overview of methods and samples used in Papers I-IV is presented in Table 2.

**Table 2.** Overview of methods and samples used in Papers I-IV.

| Paper No. | Study design | Main data sources | Study population | Main independent variable/ exposure(s)/ | Main dependent variable/ outcome(s) |
|---|---|---|---|---|---|
| I | Clinical, cross-sectional | University of Bergen project: "ADHD in adults in Norway" | Clinical sample of adult ADHD patients (n=63)<br>Comparison group (n=68) | Adult ADHD<br>Lifetime antisocial personality disorder<br>Lifetime anxiety disorder and/or lifetime major depressive disorder | Personality traits measured by TCI[a] |
| II | Registry based, nested case-control | MBRN[b]<br>NorPD[c]<br>The National registry<br>National Education Database | All individuals born in Norway 1967-2008, alive at record linkage 2012<br>Cases: Individuals being dispensed ADHD medication 2004-2012 (n=47,944)<br>Controls: all remaining individuals (n=2,274,713) | Maternal diseases:<br>MS[d]<br>Asthma<br>RA[e]<br>Hypothyroidism<br>Hyperthyroidism<br>Pregestational T1DM[f] and T2DM[g].<br>Chronic hypertension | Offspring ADHD |
| III | Registry based, cross-sectional | MBRN<br>NorPD<br>The National registry<br>National Education Database | All individuals born in Norway 1967-2011, alive and residing in Norway at record linkage 2015<br>Cases: Individuals being dispensed ADHD medication 2004-2015 (n=63,721)<br>Controls: all remaining individuals (n=2,436,397) | ADHD | Ankylosing spondylitis<br>Crohn's disease<br>Iridocyclitis<br>MS<br>Psoriasis<br>RA<br>SLE[h]<br>T1DM<br>Ulcerative colitis |
| IV[i] | Systematic review | Embase<br>Psychinfo<br>Medline | | Adult ADHD (above 18 years) | Somatic diseases |

[a]TCI = the Temperament and Character Inventory. [b]MBRN = Medical Birth Registry of Norway. [c]NorPD = Norwegian Prescription Database. [d]MS= Multiple sclerosis. [e]RA= Rheumatoid arthritis. [f]T1DM= Type 1 diabetes mellitus. [g]T2DM=Type 2 diabetes mellitus. [h]SLE= Systemic lupus erythematosus. [i]the direction between independent and dependent variables varied between the studies.

## 3.1 Study designs

### 3.1.1 **Clinical sample (Paper I)**

The ongoing project "ADHD in adults in Norway; from clinical characterization to molecular mechanisms" was initiated at the University of Bergen (UoB) in 2004, aiming to recruit a naturalistic sample of adult ADHD patients and controls. As of 2018, 855 ADHD patients and 913 controls were participating in the study. Information on ADHD symptoms, medication, psychiatric and somatic comorbid disorders, genetics, imaging and neuropsychological data as well as information about family members have been collected on all or subgroups of participants. The ADHD sample has been collected in different ways. The first group was recruited from people 18 years or older who had received central stimulant treatment due to ADHD during 1997-2005. To receive central stimulant treatment in this specific period, the ADHD diagnosis had to be evaluated by a regional Expert Committee of Hyperkinetic Disorder/ADHD. Based on information from the clinicians, the committee decided if the diagnostic assessment was of good quality, whether proper follow-up was available, and absence of potential contra-indications for therapy. If approved, medical treatment was allowed. Since referral of patients to these committees was mandatory, they composed a national cohort of medically treated adults with ADHD (n=3397). Between 2005-2007, 1700 individuals from this cohort were invited to participate, of whom 338 (20%) responded. Secondly, clinicians from all parts of Norway were encouraged to recruit adults (persons ≥18 years) with an ADHD diagnosis according to DSM-IV or ICD-10. No formal exclusion criteria were applied. The majority of controls (79%) were recruited through the Medical Birth Registry of Norway (MBRN), by random selection of individuals with similar age (18-40 years) and geographic regions as the ADHD patients. A total of 2963 individuals were invited from the MBRN, of whom 720 (24%) responded with complete questionnaires and biological samples and were included in the study. Finally, some participants were recruited as students from the UoB, friends of the patients or through advertisement at the local hospital. No formal exclusion criteria were applied, neither in the ADHD group nor in the control group.

In the period 2005-2011, a subsample of the participants in the "ADHD in adults in

Norway" project who lived in proximity to the UoB, were invited to undergo a clinical interview conducted by two psychiatrists and two medical doctors specializing in psychiatry (including the author of this thesis). At the same time, the participants also filled out a questionnaire assessing personality traits. Of total cases, 17 were recruited from the Expert Committees of Hyperkinetic Disorder/ADHD and 49 from clinicians. The 69 participants in the comparison group were included from these sources: MBRN (n=53 (77%)), students (n=13), friends of patients (n=2), advertisement at the local hospital (n=1). The use of this sample in Paper 1 is discussed in section 5.2.1.

### 3.1.2 **Norwegian population-based registries (Papers I, II and III)**

Papers II and III were based on data from several Norwegian population-based registries. Data from the registries were linked by using each individual's unique national identification number. At record linkage, data were available for years up to (and including) 2012 (Paper II), and 2015 (Paper III), respectively.

In Paper II, we examined the possible relationship between maternal inflammatory and immune system diseases and offspring ADHD. The study population included those registered in the MBRN as born during 1967-2008 and alive at record linkage in 2012. Based on information from the Norwegian Prescription Database (NorPD) on dispensed specific ADHD medication, we defined an ADHD case group (n=47,944). The rest of the population served as a control group (n=2,274,713). Data on maternal inflammatory and immune system diseases were collected from the MBRN. In Paper III, we explored possible associations between ADHD and autoimmune diseases and whether these differed by sex. The study population included those registered in the MBRN as born during 1967-2011 and alive at record linkage in 2015. As in Paper II, an ADHD case group (n=63,721) was defined as those being dispensed specific ADHD medication, and the remaining population served as a control group (n=2,436,397). Strengths and limitations of using data from population-based registries, focusing on the MBRN and NorPD, are discussed in sections 5.2.1 and 5.3.1.

#### *The Medical Birth Registry of Norway (Papers I, II og III)*

The MBRN was established in 1967 and includes information on all births in Norway including stillbirths and late miscarriages from 16 gestational weeks. The registry is

based on compulsory notification and prospectively collects data during pregnancy on maternal health both before and during pregnancy and complications or interventions during pregnancy and delivery. Birth outcomes comprising vital status of the child and neonatal diagnoses are registered. The notification form was almost unchanged until 1998, but was changed in 1999 to include more information, such as maternal smoking habits and ultrasound-based estimation of gestational age (Appendix III). Electronic birth notification was gradually implemented from 2006, and information on further variables have been added during later years. In Paper I, 77% of the comparison group were randomly recruited from the MBRN. In Papers II and III, individuals registered in the MBRN and born 1967-2008 (Paper II), and 1967-2011 (Paper III), all alive at record linkage (2012 and 2015, respectively), constituted the source population for the studies. Information on maternal diseases was collected from MBRN (Paper II), based on free text descriptions and, from 1999, also check boxes. Free text is coded at the registry using ICD; version 8 until 1998 and version 10 from 1999.

### *The Norwegian Prescription Database (Papers II and III)*

The Norwegian Prescription Database (NorPD) was established in 2004 and provides information on prescription drugs dispensed from all Norwegian pharmacies. The registry includes information on the patient (encrypted), the prescriber and the drug, including the Anatomical Therapeutic Chemical (ATC) Classification System codes. From 2008, the NorPD has recorded information on specific diagnostic codes as indications for reimbursed medication (chronic diseases), by using the International Classification of Primary Care (ICPC) or ICD-10. Information on medication received while in hospital/institution is only available as aggregate data. Information from the NorPD was used to define the ADHD cases and controls/comparisons in Papers II (2004-2012) and III (2004-2015), and to define autoimmune diseases in Paper III.

### *The Norwegian Patient Registry (Paper II)*

The Norwegian Patient Registry (NPR) was established in 1997, registering information on patients waiting for or having received treatment in specialist health care (hospitals and out-patient clinics). From 2008, the NPR includes the national identification numbers for registered patients, enabling linkage. NPR includes

diagnostic codes based on the ICD-10 and procedure codes based on The Nordic Medico-Statistical Committee classifications. In a sensitivity analysis (Paper II), we added patients registered with an ADHD diagnosis in the NPR, but without being dispensed ADHD medication, to the ADHD case population (n=2040).

#### *The National Registry and The National Education Database (Papers II and III)*

The National Registry provides each individual residing in Norway (on a permanent basis), their unique national identification number, and further includes information on e.g. date of birth, death, immigration and emigration. This registry is routinely linked with the MBRN, and provided information on emigration and dates of death used in Papers II and III. In the National Education Database, the educational level of all Norwegian citizens from the age of 16 years has been registered since 1970. Maternal educational level was used as a measure for socioeconomic status in Papers II and III.

### 3.1.3 **Systematic literature review (Paper IV)**

Paper IV is a systematic literature review, based on research results from studies on ADHD and somatic comorbidities in adults published in international peer-reviewed journals and identified by a systematic search. The results from this review will be discussed in sections 5.4.1 and 5.4.2.

## 3.2 Measurements (Paper I) and methods (Paper IV)

### 3.2.1 **Scales (Paper I)**

#### *The Temperament and Character Inventory*

The Temperament and Character Inventory (TCI) is a self-administered questionnaire measuring the seven basic personality dimensions in the psychobiological model of temperament and character (see section 1.3.2 for description of this model)[71]. These personality dimensions composed the main outcomes of Paper I. The participants filled out the 240 items long TCI version 9 with true–false responses, taking about 30 minutes to complete[162]. The results are continuous, given as a sum of the total points for each dimension. Examples of TCI items are shown in Appendix II. TCI version 9 is

developed for measuring personality dimensions in adults. Although not validated in Norway, validation of the Swedish version showed similar psychometric properties when compared to the original American version[162], and the same was true when validating the Norwegian version of the Junior TCI designed for adolescents[66]. The psychobiological model was at the time of initiation of the ADHD project one of the most commonly used personality models in ADHD research, in addition to the Five-Factor model[67]. As the psychobiological model focuses on the neurobiological basis for personality traits, it was judged to be the most suitable for this study, as well as for the main project "ADHD in adults in Norway". See section 5.2.1 for a discussion of the measurement properties and use of the TCI.

#### *Adult ADHD Self-Report Scale*

The Adult ADHD Self-Report Scale (ASRS) is an 18 item long questionnaire covering ADHD symptoms present for the last six months[163]. The ASRS was used in a subanalysis in Paper I to divide the ADHD group into subtypes.

### 3.2.2 **Interview (Paper I)**

#### *The Mini International Neuropsychiatric Interview Plus version*

The Mini International Neuropsychiatric Interview Plus (M.I.N.I. Plus) version 5.0.0 is a semi-structured interview covering major axis 1 psychiatric disorders in DSM-IV, and is also applicable for comparable disorders classified in ICD-10[8,12,164]. This interview includes substance-related-, psychotic-, mood- and anxiety disorders, among others. ASPD, which we were interested in studying, is also covered. Although not validated in Norway, we decided to use this instrument as it is extensively used in clinical practice and freely available at the Norwegian Electronic Health Library, Norwegian Institute of Public Health[165]. The Norwegian national ADHD guideline further recommends M.I.N.I Plus in the assessment of psychiatric diagnoses in adults[13]. The M.I.N.I Plus is an extended version of the The Mini International Neuropsychiatric Interview, which has shown good validity and reliability properties[164,166].

In Paper I, we collected information from the following modules: major depressive episode, panic disorder, agoraphobia, generalized anxiety disorder, alcohol dependence and abuse, substance dependence and abuse and ASPD. We merged the results from

the following modules into one category called 'lifetime anxiety and/or depressive disorder': Panic disorder, with or without agoraphobia, generalized anxiety disorder and/or MDD, both current and lifetime. See section 5.2.1 for a discussion of strengths and limitations of the M.I.N.I Plus and the use of this interview in Paper I.

### 3.2.3 Variables based on the registries (Paper II and III)

Papers II and III were based on linked registry data. In both these studies, ADHD cases were defined by information from the NorPD as individuals being dispensed reimbursed ADHD medication (ATC N06BA or specific subgroups) after excluding individuals where stimulant drugs were dispensed for narcolepsy (Papers II and III) or other sleep disturbances (Paper III). In Paper III, data from the NorPD was also used to define different autoimmune diseases by using diagnostic codes (ICD-10 or ICPC) for reimbursed medication or ATC-codes for disease-specific medication. The information on maternal diseases in Paper II was based on data from the MBRN, where data on maternal diseases before and during pregnancy is registered. See section 5.3.1 for a critical evaluation of these variables.

### 3.2.4 Study selection, data extraction, summarising the results (Paper IV)

After defining the research question, the first step in a systematic literature review is to perform a systematic literature search attempting to find all studies covering the research question[167]. A transparent search strategy is developed, making it possible for others to replicate the search[168]. It includes searching in different databases, ensuring the results to be comprehensive and not limited to specific journals. Using predefined inclusion criteria, the papers found in the search are systematically investigated to select those that will be included in the final review. First, the titles and abstracts are screened to see if the papers are relevant. If so, the whole papers are read to make a final decision of which papers to include. This process of study selection should be visible for others, commonly illustrated by using a flow chart such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram[169].

In Paper IV, our aim was to write a systematic literature review on the topic adult ADHD and comorbid somatic disease. The electronic databases Embase, Psychinfo

and Medline were explored in collaboration with a university librarian at the UoB, with expertise in performing systematic searches. (See Paper IV, Supplementary 1 for more detailed information). In total, we identified 4091 records in this systematic search. As illustrated in the flow diagram (Figure 1, Paper IV), we performed a study selection based on the findings from the systematic literature search and an additional 63 records identified through manual search. After removing duplicates, 2774 records were screened on the subject 'adult ADHD and somatic comorbidity'. Of these records, 208 full text papers were assessed for eligibility. Finally, we retrieved 98 original scientific papers investigating the associations between somatic diseases and adult ADHD. We extracted the data from the selected studies and grouped them according to the disease(s) covered in the specific paper (based on ICD-codes), then distributed to the different co-authors based on their area of expertise. Main characteristics of each paper were extracted by the first and second author and described in a table, providing an overview of the strengths and limitations of each paper. To sum up the findings, we grouped the studied diseases into three categories according to the quality of evidence describing their association with ADHD. See section 5.4.1 for discussion.

## 3.3 Statistics

Table 3 gives an overview over the statistical methods, covariates and software used to analyse data in Paper I, II and III. In Paper I, independent-sample *t*-tests were used to compare the TCI dimensions in the ADHD group with the comparison group. Similar analyses were performed in the whole sample 1) to compare the TCI dimensions in the participants fulfilling the criteria for ASPD with those not fulfilling these criteria 2) to compare the TCI dimensions between those categorized with lifetime anxiety disorder and/or lifetime MDD disorder with those not included in this category. We included ADHD, ASPD and anxiety/depression in a linear regression model to investigate which disorder had the greatest impact on the TCI dimensions scores. The threshold for statistical significance adjusted ad modum Bonferroni was 0,002. Thus, we corrected for 21 comparisons, i.e. ADHD, ASPD, anxiety/depression multiplied with the seven TCI dimensions. In Paper II and III, we used logistic regression analyses to calculate

odds ratios (OR) while adjusting for potential confounding variables. In Paper II we stratified the analyses by sex, and in Paper III we performed interaction analyses to investigate potential effect modifications. In Paper III, we corrected for the number of autoimmune diseases, i.e. nine comparisons, giving the Bonferroni-corrected p-value 0.0056. The ORs were reported with their corresponding 95% confidence intervals (CI). See section 5.2.1 (paper I) and section 5.3.1 (papers II and III) for discussion of the statistical methods.

**Table 3.** Overview of main statistical methods and software (Papers I-III).

| **Paper No.** | **Statistical methods** | **Covariates in the final regression models** | **Software** |
|---|---|---|---|
| I | Descriptive statistics with independent sample *t*-test<br>Linear regression | Lifetime antisocial personality disorder (yes/no)<br>Lifetime anxiety disorder and/or Lifetime major depressive disorder (yes/no) | PASW Statistics 18[a] |
| II | Logistic regression | Primary model:<br>Maternal age at delivery (6 categories)<br>Parity (3 categories)<br>Time period of birth (5-year interval categories 1967-2008)<br>Maternal marital status (4 categories)<br>Maternal education (3 categories)<br>Expanded models:<br>Infant birthweight (5 categories)<br>Gestational age (5 categories)<br>Each studied maternal disease (yes/no)<br>Parental ADHD (based on dispensed ADHD medication)<br>Subanalysis:<br>Maternal smoking (yes/no) | PASW Statistics 18[a]<br>Stata version 13[b] |
| III | Logistic regression | Primary model:<br>Age (continuous)<br>Maternal education (3 categories)<br>Subanalyses:<br>Maternal smoking (yes/no)<br>Maternal body mass index (continuous) | R[c]<br>RStudio[d]<br>SPSS[e] |

[a]SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc. [b]StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.[c]The R foundation for statistical computing, Vienna, Austria. [d]RStudio Team (2016). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA. [e]IBM Corp. IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.

## 3.4 Ethical considerations

The first three studies were all approved by the Regional Committee for Medical and Health research ethics of Western Norway. To acknowledge participation and compensate for use of their time, the participants in Paper I received NOK 250, - when being enrolled in the project and additional NOK 500, - when interviewed. Further, a signed consent was obtained from each participant. Papers II and III were approved by the Norwegian Data Inspectorate. These papers were based on data from national registries with compulsory notification. Information is already collected and using these data should not create extra inconvenience for the study participants. Potential disadvantages for study participants could be lack of information about the studies, and that they cannot withdraw from the study. Information about the registries are available on the websites for each registry. In the linked dataset available for researchers, no data are directly identifiable, and it is not possible to identify the participants at an individual level. Paper IV was based solely on previously published papers, and additional ethical approvals were thus not required.

Identifying possible risk factors and comorbid disorders associated with ADHD may be used to develop preventive measures and improve treatment. Such information is highly relevant for the target population of the study, i.e. individuals with ADHD and their families. For the health services and health authorities, knowledge of risk factors and comorbid disorders is important to facilitate early and adequate treatment, and to enable a holistic understanding of the individual´s various challenges and how these impact the individual´s function. In addition, the results from our research may be of value to patient organisations working with ADHD, and for the health authorities, when prioritizing health services and take measures to reduce risk factors of ADHD.

# 4. Results

## 4.1 Paper I

In Paper I, we aimed to assess personality traits in ADHD patients and a comparison group. We found that persons with ADHD as a group had significantly higher scores on both the TCI dimensions Harm Avoidance ($p< 0.05$) and Novelty Seeking ($p< 0.0005$) relative to the comparison group. A person with high Harm Avoidance tends to be fearful and pessimistic, whereas an individual with high Novelty Seeking is characterised as impulsive and quick-tempered. The ADHD group scored significantly lower on the dimensions Reward Dependence ($p< 0.0005$) and Self-Directedness ($p< 0.0005$) compared to the comparison group. People with low scores on Reward Dependence are characterised as detached, reserved and independent, whereas those with low Self-Directedness scores are described as unreliable and blaming.

Another aim of this study was to explore how these personality traits were associated with comorbid anxiety, depression and ASPD. When including ADHD and these comorbid disorders in a linear regression model, the differences in some of the personality scores between the ADHD and the comparison group changed considerably. ADHD was then no longer associated with high Harm Avoidance ($p= 0.794$) or Novelty Seeking ($p= 1.112$). However, the ADHD group still showed lower scores of Reward Dependence ($p< 0.001$) and Self-Directedness ($p= 0.04$) compared to the comparison group, although only statistically significant for Reward Dependence (with a Bonferroni-corrected level of significance, $p< 0.002$). In this model, high Harm Avoidance ($p< 0.001$) and high Novelty Seeking ($p< 0.001$) were significantly associated with lifetime anxiety and /or depression and ASPD, respectively. These findings will be discussed in section 5.2.2, focusing on the dimension Harm Avoidance.

To our knowledge, this is the first study comparing such personality traits in ADHD, ASPD, anxiety and depression in the same sample.

## 4.2 Paper II

Paper II aimed at investigating whether chronic maternal inflammatory and immune system diseases were associated with offspring ADHD. The following maternal immune system related disorders were all found to significantly increase the odds of ADHD in the offspring; Multiple sclerosis (MS) (adjusted odds ratio (adjOR) = 1.8 (95% CI(1.2–2.5))), RA (adjOR = 1.7 (1.5–1.9)), T1DM type 1 (adjOR = 1.6 (1.3–2.0)), asthma (adjOR = 1.5 (1.4–1.6)) and hypothyroidism (adjOR = 1.2 (1.1–1.4)). Chronic hypertension, hyperthyroidism and type 2 diabetes mellitus (T2DM) showed no significant associations. We adjusted for year of birth, parity, mother's age at birth, her educational level and marital status as possible confounding variables. See section 5.3.2 for discussion of the findings.

We also ran several additional statistical models including different adjustment variables, including parental ADHD (based on dispensed ADHD medication), infant birth weight and gestational age. In all models, adjustment only slightly attenuated the associations. Limiting the data to 1999 and onwards, we were also able to adjust for maternal smoking habits, which again only very slightly altered the associations, thus confirming the primary results. The same was true when adding ADHD patients only registered in the NPR to the ADHD case population. None of the associations differed significantly when stratifying by sex of the offspring.

The findings of Paper II supported the hypothesis that brain-immune interactions may be causally related to psychopathology in children[52]. As one of the first large epidemiological studies documenting maternal chronic immune related diseases as risk factors for offspring ADHD, the study has been an important addition to the scientific discussion of this hypothesis. This paper has been much cited since its publication (April 1, 2020: by 32 PubMed central articles).

## 4.3 Paper III

In Paper III, we aimed at comparing the prevalence of autoimmune diseases in individuals with and without ADHD, and evaluate whether possible associations varied by sex. When adjusting for maternal age and education, strong associations were found between ADHD and psoriasis in both females and males, however with stronger associations in females (adjOR females 1.57 (95% CI 1.46–1.68), adjOR males 1.31 (1.23–1.40), *p* value for interaction $4.4 \times 10^{-6}$). ADHD was positively associated with Crohn`s disease in females (adjOR = 1.44 (1.16–1.79)), while negatively in males (adjOR = 0.71 (0.54–0.92)), *p*-value for interaction = $3.6 \times 10^{-5}$. Further, ADHD was significantly associated with ulcerative colitis in females (adjOR = 1.28 (1.06–1.54)), but not in males (adjOR = 0.86 (0.71–1.03)), *p* -value for interaction = 0.0023. On the other hand, a lower odds of ankylosing spondylitis was found in females with ADHD (adjOR = 0.56 (0.32–0.96)), while there was no association in males (adjOR = 1.16 (0.87–1.55)), *p*-value for interaction = 0.021. There was no association between ADHD and iridocyclitis, MS, RA, systemic lupus erythematosus (SLE) or T1DM in neither males nor females.

Information on smoking habits, body mass index (BMI) and education was available for a subgroup of females giving birth from 1999. Associations between ADHD and autoimmune diseases were confirmed both when adjusting for smoking and BMI. Sensitivity analyses were performed by exploring effects of age and time period, as well as using different case definitions. The results were in line with the primary analyses for psoriasis, Crohn´s disease and ulcerative colitis for individuals born 1967–1985. No significant associations were found for those born 1986–2011.
See sections 5.3.3. and 5.4.2. for discussion of these results, focusing on the main analysis and further on the association between ADHD and psoriasis.

A possibly increased risk for autoimmune diseases in ADHD had hardly been studied at the time when Paper III was written. The paper contributed new findings to the existing literature regarding relations between psychiatric disorders and autoimmune diseases. It further provided novel information on sex differences in these relations.

## 4.4 Paper IV

Our aim in Paper IV was to summarise the current knowledge of associations between ADHD and somatic diseases in adults by doing a systematic literature review. According to the quality of evidence, the associations between the somatic comorbid diseases and adult ADHD were divided into three categories. The first category included diseases where the association with adult ADHD was well established and described in meta-analyses or reviews. Asthma, obesity and sleep disorders were placed in this category. The second category included cohort or case-control studies where adult ADHD was based on a clinical diagnosis, the somatic diseases were not only based on self-report questionnaires, and where a strong indication of an existing association was found. In this category, migraine and celiac disease were positively associated with adult ADHD, whereas cardiovascular disease showed a negative association. The majority of diseases were placed in the third category, where current evidence was too weak to make conclusions regarding associations with adult ADHD due to poor study quality, lack of studies or where the combined results clearly differed. The strengths and limitations of this categorization will be discussed in section 5.4.1.

Compared to psychiatric comorbidity, somatic comorbidity has been investigated to a much lesser degree. The research on somatic comorbidity in relation to ADHD has mainly focused on children with ADHD. At the time when paper IV was written, there was a need for a systematic review to describe what was known about somatic comorbidity in adults with ADHD, not only to get an overview over the current knowledge, but to gather information about fields warranting further attention. This review has been much cited since its publication (April 1, 2020: by 22 PubMed central articles).

# 5. Discussion

ADHD is a common, life-spanning neurodevelopmental disorder embracing a spectrum from normally distributed personality traits to substantially impairing symptoms, and well-known associated features and disorders adding to its burden. The main topic of this thesis was to elucidate some of this complexity, emphasizing gaps of knowledge in clinical and potentially causal factors associated with ADHD. The thesis aimed to give this broad perspective on ADHD by covering personality traits and comorbidities, with a special focus on the role of immune related diseases, both as prenatal risk factors and as somatic comorbidity in individuals with ADHD. It also focused on sex-specific associations. To achieve our aim, we used different research designs and methods, including a small clinical study, two large, registry-based epidemiological studies and a systematic literature review.

In the following discussion, I will first introduce terms used in the discussion of Paper I-III, then move to the discussion of these same papers. I will then discuss Paper IV, while integrating some of the topics from the discussion of Paper III.

## 5.1 Terminology

### 5.1.1 Random and systematic errors, validity, reliability

Study results are prone to be affected by errors, which can be either random or systematic. A random error is when the error occurs due to chance alone, and causes inaccurate measures of the associations[170(p.52)]. Smaller studies are subject to greater sampling variations, leading to less precise estimates[171]. Random errors can be reduced by increasing the sample size[170(p.52)].

Bias is an error which causes the results to differ systematically from the true value[90(p.53)]. Such a systematic error can lead both to underestimation or overestimation of the true effect, and is not affected by sample size[171]. Biases can further be grouped into three main categories; selection bias, information bias and confounding.

Selection bias occurs when there is a systematic difference between the characteristics of those selected to participate in the study and those not selected[172]. Thus, the selected study participants do not represent the underlying source population. This bias arises from the procedures of identifying, recruiting and follow-up of study participants[173].

Information bias relates to how the study data are measured, collected and/or classified[170,174]. Bias can occur when data are misclassified, one example being cases wrongly classified as controls, or exposure wrongly classified as non-exposure. Misclassification can be differential or non-differential. In non-differential misclassification, the probability of misclassification is equal in all study groups, as opposed to differential misclassifying where this probability varies between groups[175]. Non-differential misclassification usually leads to an underestimation of the true effect size, while differential misclassification can lead to both under-and overestimation of the true effect. One type of information bias is recall bias, due to inaccurate or incomplete memory of past events[176]. A differential recall of past events between cases and controls will lead to differential misclassification[90(p.54)]. Confirmation bias may arise if the findings support the preconception of the evaluator, who may then evaluate the findings of the case and control group differently[177].

Confounding is the confusion of the effect of an exposure. Bias due to confounding appears when parts or all of the association between exposure and outcomes is explained by (an)other variable(s)[178]. Such a variable, a confounder, is associated with the exposure, must be an independent risk factor/cause of the outcome, and should not be an effect of neither exposure nor outcome[179(p.141)]. It should thus not be an intermediate variable on the causal pathway between exposure and outcome. If the association is explained by confounding alone, the observed association is true, but not causal, and will disappear when confounding is controlled for.

Validity is a term applied to describe whether measures in a study captures what was meant to be measured and can be applied to study variables, exposures, outcomes and associations[90(p.57).] Validity can be divided into internal and external validity. Internal validity refers to how well the results from a study show the true associations in the

source population. The less selection bias, information bias and uncontrolled confounding, the higher internal validity[90(p.58),180]. External validity refers to the generalizability of the results, i.e. to what degree the results apply to the target population. High internal validity is a prerequisite for external validity. Further, conclusion about external validity is made based on knowledge of the research topic studied[181].

Reliability refers to what degree measurements/methods replicate the same results when repeated [91]. One type of reliability is inter-rater reliability, referring to the degree to which two different researchers end up with the same conclusion when the same method is used (e.g. same diagnosis when the same clinical interview is used)[91,182].

### 5.1.2 Hypotheses and statistical significance

When comparing a specific characteristic between two groups, statistical inference is based on a "null hypothesis" of no difference between the groups. The probability of getting the result obtained when comparing the two groups if the null hypothesis were true, is given by the p-value. A low p-value means a low probability for obtaining this result, leading to rejection of the null hypothesis. If the null hypothesis is rejected but is in fact true, this is referred to as making a type 1 error[183]. The acceptable probability of making a type 1 error is defined in the study design by setting a level of statistical significance. One common level is 0.05, where a p-value <0.05 leads to rejection of the null hypothesis. This implies a less than 5% risk of making a type 1 error and rejecting a true null hypothesis. Type 2 error is the failure to reject a false null hypothesis[183]. The probability of a Type 2 error decreases as the sample size increases, and the risk of random error decreases.

## 5.2 Paper I

The aim of paper I was to assess personality traits in ADHD patients and a comparison group, and further explore how these traits were associated with anxiety, depression and ASPD. The personality dimensions Novelty Seeking, Harm Avoidance and Reward Dependence were highly associated with ADHD. However, the associations

with Novelty Seeking and Harm Avoidance were partly dependent on ASPD and anxiety/depression, respectively.

### 5.2.1 **Methodological considerations**

#### *ADHD and comparison group*

As described in section 3.1.1, a subsample of the participants from the project "ADHD in adults in Norway" participated in a clinical interview. This project aimed to recruit a naturalistic sample of adult ADHD patients by including adults with ADHD as diagnosed in out-patient clinics all over the country. As we did not make a full clinical assessment to validate the ADHD diagnosis at the time of the interview, we did not know if the participants currently fulfilled the ADHD criteria. The interviews of the ADHD cases took place maximum five years after being included in the "ADHD in adults in Norway" project, and as ADHD is seen as a chronic disorder, we considered the time frame to be acceptable. One would expect selection bias in this study. Of the ADHD cases, 26% were recruited from the Expert Committees of Hyperkinetic Disorder/ADHD, i.e. from a time period when the focus on adults with ADHD was low. One could thus argue that those recruited from this Committee comprised a severe subgroup of patients. Delayed recognition and treatment of ADHD may also increase the risk for other psychiatric problems. These aspects may have contributed to strengthen the differences found between cases and controls, and to reduce the generalizability of the results to patients in other clinical settings. On the other hand, the case group was comprised by individuals actually completing questionnaires and meeting for an interview, which may be difficult for those with the most severe form for ADHD. Another aspect is that those actually participating in the study may have a motivation for participating which makes them different from the study population as a whole. The overall influence of the patient selection on our results may thus go both ways.

All the participants were categorized as having ADHD or not. Since we did not fully assess the ADHD diagnosis, and ADHD is a prevalent disorder we did expect there could be some individuals with ADHD also in the comparison group. We excluded two of the individuals in the recruited comparison group, as we suspected them to have

ADHD based on total information gathered from the interview. Further, one individual had been clinically diagnosed with ADHD and was re-categorized to the ADHD group. Consequently, 4% of the participants in the comparison group were suspected or had ADHD, a frequency comparable to the general population. In the comparison group, the majority (77%) was randomly recruited from MBRN within similar age groups and geographic regions as the ADHD patients (see section 3.1.2). However, only 24% of the invited individuals responded, and we may assume that those responding differ from non-responders by factors like higher education or high functioning. In addition, 19% in the comparison sample were medical students, who may on average be healthier and have different personality profiles than randomly selected controls. This selection bias could lead to strengthening of the associations, as the gap between the case group and the comparison group may have increased. The main results did, however, not change when only including those recruited from the MBRN in the comparison group (results not shown). On the other hand, those agreeing to participate from the randomly recruited comparison group may also include people more interested in the topic because family or friends have ADHD, or even if they suspect that they may have ADHD themselves. This could then affect the results in the opposite way, by weakening the associations. Finally, 4% of the participants from the original comparison group were excluded due to probable ADHD. This could create a selection bias in the comparison sample, towards less psychiatric disorders compared to the general population. However, we found the prevalence for lifetime anxiety and/or depression in adults with ADHD and controls to be 82.5% and 25.0%, respectively. Thus, our results are in line with high rates of psychiatric disorders both in individuals with ADHD, as described in section 1.4.1, but also significant in the control group..

### *Measure of personality traits*

As described in section 3.2.1, we used the self-report inventory TCI to assess personality traits in participants with ADHD, ASPD and lifetime anxiety and/or depressive disorder, respectively, and compared the results with participants without these disorders. Self-report personality inventories have several advantages. They are simple to administer, are not dependent on the interviewer's interpretation of behaviour

or rating of the answers and it is easy to standardize the results[184]. However, self-report inventories have some limitations, e.g. participants' lack of insight, tendency to respond on the extreme ends of the scale, or to answer in accordance with the most social desirable personality characteristics[184-186].

To investigate to what extent the TCI measures the seven personality dimensions in the specific test situation (validity), there are items in the questionnaire intending to detect inconsistent and careless reporting[81(p.75)]. Further, when 12 or more items are missing, the results are not considered valid[88]. One important aspect of evaluating the quality of self-report inventories is the reliability of the findings, in this context to what extent the scores measured are reproducible[81(p.80-81)]. One widely used measure of reliability is internal consistency, which can be measured by Cronbach´s coefficient alpha[187]. The range of Cronbachs´s alpha is between 0 and ± 1, with values > ±0.70 viewed as acceptable[188]. Including both clinical and non-clinical samples, studies from the United States of America (U.S.), Sweden and Finland have shown relatively consistent internal consistency on the TCI ranging from 0.55-0.85 for all dimensions[71,162,189]. Although showing similar results, the investigations are limited, only covering three countries.

Another type of reliability is test-retest reliability, that is to investigate the correlation between the results of an individual´s scores measured on two different occasions [81(p.81)]. Studies examining the test-retest reliability for the TCI version 9 are scarce. In a 1-year longitudinal study including 631 individuals from a U.S. community sample, correlations of the TCI traits ranged between $r$ =0.78-0.85, which is considered a strong correlation[190]. The psychometric properties of the Norwegian version have not been tested, but the Swedish version has shown good psychometric properties for internal consistency and test-retest reliability in adults[88,162]. Finally, the reliability may be affected by the small sample size, one person with ADHD deviating from the "norm" would affect the results more than if the sample was larger.

In general, shorter questionnaires have a greater chance of being completed than long ones, however the relevance of the content is also important[191]. If the questions are considered relevant, participants are more motivated to respond[191]. Another aspect is

the total burden of questionnaires and assessment[191]. The TCI version 9 is 240 items long and takes about 30 minutes to complete. The items are in true/false format, which enhances the likelihood being answered compared to more complex results answering formats[191]. The TCI was the only questionnaire the participants had to fill out at the time of the interview, which could make it more tolerable. However, the length of the questionnaire is not favourable for persons with ADHD, who may have difficulties concentrating. The validity of the TCI is dependent on people answering it properly, if people rush through the questionnaire, the answers may be less valid. On the other hand, if persons with ADHD find the topics interesting, they might be very good at concentrating. It is difficult to decide whether the participants found the questionnaire interesting, as this was not evaluated afterwards.

Another aspect is the number of participants excluded from the study due to missing items in the TCI questionnaire. If individuals with ADHD are more likely to leave out 12 or more items compared to those in the comparison group, it could lead to information bias with differential misclassification. However, only three in the ADHD case group and one in the ADHD control group left out 12 or more items and were excluded from further analyses. The ASRS scores or demographic variables for those three did not differ from the remaining sample. Therefore, it is considered as unlikely that exclusion of participants due to too many missing items will influence the main results.

The TCI is not validated in Norway (see section 3.2.1). We decided not to compare the TCI scores to validated scores from other countries, such as Sweden[88,162], as they do not specifically study ADHD or other psychiatric disorders in their validation. By comparing the scores from the TCI only within the study, the internal validity is satisfactory. However, the external validity is weakened, since we not are able to compare our results with other validated data. Personality traits can be assessed in a number of ways, such as by observer-based assessment, standard test situations, life history analysis and self-report personality inventories, among others[186]. In Paper I we used only one method to assess personality traits, although, ideally, one should compare results from multiple measurements when assessing personality traits[186].

### *Anxiety, depression and antisocial personality disorder (ASPD)*

Anxiety, depression and ASPD were measured with the M.I.N.I. Plus interview. As described in section 3.2.2, this interview is extensively used for assessing these psychiatric disorders in Norwegian research and clinical practice. Although M.I.N.I. Plus is not validated in Norway, this aspect enhances the external validity of the findings. One criticism against the M.I.N.I interview, which is relevant also for the M.I.N.I Plus interview, is the risk of overdiagnosing due to a high rate of false positives [166]. Ideally, these disorders could in addition be evaluated by other methods, such as clinical evaluation, information from family, and self-report questionnaires. Comparing or summarising results based on different methods would increase both the internal and external validity of the study.

There were no calculations of inter-rater reliability among the interviewers, which may decrease the reliability of the findings. To improve the reliability, the interviews were recorded and the results discussed between the interviewers, to ensure that the interviews were conducted as similar as possible. Further, the interviewers were not informed prior to the interview whether the participant was registered in the project as diagnosed with ADHD or not, thus reducing the risk of confirmation bias.

As presented in section 1.3.2, depression and anxiety disorders share many personality traits. The sample sizes were small for each of the types of anxiety and depressive disorders, making it challenging to compare them with each other. Thus, the different anxiety disorders (i.e. panic disorder, with or without agoraphobia, generalized anxiety disorder and/or MDD, both current and lifetime), were merged into a single category termed lifetime anxiety and/or depressive disorder. Due to the fact that these categories were partly based on retrospective data, recall bias could be a concern. The extent of inaccurate recall might have differed between persons with and without ADHD, thus leading to differential misclassification. For example, persons with ADHD might be more prone to remember past psychiatric symptoms compared to persons without ADHD. Differential misclassification may lead to either strengthening or weakening of the results, and will decrease the internal validity of the findings.

### Statistics

As described in section 3.3, the threshold for statistical significance adjusted ad modum Bonferroni was 0,002. The Bonferroni correction gives a conservative estimate of the significance level, decreasing the risk of type 1 error[192]. On the other hand, the risk of type II errors increases, and as previously described, the risk of type II errors is also increased due to the small sample size. Thus, one has to be highly aware of the possibility of type II error, and not only focus on the *p*-value. The results were also given as estimates with 95% CI, which gives information on the estimate precision in addition to information on significance. Further, we presented some of the main results as scatter plots, to visualize the actual, individual data and ease the interpretation of the findings for the reader.

The mean age at time of interview was 34 ± 9 years in the ADHD group, compared to 28 ± 6 years in the comparison group. Adjusting for age did not significantly change the results of the primary analysis, and age was thus not included in the final model. The sex distribution was quite similar between the ADHD group (women: 54.0%) and the comparison group (women: 57%). Due to the small sample size we decided not to stratify the analysis by sex.

## 5.2.2 **Discussion of findings**

In line with previous findings, we found that persons with ADHD as a group had significantly higher scores on the TCI dimension Harm Avoidance ($p< 0.05$) relative to the comparison group. Persons with high Harm Avoidance tend to be fearful and pessimistic, features which also are strongly associated with anxiety and depression (see section 1.3.2). Further, the trait Neuroticism from the Five-Factor model is correlated with Harm Avoidance, and Neuroticism is found to be associated with both ADHD, anxiety and depression[101,104,193-196(p.14)]. Thus, findings in the literature using another method of measuring personality traits, corroborate the results from our study. As the overall findings of comorbidity prevalences and personality trait profiles are in line with previous studies, we think that the findings are relevant and representative for many adults with ADHD.

When including ADHD and comorbid anxiety/depression disorders and ASPD in a linear regression model, ADHD was no longer associated with high Harm Avoidance ($p$= 0.794). In this model, Harm Avoidance was significantly associated only with anxiety/depression ($p$< 0.001). This result indicates that Harm Avoidance, is primarily associated with anxiety and depression, and not ADHD per se. This is more in line with the intuitive understanding of Harm Avoidance (or Neuroticism) to be more related symptoms of anxiety and depression than core symptoms of ADHD. However, the picture is more complex. In an Italian study by Di Nicola et al. (2014)[193], ADHD was assessed in euthymic bipolar patients and patients with MDD in remission (N ~ 100 in each group). Personality traits were measured based on the Five-Factor Model. Evaluating all the clinical subjects together in one group, those with higher levels of Neuroticism had higher frequency of ADHD. This suggests that neuroticism is not only associated with affective disorders per se, but also with ADHD itself.

As findings from Paper III show, psoriasis is associated with ADHD. According to a Turkish study by Kilic et al. (2008) individuals with psoriasis have been found to have significant higher levels of Harm Avoidance and lower levels of Self-Directedness compared to healthy controls[197]. In another Turkish study by Ak et al (2011), males with psoriasis showed significantly higher levels of Harm Avoidance and Novelty Seeking compared to a control group, even after controlling for symptoms of anxiety and depression[198]. Interestingly, this specific pattern of personality traits thus seems to be similar for psoriasis and ADHD.

The dimension Novelty Seeking has, like Harm Avoidance, consistently been associated with ADHD (see section 1.3.2). Surprisingly, when including anxiety, depression and ASPD in the same regression model, Novelty Seeking was no longer associated with ADHD, but rather with ASPD ($p$< 0.001). Further, Reward Dependence was the only TCI dimension that remained significantly associated with ADHD. These results may be somewhat contra-intuitive, as the features of Novelty Seeking (impulsive and quick-tempered) are more typical of ADHD core symptoms, whereas characteristics of Reward Dependence (detached, reserved, cold and independent) are more associated with ASPD. Our results may however have been

influenced by a relatively high overlap of ASPD and ADHD in our sample, with insufficient statistical power to detect characteristics of ADHD and ASPD, and vice versa. Further, as described in section 1.3.2, studies on TCI and ASPD are scarce and the clinical implication of this finding should be cautiously interpreted, before a replication of our findings is available.

### *Sex and age*

According to a study by Miettunen et al. (2007) personality traits differ by sex. In their meta-analysis, including 32 studies on non-clinical samples, women scored significantly higher in the dimensions Harm Avoidance and Reward Dependence compared to men ($p< 0.001$)[199]. Whether the personality profiles as measured by the TCI differ between sex in ADHD is poorly studied. A study by Jacob et al. (2007), including 173 females and 199 males with ADHD, found higher scores of Harm Avoidance ($p< 0.0001$) and Novelty Seeking ($p= 0.045$) in females compared to males, but no sex differences in Reward Dependence ($p= 0.25$)[132]. In our small sample size, it was not feasible to stratify the data by sex due to lack of statistical power. However, the difference in sex distribution between the ADHD and comparison group was not statistical significant (54.0% women in the ADHD group and 57.4% women in the comparison group). Sex was not included as a variable in the regression analyses.

We know that age influences the personality traits, e.g. Harm Avoidance has been shown to be associated with ADHD only in adults[84]. As the prevalence of anxiety and depression also changes by age, age may influence the association between comorbid anxiety/depression and ADHD with personality dimensions[200]. In our study, the mean age at time of the interview was significantly different between the ADHD group and the comparison group (34.4 ± 9.3 years in the ADHD group and 28.3 ± 6.3 years in the comparison group). However, adjusting for age did not significantly change the estimates in the primary analyses, and was therefore not included as a variable in the regression analyses.

## Clinical implications and future research

To our knowledge Paper I is the only published study with this design, thus direct comparison with other studies is not possible. One limitation of our study is the relatively small sample, with low statistical power increasing the risk of type 2 error. On the other hand, in small samples, differences that are actually detected and highly significant ($p< 0.001$), are more likely to reflect findings relevant for clinical practice. However, statistically significant results are not necessarily clinically significant. Clinically significant results are results that are relevant for clinical practice, regardless of the magnitude of statistical significance[201]. We find our results to be relevant for clinical practice, both for assessing and treating ADHD and its comorbid disorders. This single study, with its limitations, will not alone directly impact clinical practice. However, it may contribute to increase the awareness of personality traits in ADHD, and hopefully lead to new studies with improved design in the future.

Future studies could improve knowledge by addressing these questions in a community-based sample, where a cohort of randomly selected individuals is assessed for ADHD, by doing standardized diagnostic interviews and clinical assessment also for other psychiatric disorders. Ideally, a newer edition of TCI with fewer items should be used, or even rather the Five-Factor model, as this model is currently more extensively used and thus easier to compare with and inform clinical practice. In addition, the impact of sex and age should be a topic for research. It would be preferable also to do power calculations to determine what sample sizes are needed, as adequate sample size increases the precision of the results and reduces the risk of type 2 error.
Differential diagnosis and comorbidity related to ADHD is an important topic in everyday clinical practice. As some specific personality traits are associated with different psychiatric disorders, assessment of personality traits may further be used to elucidate patterns of comorbidity between the disorders[113]. Further, personality profile can be helpful when tailoring the treatment of each individual patient, shedding light on strengths and weaknesses in the person's behaviour. This knowledge can be used therapeutically, such as in personalized psychoeducation or behavioural therapy[202].

### 5.2.3 The relationship between personality traits and psychiatric disorders

I will now present different models for explaining the relationship between psychiatric disorders and personality traits[113]. I will use the temperament dimensions Novelty Seeking and Harm Avoidance in relation to ADHD to exemplify the models.

**1) Common cause:** Personality traits and psychiatric disorders arise from the same or overlapping set of aetiological determinants, with no causal influence on each other [107,113]. Shared genetic risk factors is an example of a common cause. Novelty Seeking has been found to be genetically associated with both ADHD symptom dimensions (inattention and hyperactivity-impulsivity), Harm Avoidance with inattention only[203].

**2) Spectrum:** Personality traits and psychopathology are part of the same spectrum, hence, an individual with a psychiatric disorder has an extreme score of a relevant personality trait[67,113,204]. ADHD is a heterogeneous disorder with multiple aetiological pathways, and a personality trait may be a factor in one of these pathways. Nonetheless, if a personality trait is associated with several disorders, it is less consistent with the spectrum view[113]. As other psychiatric disorders are associated with some of the same traits as ADHD, this make the spectrum model less plausible. However, a specific personality trait, for instance Harm Avoidance, might not be directly related to ADHD per se but to anxiety, a common comorbidity in ADHD. If that is the case, Harm Avoidance and anxiety can be seen as being on the same spectrum.

**3) Vulnerability:** The individual is at a greater risk of developing psychopathology due to certain personality traits[204]. Following this hypothesis, it has been claimed that personality plays a causal role in the onset of a psychiatric disorder[113]. ADHD is characterised as a neurodevelopmental disorder, implying that symptoms of ADHD appear early in life. Thus, it is unlikely that the personality traits per se will cause ADHD. However, the vulnerability model is useful in other psychiatric disorders with onset later in life, like anxiety disorder. Innate or early developed personality traits such as fearfulness and shyness, characteristic parts of the Harm Avoidance dimension, can make a person more vulnerable for developing an anxiety disorder. Thus, these personality traits act a causal influence on the manifestation of this disorder. As anxiety is a common comorbidity in ADHD, this interplay between Harm Avoidance and

anxiety development is relevant for individuals with ADHD.

**4) Pathoplastic:** The personality traits influence the course of the psychiatric disorders; such as its severity, presentation and prognosis[204]. A person with high Harm Avoidance is prone to be easily fatigued. The impairment by having ADHD may be more severe if the person is much fatigued, making it harder to accomplish daily tasks.

**5) Scar:** Psychopathology has an impact on the personality[67]. Thus, the person's personality can be changed after the development of a psychiatric disorder[204]. For example, a person with ADHD may easily be exposed to dangerous situations due to inattentive, hyperactive or impulsive behaviour. After this kind of exposure, the person may become more fearful and shy compared to earlier in life. In other words, the person will show a higher degree of Harm Avoidance.

It is plausible that one or several of these models are involved when explaining the relationship between personality dimensions and ADHD[84]. Currently, the knowledge in this field is not sufficient to draw any conclusions. A recent meta-analysis by Gomez et al. on the relationship between Cloninger's personality dimensions and ADHD showed possible support for the spectrum model[84]. As for Paper I, all the included studies lacked longitudinal data. Thus, it was not possible to assess temporal relations, which is important to evaluate the plausibility of the other models, with the exception of the spectrum model. In a previous meta-analysis by the same authors, information on ADHD and personality traits were measured by different methods including the TCI and the Five-Factor Model[67]. The results showed some support for the spectrum and the vulnerability model, but lacked information to evaluate the pathoplastic and scar models. The authors concluded that the spectrum model alone did not provide sufficient explanation for the association between personality and ADHD.

To gain further insight in which of the models are most plausible, there is a need for longitudinal studies to be able to investigate temporal associations (relevant for the vulnerability, pathoplastic and scar models)[84]. Ideally these studies should be drawn from population-based cohort studies from an early age (to avoid e.g. selection and recall bias) including information on genetic and environmental risk factors.

## 5.3 Papers II and III

The aim of Paper II was to investigate if chronic maternal inflammatory and immune system diseases are associated with ADHD in the offspring, whereas in Paper III we aimed at studying the association between ADHD and autoimmune diseases in males and females. We found that maternal MS, RA, T1DM, asthma and hypothyroidism significantly increased the risk of ADHD in the offspring. Further, compared to the general population, persons with ADHD had a higher prevalence of certain autoimmune diseases with evident sex differences, i.e. ADHD increased the odds of ulcerative colitis only in females.

### 5.3.1 **Methodological considerations**

Papers II and III are large epidemiological studies based on data from population- based registries with compulsory notification. The study populations originate from the MBRN where routine linkage with the National Registry ensures complete notification. The risk of selection bias is therefore minimal. Another major advantage is the large number of participants, which strengthens the precision of estimates, leads to less random error, and allows the study of rare events[205]. Since data are collected prospectively, recall bias is not a concern. However, these studies are observational and non-experimental by design, and may be vulnerable to information bias from various sources. The data available are routinely collected, based on standard criteria /standard registration forms, and therefore the investigator has no influence on which and how the specific data are collected[205]. Although this excludes the problem of investigator bias, the researcher is limited to study the variables already included in the registries[205].

#### *ADHD*

ADHD as a variable was based on dispensed ADHD medication as registered in the NorPD. Individuals were thus defined as having ADHD if they had been prescribed and dispensed medication used to treat ADHD from 2004, when the NorPD was established. As described in section 1.1.2, since the prescription of ADHD medication is strictly regulated in Norway and there are only few indications for these drugs,

dispensed ADHD medication is a good proxy for having received an ADHD diagnosis. The exception is when central stimulants are prescribed for narcolepsy. Individuals being prescribed central stimulants for this indication were excluded from the case population (1.4%) from 2008. However, for the period 2004-2007, the NorPD data did not include indications for prescribed medication, and there will therefore be a very small group of individuals who have received central stimulants for narcolepsy during these years, and who will be misclassified as having ADHD. But as this group is very small, it will not influence the main results.

However, our definition will miss individuals who have been treated for ADHD for a period and stopped pharmacological treatment before the NorPD was established. It will also miss individuals who have received the diagnosis, but do not use ADHD medications either due to contraindications, side effects or other reasons[13]. We will also miss individuals who in reality have ADHD, but who have not yet received the diagnosis. This can for instance be due to lack of referral of patients to the specialist health care because of mild symptoms, personality difficulties overshadowing the symptoms, or low capacity in the specialist health care. We also know that there are regional differences in referral rates[28(p.19-20)]. These individuals will all be included in the control groups of our studies.

As emphasized, our case group consists of individuals with ADHD who have received pharmacological treatment. Thus, our results may be generalized to this group of ADHD patients, whereas they may not be valid for those not having received medication. There are no certain numbers of how many persons diagnosed with ADHD use medical treatment, but during 2008-2013, around 80% of Norwegian children diagnosed with ADHD received pharmacological treatment[28(p.29)]. The sensitivity analysis in Paper II, with data from the NPR, showed that 83% of individuals with ADHD registered in NPR received ADHD medication. Adding those not treated pharmacologically to our case group did not change the overall effect estimates. This suggests that our results may also be generalized to a larger group of ADHD individuals.

To sum up, it is quite certain that those defined as ADHD cases based on dispensed medication have been diagnosed with ADHD. The risk that persons without diagnosed ADHD are misclassified as having ADHD is small, except for the very small group of narcolepsy patients receiving medication in 2004-2007. On the other hand, there will be individuals with ADHD misclassified as controls. As the control group is very large, this will not impact on the results. However, our results are not necessarily valid for individuals with ADHD who have not received ADHD medication, although our sensitivity analysis using data from NPR suggest that they may be.

### *Maternal diseases and comorbid autoimmune diseases*

In Paper II, information on the different maternal diseases (exposures) was collected from the MBRN. Not all these diseases are validated, and we may expect that ascertainment is not 100%. Some exposed mothers will therefore be misclassified as non-exposed. Ideally, we should have included information on maternal diseases from other sources for validation purposes, such as from the NorPD or the NPR, but we did not have access to such data. However, we studied diseases previously validated[206,207] or described in the literature[208-210], or for which the MBRN notification form had specific check boxes, to ensure the best possible quality of the diagnoses. Further, this misclassification will probably be non-differential, as the registration of the exposure diseases is independent of the outcome of interest - ADHD in the offspring. Thus, this misclassification will weaken the results.

The autoimmune diseases (outcome variables) in Paper III, were defined based on information from the NorPD only. We did not have the possibility to compare with data from other registries such as the NPR for validation purposes. However, the autoimmune diseases were defined on the basis of prescriptions with reimbursement codes (indications for prescribing), which implies a careful assessment from the clinician and requires the disease to have lasted three months or more. However, misclassification may be present also here. It is possible that differences in health-seeking behaviour in individuals with and without ADHD may lead to differences in being diagnosed with the studied autoimmune diseases. This might lead to differential misclassification, which could either weaken or strengthen the estimates. However,

since the studied autoimmune diseases are severe, usually affect patients' functioning, and require treatment, we believe that most patients with these diseases would seek health care for their symptoms, independent of having ADHD or not. Thus, we do not believe that the possible misclassification is a big threat to the results.

### *Confounding variables*

In addition to possible misclassification of exposure and outcome variables, misclassification can also occur in the potential confounders. One example is maternal smoking in the MBRN, available in the registry from 1999. In contrast to all other variables, mothers can refrain from registration of smoking habits resulting in a considerable amount of missing values (varying from nearly 20% to less than 10% over the years). Underreporting is also a concern with regards to smoking habits. It is possible that individuals with ADHD report their smoking habits differently than individuals without ADHD, which could lead to residual confounding. However, investigations at the MBRN have shown that the amount of missing in maternal smoking information is more linked to midwives at certain institutions not registering the information than to the mothers refraining the registration (K. Klungsøyr, personal communication). Also, the differential misclassification needs to be very large to bias the result to a large extent, which we believe is not likely. Other variables included as potential confounders in the statistical models of Papers II and III were year of birth, parity, mother's age at birth, mother's educational level and marital status, where misclassification is not a problem. We also included offspring birth weight and gestational age, where both variables have good quality. In Paper II we also adjusted for parental use of ADHD medication as a proxy for parental ADHD, and in Paper III for BMI, where the potential misclassifications are as described above.

Paper II was designed as a nested case-control study, where we required all individuals to be alive at record linkage in 2012. Potentially, different mortality rates in the ADHD group versus control group during years before 2012 could bias our results. However, the mortality was so low in both groups that it would not impact the results.

### *Statistics*

We used logistic regression models to evaluate the associations between maternal inflammatory and immune system disease and offspring ADHD (Paper II) and between ADHD and comorbid autoimmune diseases (Paper III). We adjusted for potential and known confounding factors, using maternal educational level as a proxy for maternal socioeconomic status. In Paper II, we included several models including different covariates. We also investigated possible sex differences by stratifying analyses by sex (Paper II) and performing interaction analyses (Paper III). For the purpose of this thesis, we performed interaction analyses to investigate effect modification by sex in Paper II. The results were in line with the findings from the stratified analyses (results not shown). In Paper II, covariates were categorized, since the continuous variables did not show linear relations with the outcomes, and we had sufficient power to assess the data using categories. In Paper III, we adjusted for age as a continuous variable in the main analyses, even if the relationships were not strictly linear (the exception was T1DM, where age was categorized). Thus, it could have been relevant to use spline modelling, which takes non-linearity into account, but applying this method only slightly altered the results[211(p.69)]. In Paper II we calculated cluster-robust standard errors with the mothers as a cluster variable, to take account of dependencies between infants born to the same mother, with little impact on the results.

### *Relative versus absolute effect measures*

Papers II and III were planned under a causal framework. This guided our choice of using relative effect measures, as these are commonly used when investigating causal relations. While it has been suggested that effect measures and interactions on the multiplicative scale are better suited to assess causal relations, risk differences and interactions on the additive scale are the most important to assess public health relevance, indicating what group may benefit the most from treatment or preventive measures.[179(p.6l)]. This was not the aims in Paper II and III and will thus not be focused on in this thesis. However, to provide an example using absolute effect measures, the absolute risk of ADHD in children to mothers with RA was 4.12%, while it was 2.06% for children to mothers without RA. The crude absolute risk difference was thus 2.06%

(1.56%-2.57%). That is, the absolute risk of ADHD in children to mothers with RA was only 2% higher than the risk in children to mothers without RA. On the relative scale, the risk was doubled (relative risk 2.0; 95% CI 1.8-2.3). The number needed to treat is 49, that is RA must be prevented in 49 mothers in order to avoid one case of offspring ADHD. In a clinical context, these numbers show that preventing RA in mothers is not an efficient way to prevent ADHD in children, and screening of RA is not warranted. Regarding Paper III, due to low prevalences of autoimmune diseases in the general population, the absolute risks and risk differences will remain small.

### 5.3.2 Maternal inflammatory and immune system diseases as risk factors for ADHD

In Paper II we found that maternal MS, RA, T1DM, asthma and hypothyroidism increased the risk of ADHD in offspring. There were no associations between ADHD in offspring and maternal T2DM, hyperthyroidism or chronic hypertension. None of the associations differed significantly by offspring sex, however, for asthma, the point estimates were higher for females and CI only slightly overlapped (adjOR 1.7 (95% CI 1.5–1.8)) compared to males (adjOR 1.5 (1.4–1.6)). We aimed to assess the possible relationship between maternal inflammatory/immune system disease and offspring under a causal framework, and not to emphasise clinical implications.

However, it is important to bear in mind that since Paper III is based on an observational study design, it is not possible to make firm conclusions about causality. But several factors point in the direction of a causal relationship between maternal inflammatory/immune system disease and offspring ADHD:

A main strength with a nested case-control design is the possibility to investigate temporal relationship: The exposure (maternal disease) is present before the outcome (ADHD in offspring). A temporal relationship is a prerequisite for a causal relationship.

Some of the effect measures were relatively strong, such as MS (adjOR = 1.8 (1.2–2.5)), RA (adjOR = 1.7 (1.5–1.9)), T1DM (adjOR = 1.6 (1.3–2.0)) and asthma (adjOR = 1.5 (1.4–1.6)). Stronger effects may support a causal relationship.

A limited number of studies have investigated the relationship between maternal inflammatory/immune system diseases and offspring ADHD, and our findings are

partly consistent with these findings. Increased risk of ADHD in the offspring of mothers with psoriasis[152] and T1DM have been found in large population-based register studies from Denmark and Sweden[152,212]. Contrary to our findings, maternal T2DM has also been shown to be associated with offspring ADHD in a large birth cohort study from the U.S.[213]. Maternal thyroid diseases in pregnancy have received attention, as maternal thyroid hormones pass the placenta barrier into foetal circulation, and may thus directly impact the neurodevelopment of the foetus for instance by decreased myelination or altered development of synapses between neurons[214,215]. The role of maternal thyroid disease and ADHD in offspring has also shown conflicting results. In line with our results, a large registry-based Danish study found that maternal hypothyroidism was associated with ADHD in the offspring[214]. A study including 287 mother-child pairs from a U.S birth cohort did not find an association between maternal thyroid levels as measured by blood samples in the second trimester and ADHD in the child, ADHD was here measured by a checklist. This study focused on hyperthyroidism[215], and was thus in line with our findings. Finally, a large English birth cohort comprising 2912 mother-child base-pair did not find any associations with maternal thyroid levels as measured by a blood sample in the first trimester and ADHD in the child (self-report from parents and children)[216]. There is a need for more studies on this topic, with a thorough diagnostic evaluation of ADHD in the offspring.

Another factor that may favour the likelihood of a causal relationship is whether the association is plausible and in line with current knowledge. As discussed in 1.2.2 it is biologically plausible that maternal immune factors may directly impact foetal brain development by maternal immune activation. Another example is disrupted thyroid levels in the mother as described above.

The results may, however, also be affected by unknown/unmeasured confounders. One example of a possible confounder, unmeasured in our study, is maternal use of acetaminophen. Studies have shown increased risk of offspring ADHD related to maternal use of acetaminophen, and the use of acetaminophen in mothers with inflammatory/immune system diseases may be higher compared to mothers without such diseases. However, an increased risk of offspring ADHD has been shown even

when controlling for the indication of acetaminophen use, and acetaminophen is thus likely not a strong confounder[217,218].

Another example of unmeasured confounding is familial confounding (see section 1.2.1). Familial confounding can be illustrated using smoking as an example: Across studies, a clear association between maternal smoking during pregnancy and increased risk of offspring ADHD has been shown[219]. Due to these results, maternal smoking was widely accepted as having a causal effect on the development of offspring ADHD[220]. However, conventional cohort studies have not taken shared family factors into account, including the possible genetic overlap between smoking and ADHD[221]. When controlling for this unmeasured familial confounding by using other study designs, such as sibling design, the association between maternal smoking in pregnancy and offspring ADHD is no longer significant[221-223]. In our study we did not evaluate the possibility of familial confounding, i.e. common genetic factors leading both to inflammatory/immune system diseases in the mother and ADHD in the offspring.

**Maternal versus paternal associations**

In Paper II, data on paternal diseases was not available in the main study file. However, in an additional analysis based on a different datafile, we used data from the NorPD where medication used to treat specific diseases was used as a proxy for a few inflammatory/immune system diseases in the fathers. Although we found statistically significant associations between paternal T1DM and asthma with offspring ADHD, all the risk estimates were lower than those found for maternal diseases. This is in agreement with the results from two population based Danish studies: Nielsen et al. reported maternal, but not paternal, psoriasis to be associated with offspring ADHD[152], and Andersen et al., reported the same for maternal, but not paternal hyperthyreoidism[214]. Further, Jo et al. found that, although not statistically significant, the risk of ADHD was larger if the mother had T1DM than if the father had T1DM[212].

This differences in the maternal versus paternal associations could, as discussed above, be explained by an alteration in the foetal brain development due to a maternal immune response. Another explanation is a sex-specific epigenetic effect, so-called imprinting,

in which the expression of a gene varies depending on whether it is inherited from the mother or the father[224]. Further, most autoimmune diseases are more common in females than males (ankylosing spondylitis is one of the exceptions)[225]. Thus, lack of sufficient statistical power to detect a paternal effect may be an additional explanation.

To conclude, multiple factors, also sex-specific, may contribute to the associations between maternal inflammatory/immune system diseases and offspring ADHD. Although findings from the literature support the theory of common genetic causes, some of the heterogeneity in ADHD may be explained by predominantly immune-mediated aetiologies, perhaps making it possible to subgroup the disorders according to such different aetiologies in the future[52].

### 5.3.3 ADHD and comorbid autoimmune disease

In Paper III we found that there was a close association between ADHD and several autoimmune diseases, but with evident sex differences. Relatively strong associations were found between ADHD and psoriasis regardless of sex, but significantly stronger in females than males. Further, ADHD was positively associated with Crohn`s disease in females but negatively associated in males and significantly associated with ulcerative colitis in females, but not in males. On the other hand, a lower odds of ankylosing spondylitis was found in females with ADHD, while no association in males.

This study aimed to investigate possible associations between ADHD and comorbid autoimmune diseases under a causal framework. That is, we aimed to investigate possible causal associations, not emphasising clinical implications. However, since Paper III is a cross-sectional study, we cannot draw firm conclusions concerning causality. Per design, we do not have certain information on the temporal relationship between ADHD and comorbid autoimmune diseases. But, as ADHD by definition is a neurodevelopmental disorder with onset in (early) childhood, we may assume that the autoimmune disorders usually occur after ADHD. When it comes to the disorders/diseases included in Paper III, they typically develop later in life than ADHD, with the possible exception of T1DM (see Supplementary Figure 1). One explanation

for the development of autoimmune disease is that stress related to having ADHD may be one of the causal factors[226].

Another explanation is that ADHD and the autoimmune disease share common underlying causes. In support of common genetic factors, genetic correlations have been found between ADHD and some autoimmune diseases (see section 1.4.2)[156,157]. A Swedish study by Li et al. (2019) included information on autoimmune diseases both in parents and siblings to individuals with ADHD[227]. ADHD was associated with increased risk of a number of autoimmune diseases in first-degree relatives; psoriasis, RA, MS, ulcerative colitis and Crohn's disease, among others. The authors concluded that the associations might be due to common genetic factors. A study by Hegvik et al. (2019) using family data from Swedish registries, showed that relatives of persons with ADHD (parents, full siblings, aunts, uncles and cousins) had increased odds of several autoimmune disorders such as psoriasis and RA (with the exception of RA in uncles)[228]. Thus, it is plausible, that shared genetic factors underlie these associations. Likely, however, the aetiology connecting ADHD and its autoimmune comorbid disorders is multifactorial, with several mechanisms in action. A further presentation and discussion of models on the relationship between comorbid disorders will follow in section 5.4.3, focusing on autoimmune diseases as examples.

We found no associations between ADHD and iridocyclitis, MS, RA, SLE or T1DM, regardless of sex. Why some autoimmune disorders are found to be associated with ADHD, and others not, is poorly understood. One explanation is methodological limitations (see section 5.3.2). Another possibility is that the mechanisms behind the comorbid disorders differ. Further, results from studies also differ, some studies have for example found ADHD to be associated with T1DM, in contrast to our results[131,152]. A discussion of reasons for such heterogeneity will follow in section 5.4.2.

Although ADHD and diseases related to the immune system are associated at a group level, one cannot make predictions at an individual level. Since the effect sizes are small, the findings from paper III corroborate the assumption that ADHD and related comorbidities are not explained by one or few risk factors alone. In other words,

specific inflammatory processes may contribute to the pathophysiology of ADHD and its comorbidities, but the impact is likely to be too small to help individual patients[229].

### *Sex differences*

The number of studies on sex differences in ADHD and comorbid autoimmune diseases is still scarce. In a a large register-based study from Sweden, our findings regarding the sex-specific associations in ulcerative colitis, Crohn´s disease and ankylosing spondylitis were not replicated[228]. This study used data from the Swedish prescribed drug register and the Swedish National Patient Register, and differences in how data are registered in Swedish compared to Norwegian registries may contribute to the diverse findings. However, the findings were in line with our results with regards to the stronger association between psoriasis and ADHD in females than males, with an adjOR 1.65 (1.52-1.79) in females and adjOR =1.38 (1.28-1.49) in males.

Different factors are discussed as possible contributors to sex differences, both genetic and environmental. Interestingly, most autoimmune disease are more common in females than males, and X chromosome effects may play a role in this sex pattern [225,230]. X and Y chromosomes have specific genetic effects, most immune-related genes are for example found on the X chromosome[161]. X and Y chromosomes also exert gonadal effects. One example is the higher level of oestrogen in women compared to men. Oestrogen may affect the level of thyroid hormone, and also cognitive functioning. This may lead to both thyroid disease and difficulties with attention as seen in ADHD [231]. Females do have increased immune reactivity compared to males, which may make women more prone to develop autoimmune disease[225]. Psychosocial stress and stress-related disorders probably play a role in the exacerbation of autoimmune disease[232,233]. Stressful events related to ADHD may thus lead to increased risk of autoimmune diseases, perhaps even more so in females, as men and women tend to react differently to stress[234]. Finally, different behaviours in males and females due to social or cultural diversities may lead to sex differences, such as in health-seeking behaviour[31].

## 5.4 Paper IV

In Paper IV, the aim was to summarise the current knowledge on the associations between ADHD and somatic diseases in adults by doing a systematic literature review. The associations between adult ADHD and asthma, obesity and sleep disorders were based on sound evidence from the literature.

### 5.4.1 **Methodological considerations**

A systematic review has several strengths compared to a narrative review. When writing a narrative review, the author subjectively selects studies that he/she finds relevant. The study inclusion could for instance be based on the size of the study, study quality, novel findings and so on. Thus, authors writing a review on the same theme may emphasize completely different results[235(xii)]. Although a systematic review is designed to be more objective than a narrative review, it will still always have some subjective elements, such as deciding on the search strategy and the selection of studies. As opposed to a narrative review, the mechanisms behind the decisions of which studies to select are, however, transparent[235(xxiii)].

In Paper IV, a university librarian with expertise in systematic search assisted in developing the search strategy, to ensure the quality of the search. Information on the specific search strategy, databases used in the search, language and years of publication were all included in Paper IV or it´s Supplementary material. In a systematic review, it is practically impossible to locate all the relevant studies on the defined research topic[235(p.278)]. We used general search terms such as “disease”, as it would not have been practically possible to search specifically for every known existing somatic disease. In addition to papers retrieved from the systematic search we also checked references, in order to retrieve as many relevant papers as possible. Another concern is that overall, papers in English are more likely to be included than other languages[235(p.279)]. This is also a limitation in Paper IV, as we restricted the search to English language and three major databases due to the broad theme of the paper. This selection of papers aimed to balance the quality of including as many relevant papers

as possible, and at the same time restricting the amount of results for practical purposes, i.e. to fit into one readable single paper.

Another specific concern in systematic reviews is publication bias, the fact that studies showing significant results are more easily published than those without such results[236]. We were therefore careful to focus studies both on reporting significant associations and those who did not (negative/null findings). In our review, cardiovascular disease was, for example, not associated with ADHD in adults. We further evaluated the quality of the evidence behind the reported associations. In the example of cardiovascular disease, we emphasized the lack of studies on this topic, and that more research is warranted. We did not a design-based quality checklist or rating tools to assess the quality of the different studies, which is a limitation of our review. However, we described main characteristics of all selected papers in a detailed table providing an overview of the strengths and limitations of study designs in each paper.

To sum up the findings, we grouped the included studies/diseases into 3 categories. The first category included somatic comorbid diseases investigated in several papers, including systematic reviews or meta-analyses, thus diseases where an association with adult ADHD was based on sound evidence from the literature. We placed obesity, sleep disorders and asthma in this group. Among these, asthma was the least studied, with 7 studies, versus 22 studies on obesity and 25 studies on sleep disorders.

The second category included studies which were either case-control or cohort studies, or where the diagnoses were not only based on self-report questionnaires. Migraine was placed in this category 2. Only two studies described its association with adult ADHD, and these were both Norwegian[237,238]. Although both studies had good study designs and showed significant associations with ORs around ~2, the tentative association between adult ADHD and migraine was based solely on these two studies, so information was very limited.

The third category included studies where ADHD and/or the somatic comorbidities were poorly defined, i.e. based on self-questionnaires only, or where the evidence was too weak to make conclusions. Studies on a comorbid disorder where results were

conflicting between the studies, or were important information such as age distribution or diagnostic protocols lacked, where also placed in this category. One example is RA, where one study was included, a case control study with a small sample of adults with ADHD (n=23) and controls (n=208) which found no association between RA and ADHD[239]. The result from this single study is not sufficient to conclude that ADHD and RA are not associated.

### 5.4.2 Discussion of findings

The literature on ADHD and comorbid conditions is vast and has expanded extensively since Paper IV was written. It is outside the scope of this thesis to give an updated literature review on all the conditions described in Paper IV. However, in the next section, I will present an updated systematic literature review on the possible association between ADHD and psoriasis, and then discuss the findings. I have chosen psoriasis, as this is one of the diseases investigated in Paper III. Further, the heterogeneity of findings in the literature on ADHD and comorbid somatic disease will be discussed, and models on the relations between ADHD and comorbid disorders presented.

#### *Psoriasis as an example of comorbid autoimmune disease in ADHD*

Psoriasis is a skin disease characterised by itchy, red and scaly skin lesions, also often affecting nails and joints. Although the aetiology behind the disease is unclear, it is currently understood as an autoimmune disease[240]. The prevalence in Europe is about 2-4%, affecting both sexes at an equal rate, with increased frequency by age[241].

A systematic literature search was performed in December 2019 on the topic ADHD and comorbid psoriasis (Appendix IV). The search retrieved six eligible papers, in addition to data from an unpublished papers, published as a manuscript in a thesis[228] (Appendix V). Main study characteristics and results are listed in Table 4.

The included studies showed mixed results. Two studies found a clear association between ADHD and psoriasis; Paper III (adjOR=1.41(1.34-1.47)) and the Swedish study using register data (adjOR=1.48 (1.40−1.57))[228]. Moreover, these two studies were the only studies showing results stratified by sex. Paper III based on Norwegian

**Table 4.** Study characteristics of individual studies included in the systematic literature review of ADHD and psoriasis.

| Ref. | Country | Study design & selection | Total number | Psoriasis | | ADHD | | Covariates | Results |
|---|---|---|---|---|---|---|---|---|---|
| | | | N | N (%) | Diagnosis | N (%) | Diagnosis | | |
| Ahn et al., 2019[244] | Republic of Korea | Cross-sectional.<br>Korean National Health Insurance Research Database (2015):<br>Those registered with atopic dermatitis (n=42,641) and with nonatopic eczema, urticaria, and psoriasis (n=139,486)<br>All ages included.<br>Females: 43% | 182,127 | 5,323 (3) | ICD[1]-10: L40.9 (medical records) | 895 (0.5) | ICD 10: F90.0 (medical records) | Age, gender, economic status, severity of atopic dermatitis, history of atopic dermatitis, concomitant allergic disease. | Prevalence of ADHD among those with atopic dermatitis: 0.56%.<br>Prevalence of ADHD among those with non-atopic eczema, urticaria, and psoriasis (merged into one category): 0.47%. No significantly increased risk of ADHD prevalence among patients with psoriasis compared to those with atopic dermatitis. |
| Alabaf et al., 2019[139] | Sweden | General population cohort of twins.<br>Born 1992-2006<br>Age: 9 or 12 years<br>Females: 49.6% | 28,058 | 87 (0.3) | Telephone interview. Question to parents: "Has he/she ever had psoriasis?" | 377 (1,3) | Telephone interview: A-TAC[2] | None | 2 cases with ADHD and psoriasis.<br>Odds Ratio (OR) = 1.3 (95%). Confidence Interval (CI) 0.3-5.2) |
| Hegvik et al., 2018[245] | Norway | Population-based, cross-sectional (2004-2015).<br>The Medical Birth Registry of Norway, The Norwegian Prescription Database.<br>Females: 49.3%<br>Born: 1967-2011 | 2 475,341 | 62,418 (2.5) | Prescribed and dispensed medication for psoriasis: ICD-10 L40 or ICPC[3] S91 | 63,721 (2.6) | Prescribed and dispensed medication for ADHD: ATC[4]-code N06BA | Maternal education, sex, age. | Adjusted (adj) OR = 1.41 (1.34-1.47), (result direct from Hegvik). By sex:<br>Females: adjOR = 1.57 (1.46–1.68). Males adjOR = 1.31 (1.23–1.40)<br>(Unadjusted ORs not published). |
| Hegvik et al., 2019[228] | Sweden | Swedish Total Population Register, cohort born 1960-2010 with biological mother | 5 178,225 | 45,954 (0.9) | The Swedish Prescribed Drug Register | 118,927 (2.3%) | The Swedish Prescribed Drug Register The Swedish | | AdjOR=1.48 (1.40−1.57) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | known, data included 2013<br>Females: 48,6% | | | | | National Patient Register | | By sex:<br>Females: adjOR 1.65 (1.52-1.79)<br>Males: adjOR =1.38 (1.28-1.49) |
| Kara et al, 2019[243] | Turkey | Prospective case-control study. All participants selected from children (8-16 years) presented to a hospital dermatology department. Cases: Children with psoriasis monitored by dermatologic clinic Controls: healthy children (no more specific information provided)<br>Females: 48%. | 108 | 54 | Children diagnosed with psoriasis by a dermatologist. monitored by dermatologic clinic. | 14 | K-SADS PL[5] | None | Psoriasis: 10 with ADHD<br>Not psoriasis: 4 with ADHD<br><br>$p$ = .086 (chi square test) |
| Nielsen et al., 2017[152] | Denmark | Cohort, all singeltons born in Denmark 1990-2007, followed up 1995-2012,<br>8,9 million person years.<br>Danish National Hospital register, Danish Psychiatric Central Research Register<br>Male/female ratio: no information | 983,680 | | Admitted or outpatient care for psoriasis: ICD-8: 696.09, 696.10, 696.19, ICD-10 L40 except L40.4 | 23,645 (2.4) | Admitted to psychiatric hospital or outpatient care for ADHD: ICD-10: F 90.x +F98.8 | Calender year, sex, interaction of sex with age, parental history psychiatric admission. | 19 cases with ADHD and psoriasis.<br>Unadjusted incidence rate ratio (IRR) = 1,52 (0,93-2,31)<br>Adjusted IRR = 1,39 (0,85-2,11) |
| Radtke et al., 2017[242] | Germany | Population-based, cross-sectional.<br>German National Health Insurance in the year 2009.<br>Adults ≥ 18 years.<br>Male/female ratio: no information | 1 342,671 | 37,456 (2.8%) | Ambulatory /hospital treatment for psoriasis ICD-10 : L40 | | Ambulatory /hospital treatment for ADHD: diagnostic codes not specified. | None | 0.23% of those with ADHD had psoriasis.<br>Prevalence ratio with/without psoriasis: 0,82 (0,66-1,01) |

[1]the International Statistical Classification of Diseases and Related Health Problems. [2]ADHD and other Comorbidities Inventory; fully structured interview based on the diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders IV. [3]the International Classification of Primary Care[4].Anatomical Therapeutic Chemical Classification System codes. [5]the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version.

data showed a significantly higher OR in females than in males, with adjOR=1.57 (1.46-1.68) and adjOR=1.31 (1.23-1.40), respectively. The Swedish study showed the same pattern, with adjOR=1.65 (1.52-1.79) for females and adjOR =1.38 (1.28-1.49) for males. Four of the studies found no significant association between ADHD and psoriasis[139,152,242,243]. In a Turkish case-control by Kiri et al, children with psoriasis (n= 54) and healthy controls (n=54) were recruited from a dermatological department at a Turkish hospital[243]. The details on the recruitment of the control group were sparse, making it difficult to evaluate the risk of selection bias, and the results only showed crude associations. Also, in the study by Radtke et al, using German insurance data, there were no adjustments for covariates. Thus, the impact of important covariates such as sex and age is not known. In addition, ADHD was defined by using the results from a questionnaire, without any clinical assessment[242]. The Swedish twin study by Alabaf et al. only included two individuals with both ADHD and psoriasis. Further, the prevalence of psoriasis was only 0.3%, most likely due to the young age of the participants. Hence, many of the participants were too young to have developed psoriasis and the association between ADHD and psoriasis might have been underestimated[139]. The same mechanism may also apply for the Danish population-based register study by Nielsen et al. This study showed, although not statistically significant, an adjusted incidence rate ratio of 1.39 (95% CI 0.85-2.11), implying a possible association between ADHD and psoriasis[152]. Interestingly, this study also showed an increased risk of ADHD in children of mothers with psoriasis. The final study retrieved in the search was a study by Ahn et al. using Korean insurance data[244]. The exposures were different skin disorders with ADHD as outcome; no control group was included. The study showed no significantly increased risk of ADHD prevalence among patients with psoriasis compared to those with atopic dermatitis (AD). To conclude, based on the current evidence emphasising the results from the studies with the highest design quality, it is plausible that ADHD and psoriasis are associated conditions.

### *Heterogeneity of findings on ADHD and somatic disease*

As seen in the example of psoriasis, the results between the studies were diverging. Some studies found an association between ADHD and psoriasis, others not. Such contrasting results have also been found for other diseases such as T1DM, autoimmune thyroiditis, RA and MS[152,155,228,245]. Other diseases, such as SLE and iridocyclitis, have not shown any association with ADHD[152,155,245].

ADHD has been reported to be associated with migraine, but not with tension headache [142,143]. One study also found migraine to be significantly more common in mothers to children with ADHD compared to mothers whose children did not have ADHD[142]. The fact that the pathophysiology of these two kinds of headaches is believed to differ[246], corroborates the hypothesis of a common aetiology between ADHD and migraine, but not between ADHD and tension headache. Individuals with ADHD are more in contact with health services and thus probably more prone to be diagnosed with headache relative to people without other chronic conditions. However, the differences in in health seeking behaviour would not explain the differences in associations found for tension headache and migraine.

The reasons for the conflicting results are not known, but could partly be explained by methodological differences between studies. Some studies do not control, or inadequately control, for possible confounding factors, as discussed above. Further, ADHD or the comorbid somatic disease may be poorly defined, for example screening questionnaires are considered to be less valid than an extensive clinical evaluation. Moreover, the samples could be non-representative. One example is the study by Nielsen et al., where the oldest participants were only 30 years old[152]. As autoimmune diseases usually develop later in life, this could lead to underrepresentation of cases with lifetime psoriasis. Finally, although following the same diagnostic criteria, various countries have different traditions regarding how ADHD is diagnosed. In Norway, ADHD is diagnosed in secondary health care by medical doctors specializing in clinically relevant fields, psychiatrists, psychologists or paediatricians. This as opposed to the U.S, where about half of children are diagnosed in primary care by paediatricians

or general health physicians[247]. Thus, symptoms may be emphasized differently, leading to diverse diagnostic practice and heterogeneity of the findings.

### 5.4.3 Models on the relations between ADHD and comorbid disorders

Several models of the mechanisms behind the association between ADHD and its comorbid disorders have been proposed:

1) The disorders co-occur by chance; no aetiological relationship between them[115].

2) The association between the disorders can be explained by a common cause or common risk factor[120]. During the last years, the influence of genes as common factors explaining comorbidity has been emphasised. The same set of genes have been found to influence a variety of neuropsychiatric disorders, including ADHD[248]. Moreover, it is likely that a subgroup of genes coding for obesity also increases the risk of ADHD[141]. In a large, population-based study from the U.S. by Wang et al., significant genetic correlations were found between ADHD and psoriasis, migraine and inflammatory bowel disease. No common, persisting environmental associations were found between these conditions[249]. This is in line with two genome-wide association studies, finding significant genetic correlations between ADHD and MDD, psoriasis, RA, insomnia and obesity, among others[156,157].

3) One disorder or the treatment of this disorder directly causes another disorder. This model is called the direct causal model[250]. One example is stimulant treatment for ADHD causing hypertension[251].

4) Disorders are not really distinct disorders, but only reflect different aspects of the same syndrome[252]. This can be true for specific syndromes caused by chromosomal aberrations such as trisomy 21 and fragile X syndrome[253]. One can here argue that the ADHD diagnosis is a part of the syndrome itself, and not a distinct disorder.

5) One disorder increases the risk of having another disorder[250]. One example is the

relation between AD and ADHD. Itching, a symptom of AD, often leads to disturbance of sleep[226]. Such disturbance may result in disruptive and hyperactive behaviour, poor memory and lack of concentration[226,254,255]. AD usually occurs prior to 3 years of age, before the full clinical picture of ADHD has developed[226,256]. Thus, it has been hypothesised that AD may cause ADHD symptoms, so-called "AD-induced ADHD"[226]. It can also be the other way around, emotional and psychosocial stress related to having ADHD may be an exacerbating or underlying cause of AD ("ADHD-induced AD")[226].

6) There is no real comorbidity, meaning that the validity of one of the diagnoses could be questioned. For example, that ADHD symptoms are better explained by symptoms of another condition, such as sleep disorders[257]. To use the example of AD, sleep disturbances which are related to AD leads to symptoms of ADHD, but not ADHD per se. Another example is hypothyroidism, which can cause symptoms mimicking ADHD symptoms such as reduced attention and memory[258].

The clinician must consider whether the symptoms of the comorbid disorder could explain the ADHD symptoms. Both NICE and Norwegian ADHD guidelines emphasize that symptoms of disorders which may mimic ADHD must be considered when diagnosing ADHD[13,259(p.25)]. However, if the individual also fulfil the criteria for the ADHD diagnosis, it is important to acknowledge this diagnosis to be able to offer adequate treatment, both for ADHD and for the comorbid condition[260].

# 6. Conclusions

- Specific personality dimensions such as Novelty Seeking, Harm Avoidance and Reward Dependence were highly associated with ADHD. The associations with Novelty Seeking and Harm Avoidance were partly dependent on ASPD and anxiety/depression, respectively.

- Some maternal immune related diseases such as asthma, MS and RA are shown to be associated with ADHD in the offspring.

- Compared to the general population, persons with ADHD have a higher prevalence of certain autoimmune diseases, such as psoriasis, asthma, ulcerative colitis and Crohn's disease.

- Sex is shown to significantly modify the association between ADHD and some autoimmune diseases. The risk of ulcerative colitis and Crohn's disease is higher in females than males with ADHD.

- Adults with ADHD are at higher risk than adults in the general population of suffering from a range of somatic diseases. The best documented comorbid diseases are obesity, asthma and sleep disorders such as insomnia.

- Information on personality traits, underlying risk factors and comorbid psychiatric and somatic diseases may be useful to improve the understanding of the individual ADHD patient, to provide the best treatment, and to inform further studies on the aetiology behind the disorders.

# 7. Future Perspectives

The results from this thesis underscore the importance of a comprehensive approach when assessing and treating individuals with ADHD. There is a need to go beyond the classic symptom domains of ADHD and also pay attention to its associated personality traits and comorbid disorders and diseases. Thus, ADHD can be considered as extreme dimensions of normal conduct[261], occurring along a spectrum of clinical presentations[262]. Altogether, the results of Paper I show that awareness about the role of personality traits in ADHD and common psychiatric comorbid disorders should be subject to further studies, as such knowledge is useful not only when treating the individual ADHD patients, but also to improve our understanding of underlying pathophysiology behind this condition and make assumptions on causality.

The results of Paper II and III underscore the relation between inflammatory and immune system diseases and ADHD, both as prenatal risk factors and comorbid diseases. However, caution is needed when interpreting associations found in epidemiological observational studies and clinical studies, as association does not necessarily mean causation. Using different approaches to assess the same underlying causal question is helpful to gain deeper insight into possible causal effects. These approaches should ideally have different potential biases. Integration of such research findings is known as triangulation. If different study designs and type of results lead to the same conclusion, the confidence in a finding is strengthened[263]. In addition to independent replication of results from previous studies, triangulation can be a powerful tool to advance from associative to causative relationships. In the ADHD research field, a recent example of triangulation is found in the large population-based study by Solberg et al[264]. Based on Norwegian registry data, the adjusted prevalence ratio of substance use disorder in adults with ADHD compared to the remaining adult population was 6.2 (6.1-6.4). In addition, genetic correlations were calculated showing significant genetic correlations between ADHD and proxies of substance use disorder. Thus, genetic correlations corroborated the results from the investigation based on registry data. Ideally, the investigations from the Papers in this thesis should be replicated and also the same topics studied using other research designs.

Special attention should be given to investigate the possibility of grouping ADHD patients based on specific comorbidity patterns. Such patterns could be comprised of certain personality traits, particular psychiatric or somatic disorders/diseases, and also include lifespan symptom profile and sex[125]. These subgroups may potentially have their specific aetiology, modifying risk factors as well as different outcomes[114]. On the other hand, all persons with ADHD have their own individual symptom expression and specific biological profile. To increase the understanding of the aetiology behind ADHD, one approach is to study characteristics of ADHD and its comorbidities not only at group level, but also at individual level[265]. Longitudinal studies are strongly warranted, as such studies may identify specific lifetime trajectories both individually and across generations[3]. Information from other family members is of great value, making it possible to apply different family-designs, like twin, - sibling,-, half,-sibling and cousins comparisons. Such approaches are useful to detect genetic and environmental risk factors, both within families and across generations.

In my work, findings from Paper III and IV show to which extent individuals with ADHD are more prone to develop some somatic comorbidities compared to the general population. In my opinion, the importance of comorbidities in ADHD, especially somatic comorbidities, has not yet been fully appreciated, neither in research nor in clinical practice. The work in this thesis is a contribution to focus on these essential issues.

When assessing comorbidity, it is most common to focus on a single index disorder and how other disorders/diseases are related to this disorder. A different approach is to investigate the causes or consequences of multiple conditions at even terms, without giving any condition priority over the others[122]. Knowledge on the total morbidity burden is important to broaden the perspective from a narrow focus on single diseases to the overall health of each patient[266]. In this context, it is also natural to consider the impact of both psychiatric and somatic conditions as a whole. As Are Brean, a Norwegian neurologist (2015) stated: *"We are not a mind and a body, but both, inseparably and at the same time"*[267].

## APPENDIXES

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# APPENDIX I

**Appendix I.** Diagnostic criteria according to DSM-5.

**Attention-Deficit/Hyperactivity Disorder (ADHD) 314.0X**

**A.** A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

**1. Inattention**: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

a. Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities.

b. Often has difficulty sustaining attention in tasks or play.

c. Often does not seem to listen when spoken to.

d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace.

e. Often has difficulty organizing tasks and activities.

f. Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort.

g. Often loses things necessary for tasks or activities.

h. Is often easily distracted by extraneous stimuli.

i. Is often forgetful in daily activities.

**2. Hyperactivity and impulsivity**: Six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities:

a. Often fidgets with or taps hands or feet or squirms in seat.

b. Often leaves seat in situations when remaining seated is expected.

c. Often runs about or climbs in situations where it is inappropriate. (Note: In adolescents or adults, may be limited to feeling restless).

d. Often unable to play or engage in leisure activities quietly.

e. Is often "on the go," acting as if "driven by a motor".

f. Often talks excessively.

g. Often blurts out an answer before a question has been completed.

h. Often has difficulty waiting his or her turn.

i. Often interrupts or intrudes on others.

Note: The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or a failure to understand tasks or instructions. For older adolescents and adults (≥ 17), at least five symptoms are required.

**B.** Several inattentive or hyperactive-impulsive symptoms were present prior to age 12 years.

**C.** Several inattentive or hyperactive-impulsive symptoms are present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities).

**D.** There is clear evidence that the symptoms interfere with, or reduce the quality of, social, academic, or occupational functioning.

**E.** The symptoms do not occur exclusively during the course of schizophrenia or another psychotic disorder and are not better explained by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, personality disorder, substance intoxication or withdrawal).

**Specify whether:**
314.01 Combined presentation: If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months.
314.00 Predominantly inattentive presentation: If Criterion A1 (inattention) is met but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months.
314.01 Predominantly hyperactive/impulsive presentation: If Criterion A2 (hyperactivity and impulsivity) is met but Criterion A1 (inattention) is not met over the past 6 months.

# APPENDIX II

**Appendix II. Examples of TCI items :**

*Novelty Seeking:*

“It is difficult for me to keep the same interests for a long time because my attention often shifts to something else.”

“I lose my temper more quickly than most people.”

“I often follow my instincts, hunches, or intuition without thinking through all the details.”

“I like it when people can do whatever they want without strict rules and regulations”.

*Harm Avoidance:*

“I need much extra rest, support, or reassurance to recover from minor illnesses or stress”.

“I often feel tense and worried in unfamiliar situations, even when I others feel there is little to worry about”.

“I usually stay away from social situations where I would have to meet strangers even if I am assured that they will be friendly”.

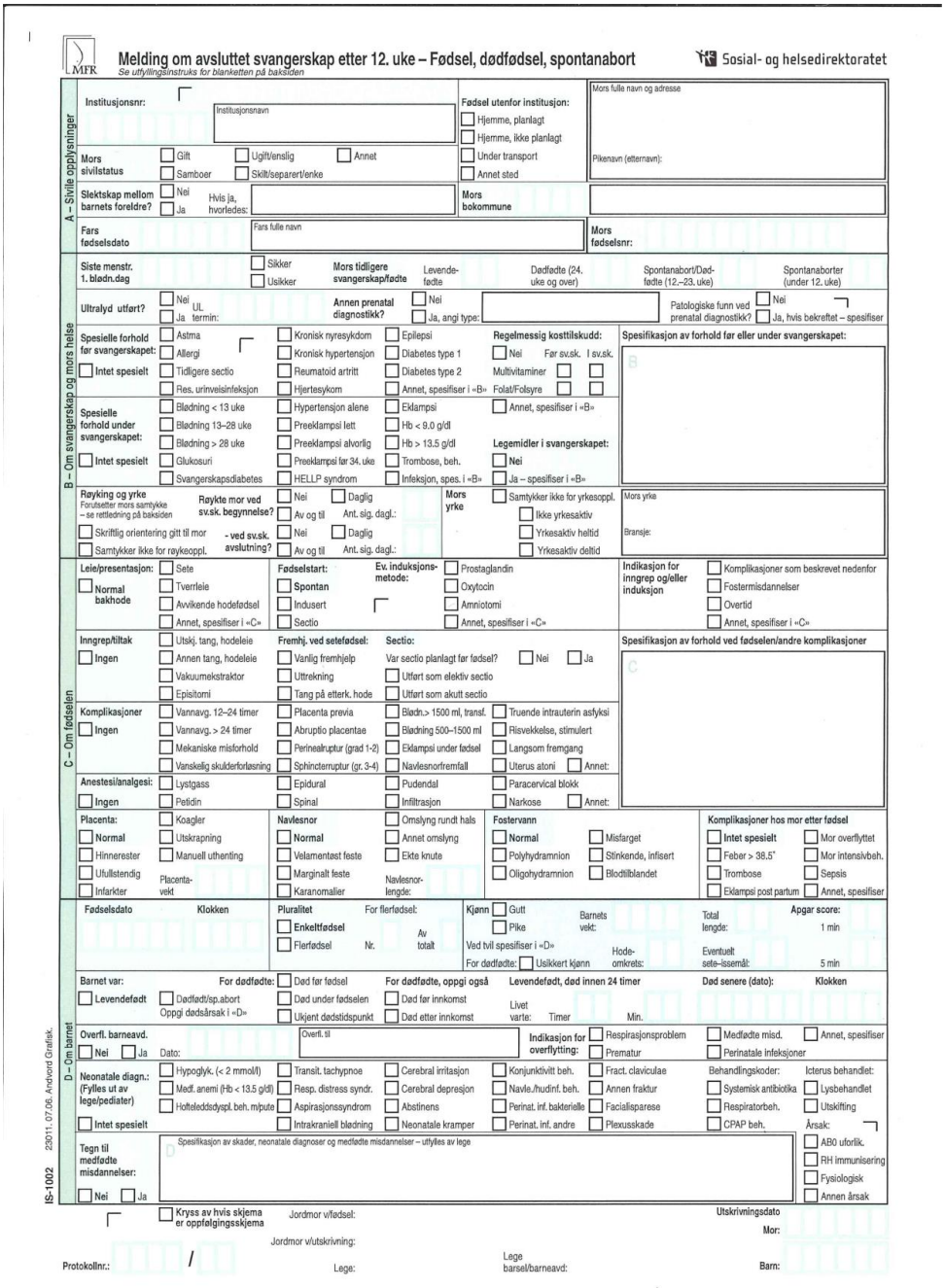
*Reward Dependence:*

“I would like to have warm and close friends with me most of the time”.

“ I usually do things my own way - rather than giving in to the wishes of other people”.

“I like to please other people as much as I can”.

# APPENDIX III



Melding om avsluttet svangerskap etter 12. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

Sosial- og helsedirektoratet

MFR

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn | Fødsel utenfor institusjon: Hjemme, planlagt; Hjemme, ikke planlagt; Under transport; Annet sted | Mors fulle navn og adresse | Pikenavn (etternavn):

Mors sivilstatus: Gift; Samboer; Ugift/enslig; Skilt/separert/enke; Annet

Slektskap mellom barnets foreldre? Nei; Ja. Hvis ja, hvorledes: | Mors bokommune

Fars fødselsdato | Fars fulle navn | Mors fødselsnr:

B – Om svangerskap og mors helse

Siste menstr. 1. bløtn.dag: Sikker; Usikker | Mors tidligere svangerskap/fødte: Levendefødte | Dødfødte (24. uke og over) | Spontanabort/Dødfødte (12.–23. uke) | Spontanaborter (under 12. uke)

Ultralyd utført? Nei; Ja. UL termin: | Annen prenatal diagnostikk? Nei; Ja, angi type: | Patologiske funn ved prenatal diagnostikk? Nei; Ja, hvis bekreftet – spesifiser

Spesielle forhold før svangerskapet: Intet spesielt
Astma; Allergi; Tidligere sectio; Res. urinveisinfeksjon; Kronisk nyresykdom; Kronisk hypertensjon; Reumatoid artritt; Hjertesykom; Epilepsi; Diabetes type 1; Diabetes type 2; Annet, spesifiser i «B»

Regelmessig kosttilskudd: Nei. Før sv.sk. I sv.sk.: Multivitaminer; Folat/Folsyre

Spesifikasjon av forhold før eller under svangerskapet: B

Spesielle forhold under svangerskapet: Intet spesielt
Blødning < 13 uke; Blødning 13–28 uke; Blødning > 28 uke; Glukosuri; Svangerskapsdiabetes; Hypertensjon alene; Preeklampsi lett; Preeklampsi alvorlig; Preeklampsi før 34. uke; HELLP syndrom; Eklampsi; Hb < 9.0 g/dl; Hb > 13.5 g/dl; Trombose, beh.; Infeksjon, spes. i «B»; Annet, spesifiser i «B»

Legemidler i svangerskapet: Nei; Ja – spesifiser i «B»

Røyking og yrke. Forutsetter mors samtykke – se nettledning på baksiden. Skriftlig orientering gitt til mor; Samtykker ikke for røykeoppl.

Røykte mor ved sv.sk. begynnelse? Nei; Daglig; Av og til; Ant. sig. dagl.:

– ved sv.sk. avslutning? Nei; Daglig; Av og til; Ant. sig. dagl.:

Mors yrke: Samtykker ikke for yrkesoppl.; Ikke yrkesaktiv; Yrkesaktiv heltid; Yrkesaktiv deltid | Mors yrke | Bransje:

C – Om fødselen

Leie/presentasjon: Normal bakhode
Sete; Tverrleie; Avvikende hodefødsel; Annet, spesifiser i «C»

Fødselstart: Spontan; Indusert; Sectio

Ev. induksjonsmetode: Prostaglandin; Oxytocin; Amniotomi; Annet, spesifiser i «C»

Indikasjon for inngrep og/eller induksjon: Komplikasjoner som beskrevet nedenfor; Fostermisdannelser; Overtid; Annet, spesifiser i «C»

Inngrep/tiltak: Ingen
Utskj. tang, hodeleie; Annen tang, hodeleie; Vakuumekstraktor; Episiotomi

Fremhj. ved setefødsel: Vanlig fremhjelp; Uttrekning; Tang på etterk. hode

Sectio: Var sectio planlagt før fødsel? Nei; Ja. Utført som elektiv sectio; Utført som akutt sectio

Spesifikasjon av forhold ved fødselen/andre komplikasjoner: C

Komplikasjoner: Ingen
Vannavg. 12–24 timer; Vannavg. > 24 timer; Mekaniske misforhold; Vanskelig skulderforløsning; Placenta previa; Abruptio placentae; Perinealruptur (grad 1-2); Sphincterruptur (gr. 3-4); Blødn.> 1500 ml, transf.; Blødning 500–1500 ml; Eklampsi under fødsel; Navlesnorfremfall; Truende intrauterin asfyksi; Risvekkelse, stimulert; Langsom fremgang; Uterus atoni; Annet:

Anestesi/analgesi: Ingen
Lystgass; Petidin; Epidural; Spinal; Pudendal; Infiltrasjon; Paracervical blokk; Narkose; Annet:

Placenta: Normal
Koagler; Utskrapning; Manuell uthenting; Hinnerester; Utullstendig; Infarkter; Placenta-vekt

Navlesnor: Normal
Omslyng rundt hals; Annet omslyng; Ekte knute; Velamentast feste; Marginalt feste; Karanomalier; Navlesnor-lengde:

Fostervann: Normal
Misfarget; Polyhydramnion; Stinkende, infisert; Oligohydramnion; Blodtilblandet

Komplikasjoner hos mor etter fødsel: Intet spesielt
Mor overflyttet; Feber > 38.5°; Mor intensivbeh.; Trombose; Sepsis; Eklampsi post partum; Annet, spesifiser

D – Om barnet

Fødselsdato | Klokken | Pluralitet: Enkeltfødsel; Flerfødsel. For flerfødsel: Nr.; Av totalt | Kjønn: Gutt; Pike. Barnets vekt: | Total lengde: | Apgar score: 1 min; 5 min. Ved tvil spesifiser i «D». For dødfødte: Uslikkert kjønn. Hode-omkrets: | Eventuelt sete–issemål:

Barnet var: Levendefødt; Dødfødt/sp.abort. Oppgi dødsårsak i «D»

For dødfødte: Død før fødsel; Død under fødselen; Ukjent dødstidspunkt

For dødfødte, oppgi også: Død før innkomst; Død etter innkomst

Levendefødt, død innen 24 timer: Livet varte: Timer Min.

Død senere (dato): | Klokken

Overfl. barneavd.: Nei; Ja. Dato: | Overfl. til

Indikasjon for overflytting: Respirasjonsproblem; Prematur; Medfødte misd.; Perinatale infeksjoner; Annet, spesifiser

Neonatale diagn.: (Fylles ut av lege/pediater) Intet spesielt
Hypoglyk. (< 2 mmol/l); Medf. anemi (Hb < 13.5 g/dl); Hofteleddsdyspl. beh. m/pute; Transit. tachypnoe; Resp. distress syndr.; Aspirasjonssyndrom; Intrakraniell blødning; Cerebral irritasjon; Cerebral depresjon; Abstinens; Neonatale kramper; Konjunktivitt beh.; Navle./hudinf. beh.; Perinat. inf. bakterielle; Perinat. inf. andre; Fract. claviculae; Annen fraktur; Facialisparese; Plexusskade

Behandlingskoder: Systemisk antibiotika; Respiratorbeh.; CPAP beh.

Icterus behandlet: Lysbehandlet; Utskifting. Årsak:

Tegn til medfødte misdannelser: Nei; Ja. Spesifikasjon av skader, neonatale diagnoser og medfødte misdannelser – utfylles av lege: D

ABO uforlik.; RH immunisering; Fysiologisk; Annen årsak

IS-1002 23011: 07.06. Andvord Grafisk

Kryss av hvis skjema er oppfølgingsskjema

Jordmor v/fødsel: | Jordmor v/utskrivning: | Utskrivningsdato: Mor:

Protokollnr.: / | Lege: | Lege barsel/barneavd: | Barn:

The Medical Birth Registry of Norway registration form; the paper form used from 1999 to 2006-2014.

# APPENDIX IV

## Appendix IV. SEARCH STRATEGY ADHD OG PSORIASIS

**Pubmed (December 11, 2019). – 17 studies.**

((attention deficit disorder [TW]) OR (adhd [TW]) OR (addh [TW]) OR (hyperkinetic disorder [TW]) OR (attention deficit hyperactivity disorder [TW])) AND ((Psoriatic* [TW]) OR (psorias* [TW]))

**Embase (December 11, 2019) – 95 studies**

1 (ADHD or attention deficit* or hyperactivity disorder* or hyperactive child syndrome or childhood hyperkinetic syndrome or addh or overactive child syndrome or (attent* adj3 (disorder* or hyperactiv* or hyper?activ* or adhd or addh or ad??hd)) or ((hyperkin* or hyper?kin*) adj3 (disorder* or syndrome* or hkd))).mp.

2 psoriasis.mp.

3 psoriatic*.mp.

4 2 OR 3

5 1 AND 4

6 Limit 5 to human

7 Limit 6 to conference abstract

8 6 NOT 7

9 Limit 8 to (books or chapter or "conference review")

10 8 NOT 9

11 Limit 10 to clinical trial

12 10 NOT 11

**Psychinfo (December 11, 2019) – 8 studies**

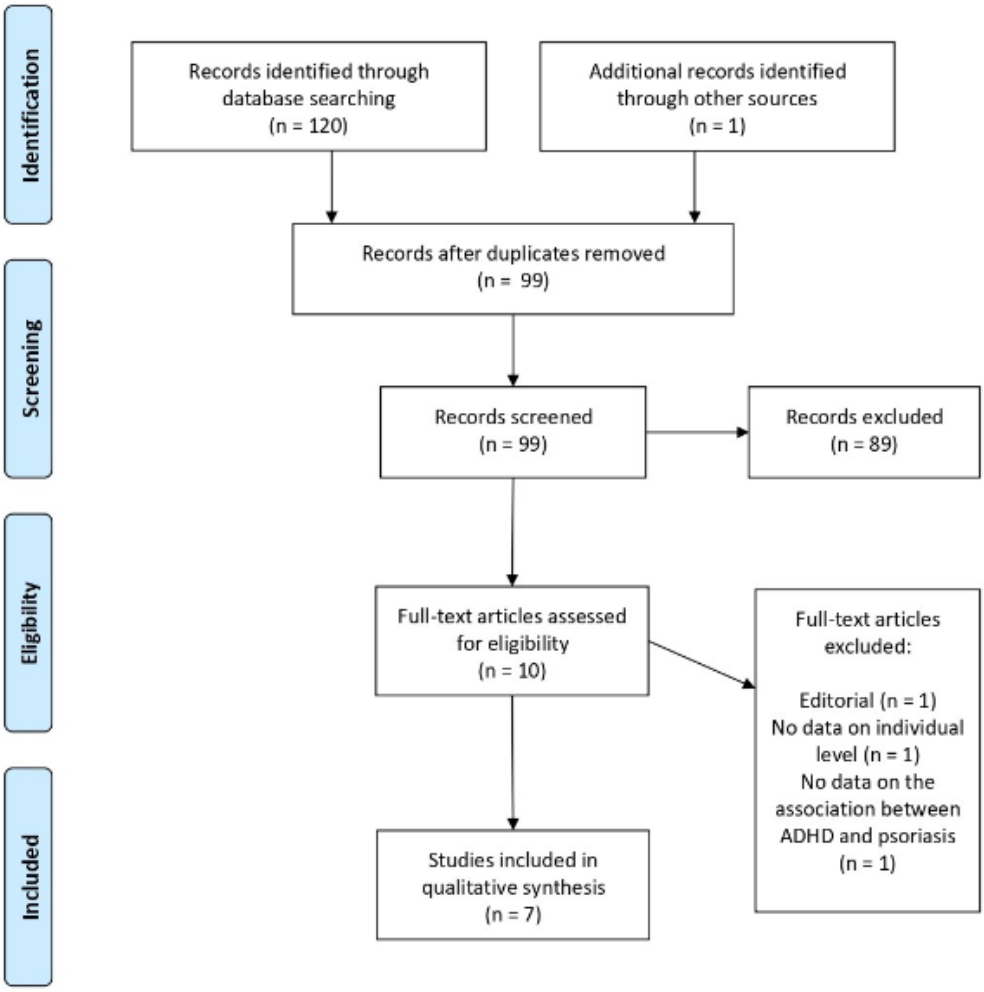
1 (ADHD or attention deficit* or hyperactivity disorder* or hyperactive child syndrome or childhood hyperkinetic syndrome or addh or overactive child syndrome or (attent* adj3 (disorder* or hyperactiv* or hyper?activ* or adhd or addh or ad??hd)) or ((hyperkin* or hyper?kin*) adj3 (disorder* or syndrome* or hkd))).mp.

2 psoria*.mp.

3 1 AND 2

# APPENDIX V

**Flowchart: study selection, the systematic literature review on ADHD and psoriasis.**




*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

# I

*Article*

# Personality Traits and Comorbidity in Adults With ADHD

Journal of Attention Disorders
2016, Vol 20(10) 845–854

DOI: 10.1177/1087054713511986
jad.sagepub.com
SAGE

**Johanne Telnes Instanes[1], Jan Haavik[1,2], and Anne Halmøy[1,2]**

**Abstract**

**Objective:** To assess personality traits using the Temperament and Character Inventory (TCI) in a group of 63 previously diagnosed ADHD patients and 68 population controls and investigate the impact of common comorbid psychiatric disorders on these personality measures. **Method:** Psychiatric comorbidity was assessed with the Mini International Neuropsychiatric Interview Plus and personality traits by the TCI. **Results:** The patient group had significantly higher scores on the TCI dimensions Harm avoidance and Novelty seeking compared with the control group. However, when adjusting for comorbid anxiety and depressive disorder, the ADHD group no longer showed higher Harm avoidance than the control group. The difference in Novelty seeking between the patient and control groups was correlated with lifetime diagnosis of antisocial personality disorder (ASPD). **Conclusion:** It is important to take comorbid psychiatric disorders into account while investigating personality traits in ADHD. *(J. of Att. Dis. 2016; 20(10) 845-854)*

**Keywords**

ADD/ADHD, personality, depression, antisocial personality disorder, anxiety

ADHD is a neurodevelopmental disorder characterized by symptoms of hyperactivity, impulsivity, and inattention. According to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; American Psychiatric Association [APA], 2000), ADHD is divided into three subgroups: the predominantly inattentive, the predominantly hyperactive/impulsive, and the combined type (APA, 2000). Adults with ADHD are a heterogeneous group showing high comorbidity with other psychiatric disorders like anxiety disorders, mood disorders, substance use disorders, and personality disorders (Downey, Stelson, Pomerleau, & Giordani, 1997; Kessler et al., 2006).

ADHD has also been associated with specific personality traits. The Temperament and Character Inventory (TCI) by C. R. Cloninger (Cloninger, Svrakic, & Przybeck, 1993) describes a person's temperament and character using seven different dimensions. The four temperament dimensions Harm avoidance, Novelty seeking, Reward dependence, and Persistence are according to Cloninger's model moderately heritable and stable throughout life (Klein et al., 2012). The three character dimensions Self-directedness, Cooperativeness, and Self-transcendence are more influenced by social learning and develop throughout life.

Studies have shown an association between adult ADHD and these dimensions, and adults with ADHD have consistently been found to have high scores on Novelty seeking (Anckarsater et al., 2006; Downey, Pomerleau, & Pomerleau, 1996; Downey et al., 1997; Faraone, Kunwar, Adamson, & Biederman, 2009; Gomez, Woodworth, Waugh, & Corr, 2012; Jacob et al., 2007; Lynn et al., 2005; Sizoo, van den Brink, Gorissen van Eenige, & van der Gaag, 2009; Smalley et al., 2009). This is to be expected, as people with high Novelty seeking tend to be impulsive, quick-tempered, easily bored, and behaving disorderly (Cloninger, Przybeck, Svaric, & Wetzel, 1994), all of which are symptoms common in ADHD. An association between high Harm avoidance and adult ADHD has also been found (Anckarsater et al., 2006; Downey et al., 1996; Downey et al., 1997; Faraone et al., 2009; Gomez et al., 2012; Jacob et al., 2007; Sizoo et al., 2009). Individuals with high Harm avoidance are portrayed to be cautious, careful, nervous, and negativistic (Cloninger et al., 1994). However, Smalley et al. (2009) reported no association of Harm avoidance with ADHD (Smalley et al., 2009). Thus, the findings regarding Harm avoidance and ADHD are less consistent than for Novelty seeking, and also less intuitive, as the characteristics of Harm avoidance are very different from the core symptoms of ADHD.

Furthermore, a few studies have shown an association between adult ADHD and low scores on the dimensions Persistence (Faraone et al., 2009), Reward dependence

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(Anckarsater et al., 2006; Faraone et al., 2009; Gomez et al., 2012; Jacob et al., 2007), Self-directedness (Anckarsater et al., 2006; Gomez et al., 2012; Sizoo et al., 2009; Smalley et al., 2009), and Cooperativeness (Anckarsater et al., 2006; Faraone et al., 2009; Gomez et al., 2012; Sizoo et al., 2009). A high score on Self-transcendence has been shown in adults with ADHD (Faraone et al., 2009; Lynn et al., 2005; Sizoo et al., 2009; Smalley et al., 2009).

However, most previous studies have not controlled for psychiatric comorbidity. Depression and anxiety disorders are associated with high Harm avoidance (Celikel et al., 2009; Cloninger et al., 1994; Cloninger, Zohar, Hirschmann, & Dahan, 2012), and it has been discussed whether the high scores on Harm avoidance in adults with ADHD may be due to the comorbidy with anxiety or depressive disorders (Cho et al., 2008; Downey et al., 1996). According to Downey et al. (1997), ADHD patients with concurrent axis 1 psychopathology had higher scores on Harm avoidance than ADHD patients without such psychopathology. However, Faraone et al. (2009) adjusted for comorbidity and concluded that the group differences they observed were not accounted for by anxiety disorders and depression.

The relationship between the TCI dimensions and the different subtypes of ADHD has also been examined. On a dimensional and symptomatic level, high Harm avoidance has been associated with inattention and high Novelty seeking with hyperactivity/impulsivity (Gomez et al., 2012; Muller et al., 2010; Salgado et al., 2009). Interestingly, in a recent twin study, Novelty seeking was genetically associated with inattention and hyperactivity/impulsivity, and Harm avoidance with inattention symptoms alone (Merwood, Asherson, & Larsson, 2012).

ADHD has been associated with different personality disorders, in particular borderline and antisocial personality disorder (ASPD; Kooij et al., 2012; Sobanski, 2006). However, other Clusters B and C personality disorders like narcissistic and avoidant personality disorders are also reported to be more common in adults with ADHD (Cumyn, French, & Hechtman, 2009; Matthies et al., 2011; Miller et al., 2008). In general, the TCI dimensions low Self-directedness and in particular low Cooperativeness indicate a personality disorder (Richter & Brandstrom, 2009). ASPD has, similarly to ADHD, in some studies been related to high scores of Novelty seeking (Basoglu et al., 2011), high scores of Harm avoidance (Basoglu et al., 2011; Svrakic, Whitehead, Przybeck, & Cloninger, 1993), and low scores of Self-directedness (Basoglu et al., 2011). To our knowledge, the impact of comorbid ASPD on the TCI dimensions in adult ADHD patients has not been studied.

The aims of this study were to examine personality traits using the TCI in adult ADHD patients compared with a control group and to investigate the impact of common comorbid psychiatric disorders on these personality measures. We hypothesized that comorbid anxiety or mood disorder could account for high scores of Harm avoidance and that a high score on Novelty seeking would be related primarily to ADHD.

## Method

### *Sample*

This study is a part of a long-term project at the University of Bergen that includes almost 800 adult ADHD patients (>18 years) who have been diagnosed at outpatient clinics or hospitals in Norway, and a population-derived control group. The recruitment procedure has been described in detail in former publications (Halleland, Lundervold, Halmoy, Haavik, & Johansson, 2009; Halmoy, Fasmer, Gillberg, & Haavik, 2009; Halmoy et al., 2010; Johansson et al., 2008). Our aim was to study a representative sample of ADHD patients as they are naturally encountered in clinical practice. Thus, the patients were not rediagnosed after inclusion and there were no exclusion criteria. All participants completed questionnaires concerning past and current ADHD symptoms, comorbid psychiatric disorders, and substance abuse. There was no specific information regarding ADHD subtype, as the different subtypes are not specifically coded in the diagnostic manual formally used in Norway; the International statistical classification of diseases and related health problems 10th revision (ICD-10; World Health Organization, 2008).

In this study, a subsample of 66 patients and 69 controls living in and nearby Bergen were subjected to further clinical assessments. Most of the controls were randomly selected from the database of the Medical Birth Registry of Norway ($n = 53$), and the remaining were students from the University of Bergen ($n = 13$), friends of the patients ($n = 2$), or recruited through advertisement at the local hospital ($n = 1$). The controls were not screened for ADHD before inclusion. However, after the clinical assessment two controls were excluded because they had symptoms consistent with persistent ADHD.

Comorbidity was assessed with the Mini International Neuropsychiatric Interview Plus (M.I.N.I. Plus) and personality traits by the TCI. The interviews were carried out between 2005 and 2011 by two clinical psychiatrists and two MDs specializing in psychiatry. The interviewers were blinded regarding ADHD diagnosis.

In addition to the psychiatric interview, the participants were also subjected to neuropsychological testing (Halleland, Haavik, & Lundervold, 2012). Neuropsychological data showed that two patients had an IQ below 80. None of the participants had mental retardation, that is, IQ below 70 (Widiger & Costa, 2012).

### Measures

All participants completed a Norwegian version of the Adult ADHD Self-Report Scale (ASRS) as described by Kessler in 2005 (Kessler et al., 2005). The ASRS consists of 18 items where the first nine items address symptoms of inattention and the last nine items symptoms of hyperactivity and impulsivity. Using the *Diagnostic and Statistical Manual of Mental Disorders* (APA, 2000) criteria adapted to adults, it is designed to measure ADHD symptoms during the last 6 months on a 5-point Likert-type item scale (0 = *never/seldom* and 4 = *very often*), giving a maximal score of 72 points. We used the ASRS to define subtypes of ADHD categorically. The inattentive subtype was defined as having a score of 21 or more on the first nine items (Part 1), the hyperactive/impulsive subtype as having a score of 21 or more on the last nine items (Part 2), and the combined subtype having a score of 21 on both parts.

The TCI is a self-administered paper-and-pencil questionnaire. The participants completed a Norwegian translation of the TCI version 9 that includes 240 items with a true–false response format (Cloninger et al., 1994).

The M.I.N.I. Plus (Mini International Neuropsychiatric Interview Plus version 5.0.0; Sheehan et al., 1998) is a structured interview for the major axis 1 psychiatric disorders in *DSM-IV* and ICD-10. It also includes modules for ADHD and ASPD.

The M.I.N.I Plus, the ASRS, and the TCI have not yet been formally validated in Norwegian adults, but are currently being used in clinical practice and research (Bjørnebekk, Westlye, Fjell, Grydeland, & Walhovd, 2012; Halmoy et al., 2009; Westlye, Bjørnebekk, Grydeland, Fjell, & Walhovd, 2011).

### Statistical Analyses

All analyses were carried out with PASW Statistics 18. Participants with 12 or more missing items on the total TCI were excluded from the study. A TCI dimension was omitted from the analysis if one or more items were missing in that dimension. Thus, the number of participants for each dimension varies slightly.

The data were first analyzed using descriptive methods. Independent-sample *t* tests were used for the comparisons of the TCI dimensions between the ADHD and control groups, and Regression Analyses were performed to adjust for comorbid disorders. We reported the difference to be significant at the Bonferroni-corrected level of .002 (i.e., corrected for 21 comparisons).

### Ethics

Written consent was obtained from the participants when joining the study and at the time of the interview. The ADHD study has been approved by the Regional Committee for medical and health research ethics of Western Norway (IRB #3, FWA00009490, IRB00001872).

## Results

### Clinical Characteristics

Three patients and one control were omitted from the analyses due to 12 or more missing items on the 240-item TCI questionnaire. The demographic variables or ASRS scores of the excluded patients did not differ from the rest of the sample (data not shown). In Table 1, demographic and clinical characteristics including comorbid disorders of the included participants are presented. The mean age at the time of the interview was 34.4 ± 9.3 years in the patient group ($n = 63$), compared with 28.3 ± 6.3 years for the controls ($n = 68$). Although the difference in age distribution between the groups was significant, adjusting for age gave no significant change in the primary analyses, and age was therefore not included as a variable for further analyses. There was no significant difference in the sex distribution between the patient and control group (54.0% women in the ADHD group vs. 57.4% in the control group). Thus, gender was also omitted from further analysis. The most common comorbidities among the participants with ADHD were major depressive disorder in the past (74.6%) and lifetime ASPD (40.3%; Table 1).

Of the participants diagnosed with adult ADHD 12.7% had been officially diagnosed with ADHD during childhood and 60% used ADHD medication, of whom 84% used methylphenidate only.

### TCI Measures

As shown in Table 2, the patient group had significant higher scores on Harm avoidance (Figure 1), Novelty seeking (Figure 2), and Self-transcendence, and significant lower scores on Reward dependence, Self-directedness, and Cooperativeness compared with the control group. There was no significant difference in the Persistence dimension between the groups.

The participants with ASPD (25 patients and 1 control) showed as a group significantly higher Novelty seeking and Self-transcendence and lower Cooperativeness compared with participants without ASPD. Participants with anxiety disorders and/or mood disorders (52 patients and 17 controls) had significantly higher Novelty seeking, Harm avoidance and Self-transcendence, and lower Self-directedness.

Significantly higher scores on Novelty seeking and Self-transcendence also correlated with current or past alcohol abuse or dependence, current or past substance dependence and current substance abuse. Persons with current alcohol

**Table 1.** Demographic and Clinical Characteristics of ADHD Patients and Controls.

| | Control group | | ADHD group | |
|---|---|---|---|---|
| | % | *n*/total *n* | % | *n*/total *n* |
| Number (total) | | 68 | | 63 |
| Sex (women) | 57.4 | 39/68 | 54.0 | 34/63 |
| Age (in years) | 28.3[a] | ±6.3[b] | 34.4[a] | ±9.3[b] |
| Major depressive episode, current | 2.9 | 2/68 | 16.1 | 10/62 |
| Major depressive episode, past | 23.5 | 16/68 | 74.6 | 47/63 |
| Anxiety disorder, current[c] | 2.9 | 2/68 | 27.0 | 17/63 |
| Anxiety disorder, past[d] | 10.3 | 7/68 | 31.7 | 19/60 |
| Anxiety disorder and/or depression, lifetime[e] | 25.0 | 17/68 | 82.5 | 52/63 |
| Antisocial personality disorder, lifetime | 1.5 | 1/66 | 40.3 | 25/62 |
| Alcohol abuse or dependence, current | 4.4 | 3/68 | 6.5 | 4/62 |
| Alcohol abuse or dependence, lifetime | 9.1 | 6/66 | 32.8 | 20/61 |
| Nonalcohol substance abuse or dependence, current | 1.5 | 1/68 | 4.8 | 3/62 |
| Nonalcohol substance dependence, lifetime | 3.1 | 4/68 | 32.3 | 20/62 |

[a]Mean.
[b]Standard deviation.
[c]Current panic disorder with or without agoraphobia and current generalized anxiety disorder are merged into one category called "anxiety disorder, current."
[d]Generalized anxiety disorder and panic disorder, with or without agoraphobia, in the past, are merged into one category called "anxiety disorder, past."
[e]Current and/or past anxiety disorder and/or major depressive episode.

**Table 2.** Temperament and Character Inventory Scores (Mean and *t* Tests) for Participants With ADHD, Antisocial Personality Disorder (ASPD), and Anxiety/Depression.[b]

| | ADHD | | | | ASPD[a] | | | | Anxiety/depression[a,b] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control group | | ADHD group | | ASPD÷ | | ASPD+ | | Anxiety/depression÷ | | Anxiety/depression+ | |
| | Score (*SD*) | *n* | Score (*SD*) | *n* | Score (*SD*) | *n* | Score (*SD*) | *n* | Score (*SD*) | *n* | Score (*SD*) | *n* |
| Harm avoidance | 13.7 (5.2) | 66 | 16.9 (8.0)* | 57 | 15.0 (6.6) | 97 | 16.3 (7.9) | 24 | 12.2 (5.1) | 58 | 17.9 (7.1)** | 65 |
| Novelty seeking | 19.3 (6.1) | 65 | 25.3 (6.4)** | 56 | 20.7 (6.1) | 97 | 28.8 (5.9)** | 22 | 19.0 (6.1) | 58 | 24.8 (6.5)** | 63 |
| Reward dependence | 16.9 (3.6) | 61 | 14.1 (3.8)** | 56 | 15.8 (4.0) | 93 | 14.6 (3.5) | 23 | 15.8 (3.7) | 55 | 15.3 (4.1) | 62 |
| Persistence | 4.3 (1.9) | 67 | 4.8 (1.9) | 62 | 4.5 (1.8) | 102 | 4.6 (2.1) | 25 | 4.5 (1.9) | 61 | 4.6 (1.9) | 68 |
| Self-directedness | 34.8 (6.3) | 59 | 26.7 (8.7)** | 53 | 32.1 (7.9) | 90 | 25.5 (9.6)* | 20 | 35.0 (5.5) | 54 | 27.3 (9.2)** | 58 |
| Cooperativeness | 34.0 (4.9) | 61 | 31.6 (5.9)* | 51 | 33.8 (4.6) | 88 | 29.5 (7.4)* | 22 | 33.4 (5.2) | 56 | 32.4 (5.8) | 56 |
| Self-transcendence | 7.7 (5.1) | 65 | 11.9 (6.1)** | 53 | 8.6 (5.6) | 95 | 14.2 (5.5)* | 21 | 7.8 (5.1) | 57 | 11.2 (6.2)* | 61 |

*Note.* *t* tests: ADHD vs. control group, ASPD+ vs. ASPD÷, and anxiety/depression+ vs. anxiety/depression÷. "÷" = not fulfilling diagnostic criteria; "+" = fulfilling diagnostic criteria.
[a]Includes ADHD patients and controls.
[b]Lifetime anxiety disorder (generalized anxiety disorder and panic disorder, with or without agoraphobia) and/or lifetime major depressive disorder.
*$p < .05$. **$p < .0005$.

abuse and dependence reported significantly lower scores on Cooperativeness.

The sample sizes for each of the types of anxiety and depressive disorders were small, making it difficult to compare them with one another. Thus, current and lifetime panic disorder, with or without agoraphobia, generalized anxiety disorder and major depressive disorder were merged into a single category, termed lifetime anxiety and/or depressive disorder. The mean Harm avoidance scores for adults with ADHD and controls were 16.9 ± 8.0 and 13.7 ± 5.2, respectively. When controlling for lifetime anxiety and/or depression, the association between high Harm avoidance and ADHD was no longer significant (Table 3). Thus, the high Harm avoidance score in the ADHD group was explained by the high rate of comorbid anxiety and depressive disorders. The association with low Reward dependence for ADHD remained significant, whereas ADHD was no longer

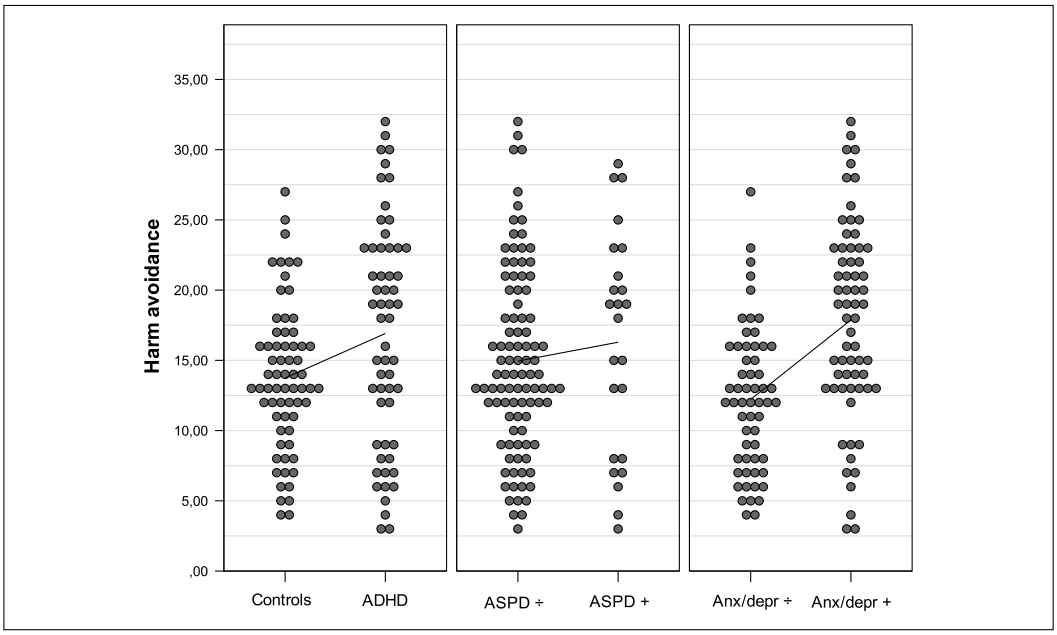


**Figure 1.** Harm avoidance scores for the whole sample of ADHD patients and controls, including grouping by comorbid disorders.
*Note.* The line indicates the mean Harm avoidance scores in the different groups of ADHD and controls, ASPD+, ASPD÷, anx/depr+, and anx/depr÷. ASPD = antisocial personality disorder; "+" = fulfilling diagnostic criteria; "÷" = not fulfilling diagnostic criteria; anx/depr = lifetime anxiety disorder (generalized anxiety disorder and panic disorder, with or without agoraphobia) and/or lifetime major depressive disorder.

associated with high Novelty seeking, high Self-transcendence, low Self-directedness, and low Cooperativeness after controlling for comorbidity. Participants with ASPD showed significantly higher Novelty seeking compared with those without, also when taking comorbidity into account ($p < .001$).

When adjusting for the effect of alcohol and substance use disorders, the results were essentially the same as when controlling for ASPD (results not shown).

We did not have any baseline information regarding ADHD subtype. As referred to in the "Method" section, using the ASRS score we divided the adult ADHD group into three subtypes; inattentive ($n = 13$), hyperactive/impulsive ($n = 2$), and combined ($n = 41$). Due to the small sample size, the hyperactive/impulsive group was omitted from further analysis. Analyses by subtypes did not change the results.

## Discussion

In accordance with previous findings, we found that the ADHD group had significantly higher Novelty seeking and Harm avoidance compared with the control group (Anckarsater et al., 2006; Downey et al., 1996; Downey et al., 1997; Faraone et al., 2009; Gomez et al., 2012; Jacob et al., 2007; Lynn et al., 2005; Sizoo et al., 2009; Smalley et al., 2009; Svrakic et al., 1993). However, when adjusting for lifetime anxiety and/or depressive disorder, the difference in Harm avoidance was no longer significant. The difference in Novelty seeking was correlated with ASPD and lifetime anxiety/depression, with ASPD having the greatest impact. The adult ADHD group was still associated to low scores in Self-directedness adjusting for these comorbid conditions.

People with high scores on Harm avoidance tend to be fearful, nervous, tense, and negativistic, traits that are closely related to anxiety and depression. In our study, 16.1% of the adults with ADHD filled the criteria for current major depressive disorder and 27% for current anxiety disorder, as opposed to 2.9% for both disorders, respectively, in the control group. Ongoing depression has shown to correlate to some extent with high scores on Harm avoidance (Joffe, Bagby, Levitt, Regan, & Parker, 1993; Nery et al., 2009; Svrakic, Przybeck, & Cloninger, 1992), and Cloninger has suggested that current level of the participants' mood and anxiety should be taken into account when interpreting TCI results (Cloninger et al., 1994). When restricting our analyses to current major depression only, the mean Harm avoidance score increased from $17.9 \pm 7.1$ to $22.1 \pm 6.6$, but did not change the main results.

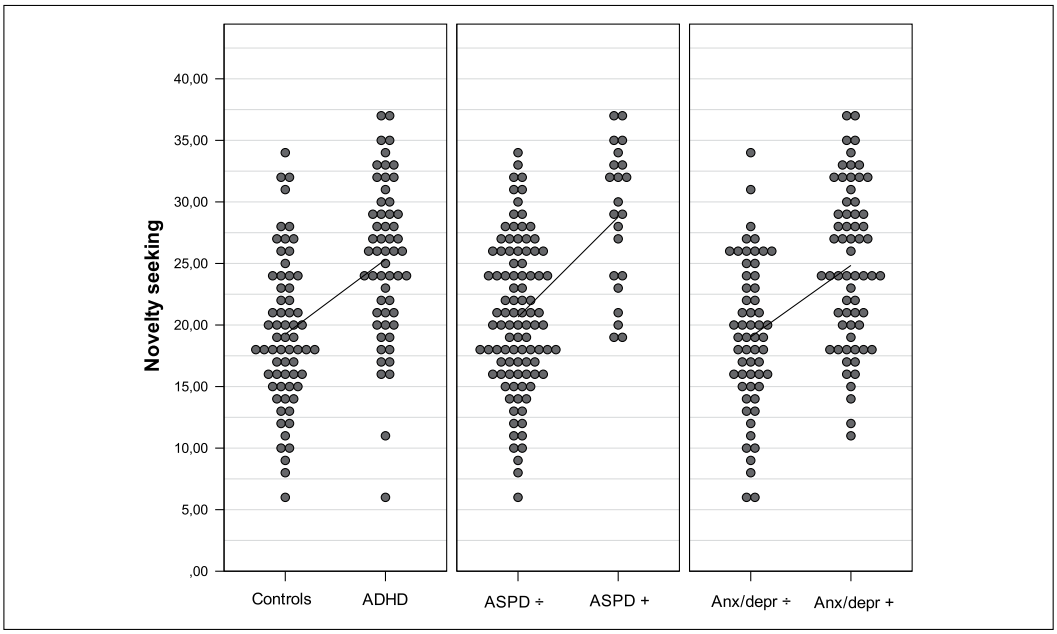


**Figure 2.** Novelty seeking scores for the whole sample of ADHD patients and controls, including grouping by comorbid disorders.
*Note.* The line indicates the mean Novelty seeking scores in the different groups of ADHD and controls, ASPD+, ASPD÷, anx/depr+, and anx/depr÷. ASPD = antisocial personality disorder; "+" = fulfilling diagnostic criteria; "÷" = Not fulfilling diagnostic criteria; anx/depr = lifetime anxiety disorder (generalized anxiety disorder and panic disorder, with or without agoraphobia) and/or lifetime major depressive disorder.

**Table 3.** Correlation Between TCI Scores and ADHD, ASPD, and Anxiety/Depression (Results From Linear Regression Analyses[a]).

| | ADHD | | | ASPD[b,c] | | | Anxiety/depression[c,d] | | |
|---|---|---|---|---|---|---|---|---|---|
| | *B* | 95% CI | *p* | *B* | 95% CI | *p* | *B* | 95% CI | *p* |
| Harm avoidance | 0.40 | [−2.6, 3.4] | .794 | −1.47 | [−4.7,1.8] | .374 | 5.96 | [3.2, 8.7] | <.001*** |
| Novelty seeking | 2.18 | [−0.5, 4.9] | .112 | 5.58 | [2.5, 8.6] | <.001*** | 2.93 | [0.4, 5.4] | .022 |
| Reward dependence | −3.78 | [−5.5, −2.0] | <.001*** | 0.37 | [−1.5, 2.3] | .698 | 1.67 | [0.1, 3.3] | .041 |
| Persistence | 0.67 | [−0.2, 1.5] | .128 | −0.23 | [−1.2, 0.7] | .634 | −0.29 | [−1.1, 0.5] | .479 |
| Self-directedness | −5.20 | [−8.7, −1.7] | .004 | −1.71 | [−5.7, 2.3] | .403 | −4.67 | [−8.0, −1.4] | .006 |
| Cooperativeness | −1.41 | [−4.1, 1.3] | .308 | −3.74 | [−6.6, −0.8] | .012 | 0.75 | [−1.7, 3.2] | .548 |
| Self-transcendence | 2.10 | [−0.6, 4.8] | .126 | 3.83 | [0.9, 6.8] | .012 | 1.26 | [−1.2, 3.8] | .317 |

[a]The model includes ADHD, antisocial personality disorder, and anxiety/depression as independent variables with a Bonferroni-corrected level of significance $p < .002$.
[b]ASPD = lifetime antisocial personality disorder.
[c]Includes ADHD patients and controls.
[d]Lifetime anxiety disorder (generalized anxiety disorder and panic disorder, with or without agoraphobia) and/or lifetime major depressive disorder.
***$p < .002$.

Most of our patients used medication for ADHD, and one could question if, and how, medical treatment could potentially influence TCI scores. The cross-sectional nature and relatively small sample sizes of subgroups in our study did however not permit any informative analyses on this subject. To our knowledge, no studies have so far investigated how TCI scores may be influenced by ADHD medication.

Due to the high comorbidity it is important to adjust for common comorbid psychiatric disorders when assessing personality traits. We found that lifetime anxiety and/or depression actually accounted for the differences in Harm

avoidance between the adults with ADHD and the control group. A few other studies have investigated the possible impact of comorbidity on these personality traits in adult ADHD. Our results are in line with Downey et al. (1997), who found that ADHD patients with concurrent axis 1 psychopathology had higher scores on Harm avoidance than ADHD patients without. However, Faraone et al. (2009) did not find that comorbid anxiety and depressive disorders accounted for the high Harm avoidance in adult ADHD. This may be due to differences in the sample size, selection of the participants, or different comorbidity profile.

Novelty seeking includes items like "It is difficult for me to keep the same interests for a long time because my attention often shifts to something else," "I lose my temper more quickly than most people," and "I often follow my instincts, hunches, or intuition without thinking through all the details." Such items describe clinical features of ADHD, like impulsivity and quick-temperedness, and also seem related to ASPD. Our results showed a close connection between ASPD and Novelty seeking. Somewhat unexpected, Novelty seeking was more closely connected to anxiety/depression than to ADHD alone, in an adjusted regression model. There may be several explanations to this finding. First, a great majority of the ADHD patients have a history of comorbid anxiety and depression, and ADHD without such comorbidity might not be representative for a clinical adult ADHD population. Second, although comorbid anxiety and depression often co-occur, the two kinds of disorders may be differentially related to Novelty seeking. In particular, ADHD with comorbid depression may be part of bipolar spectrum disorders or borderline personality disorder, which have been associated with high Novelty seeking (Fassino et al., 2009; Young et al., 1995). Harm avoidance may, however, be more connected with anxiety disorders and related depressive symptoms (Nery et al., 2008). Due to small subsamples, we were not able to disentangle between the different disorders, but these differential relations could be addressed in larger studies.

According to Cloninger's model, ASPD is characterized by low Harm avoidance, high Novelty seeking, and low Reward dependence (Cloninger et al., 1994; Svrakic et al., 1993). When adjusting for comorbidity, we found that the ASPD group showed a low score of Cooperativeness. Low score on Cooperativeness is considered to be an important indicator of a personality disorder (Richter & Brandstrom, 2009), and individuals low on Cooperativeness are characterized as revengeful, intolerant, self-absorbed and primarily looking out for themselves (Cloninger et al., 1994). Such features are consistent with one of the core traits in ASPD: "lack of remorse, as indicated being indifferent to or rationalizing having hurt, mistreated, or stolen from another" (APA, 2000, p. 292). Although ASPD and ADHD have some symptoms in common, these conditions seem to be correlated with different TCI profiles theoretically and empirically.

A person who has low scores on Reward dependence can be described as practical, independent, and unresponsive to social pressure, and an individual who has low scores on Self-directedness is often characterized as irresponsible, unreliable, blaming, and weak-willed (Cloninger et al., 1994). Reward dependence and Self-directedness were lower in the ADHD group compared with the control group, although only the difference in Reward dependence was statistically significant (corrected $p < .002$). This is consistent with earlier findings, and suggests that low Reward dependence and low Self-directedness tap personality traits common in adult ADHD. However, the score on Reward dependence and Self-directedness in the ASPD group did not differ significantly from the control group. According to Cloninger's model and from the existing previous studies, Reward dependence and Self-directedness were expected to show significantly lower scores in the ASPD group as well (Basoglu et al., 2011; Cloninger et al., 1994; Svrakic et al., 1993).

The correlation between ASPD, alcohol and substance use, is well known (De Fruyt et al., 2006; Kessler et al., 2006). In our study, the effects of alcohol and substance use disorders on the TCI dimensions were closely related to ASPD.

In our sample, 40.3% in the adult ADHD group had comorbid lifetime ASPD. This is higher than in other studies, which show prevalences of 12% to 16% (Downey et al., 1997; Klein et al., 2012). We used the M.I.N.I Plus to assess for comorbidity. The M.I.N.I Plus covers only one personality disorder, and the interview mainly focuses on antisocial behavior rather than personality traits, which are a part of the ASPD diagnosis. This might explain the high rate of ASPD found in our adult ADHD group, and why the personality traits for ASPD in this study differ from other findings. In clinical practice more information about the patient would normally be collected before a diagnosis of personality disorder is to be given. Ideally, it would have been of interest to have the possibility to adjust for other personality disorders than ASPD, for instance to adjust for cluster C personality disorders in Harm avoidance.

ASRS scores were used to classify the adult ADHD group into subgroups, and it can be discussed how suitable the ASRS is for this purpose. In contrast to previous studies, our results showed no significant differences in TCI scores between the ADHD subtypes.

The patients included had previously been diagnosed with adult ADHD in clinical practice and were not diagnosed again at the time of interview. We wanted to assess a representative sample of adults with ADHD. Due to this naturalistic study design, our sample might be more heterogeneous compared with samples in other studies. Although a diagnosis of ADHD in adults requires the presence of symptoms and behavior of ADHD from childhood, only 12.7% of our adult patients had been formally diagnosed with ADHD as children. This may reflect the low

awareness and diagnostic rate of ADHD in Norway at the time when these adults grew up. There were no significant differences in the TCI dimensions between those previously diagnosed in childhood and the other patients, except for Self-transcendence, which was higher in the group only diagnosed as adults (data not shown).

Personality traits can be described in different ways, and one widely used model is the Five-Factor Model of personality (De Fruyt, Mervielde, Hoekstra, & Rolland, 2000). The NEO Personality Inventory–Revised (NEO PI-R) is frequently used to assess personality according to this model (Glover, Crego, & Widiger, 2012). NEO PI-R includes five different domains: Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness. Individuals with high Neuroticism are described as fearful, anxious, depressed, helpless, and unable to resist impulses (De Fruyt et al., 2000). ADHD has been associated with high Neuroticism (Di Nicola et al., 2014), and it has been discussed whether there is a link between symptoms of inattention and anxiety/depression (Widiger, Lynam, Miller, & Oltmanns, 2012). This would be in line with our results, as Harm avoidance has been positively correlated with Neuroticism (Nigg et al., 2002).

Some of the heterogeneity in ADHD can be explained by associated personality traits and comorbidity profile. The high level of anxiety and depressive disorders among adults with ADHD may indicate that ADHD with comorbid anxiety/depression makes up an important subgroup of ADHD. Our findings show the importance of taking comorbidity into account when examining personality traits in ADHD. Studies exploring the biological underpinnings of these personality dimensions could expand our understanding of the complex relation between temperament, character, and disorder (Tuominen et al., 2013). Longitudinal studies are needed to explore the direction of these associations, that is, do certain personality traits precede the development of depression or antisocial behavior, or is the personality profile we measure in adults a result of lifelong comorbidity? In clinical practice, comorbidity profile and personality traits are important factors to improve the understanding of each ADHD patient, and to optimize the treatment for the individual patient.

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## Declaration of Conflicting Interests

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# II

Archival Report

Biological Psychiatry

# Attention-Deficit/Hyperactivity Disorder in Offspring of Mothers With Inflammatory and Immune System Diseases

Johanne T. Instanes, Anne Halmøy, Anders Engeland, Jan Haavik, Kari Furu, and Kari Klungsøyr

## ABSTRACT

**BACKGROUND:** Prenatal inflammatory mechanisms may play a role in the pathogenesis of psychiatric disorders and could be relevant for attention-deficit/hyperactivity disorder (ADHD). We investigated maternal chronic somatic diseases with immune components as possible risk factors for ADHD in offspring.

**METHODS:** We performed a population-based nested case-control study by linking data from longitudinal Norwegian registers. We included all individuals born during the period 1967–2008 and alive at record linkage (2012). Individuals receiving ADHD medication during the years 2004–2012 were defined as patients with ADHD ($N$ = 47,944), and all remaining individuals ($N$ = 2,274,713) were defined as control subjects. The associations between maternal diseases and ADHD in offspring were analyzed using logistic regression models.

**RESULTS:** The following chronic diseases with immune components were related to ADHD in offspring: multiple sclerosis (adjusted odds ratio [OR] = 1.8; 95% confidence interval [CI] = 1.2–2.5), rheumatoid arthritis (adjusted OR = 1.7; 95% CI = 1.5–1.9), type 1 diabetes (adjusted OR = 1.6; 95% CI = 1.3–2.0), asthma (adjusted OR = 1.5; 95% CI = 1.4–1.6), and hypothyroidism (adjusted OR = 1.2; 95% CI = 1.1–1.4). In contrast, chronic hypertension and type 2 diabetes showed no significant associations. Estimates were almost unchanged with additional adjustment for parental ADHD, infant birth weight, and gestational age. Although point estimates for male and female offspring were different for some diseases (e.g., maternal asthma [adjusted OR = 1.7; 95% CI = 1.5–1.8 for female offspring and adjusted OR = 1.5; 95% CI = 1.4–1.6 for male offspring]), none of the associations differed significantly by offspring sex.

**CONCLUSIONS:** Several maternal somatic diseases with immune components were found to increase the risk of ADHD in offspring. The associations could involve several causal pathways, including common genetic predisposition and environmental factors, and increased insight into the mechanisms behind these relationships could enhance our understanding of the etiology of ADHD.

*Keywords:* ADHD, Attention-deficit/hyperactivity disorder, Immune disease, Inflammatory disease, Maternal effects, Risk factors

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects children and adults worldwide, with prevalence estimates ~5% in children (1) and 3% in adults (2). The prevalence varies among studies; in a Norwegian study of children 8–10 years old, it was estimated to be 1.7% (3). The disorder is two to three times more frequent in boys than girls (4), although the sex distribution becomes more equal with age (5). The etiology of ADHD is complex, involving interactions between genetic and environmental factors, and many risk pathways may lead to its clinical features (6).

Previous studies described several prenatal and perinatal risk factors for ADHD. Low birth weight (7–12), preterm birth (8,9,13–16), and small size for gestational age (8,16) have consistently been related to an increased risk of ADHD or ADHD symptoms. Exposure to maternal smoking (17) and other substances in utero (6) also have been reported to be associated with increased risk of ADHD. Furthermore, associations with ADHD in offspring have been found for some maternal medical conditions, including obesity (18) and epilepsy (8). It has been hypothesized that ADHD may be caused by an exaggerated central nervous system inflammatory response in the fetus caused by maternal inflammation, such as in allergy or autoimmune disease (19). It is difficult to draw conclusions about causal pathways, as associations between maternal diseases and ADHD in offspring can involve several different, partly overlapping, causal pathways. Common genetic predisposition, environmental factors such as maternal medication exposures, and fetal inflammatory response are examples of such causes. Because few studies have





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evaluated maternal immune system diseases, we investigated whether such diseases were associated with ADHD in offspring using data from nationwide registers in Norway. Additionally, we assessed whether these risk factors differed by patient's sex.

## METHODS AND MATERIALS

This study was approved by the Norwegian Data Protection Authority, the Norwegian Directorate of Health, and the Regional Committee for Medical and Health Research Ethics (2011/2272). The data were treated anonymously, and so no further consent was required.

We performed a population-based nested case-control study by linking information from the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Database (NorPD), and the National Educational Database. In a sensitivity analysis, we also included data from the Norwegian Patient Registry.

The nationwide MBRN was established in 1967 and contains information on nearly 2.6 million births up to 2012. The registration is based on compulsory notification and includes information on all live births and fetal losses/stillbirths from 16 weeks of gestation. A standardized form is used to document information on maternal health before and during pregnancy, complications during pregnancy and delivery, and birth outcomes. For the years 1967–1998, information was mainly documented as free text specifications to items such as "Maternal health before pregnancy," "Maternal health during pregnancy," "Complications in relation to birth," and "Infant outcomes." A more detailed documentation form, introduced in 1999, included information on maternal smoking habits and check boxes for specific conditions in addition to free text (20). The NorPD covers all prescribed drugs dispensed to individuals in Norway since 2004. From 2008, NorPD includes diagnostic codes (ICD-10/International Classification of Primary Care, Second edition) for reimbursed drugs (21). The level of education of all Norwegian inhabitants from 16 years of age is registered annually in the National Education Database. The Norwegian Patient Registry provides information on diagnoses of all patients having contact with specialist health services from 2008.

### Study Population and Variable Information

Record linkage was established by using the personal identity number unique to every Norwegian resident. This study included all individuals born from 22 weeks of gestation or with birth weight at least 500 g in Norway during the period 1967–2008 who were still alive at record linkage in 2012 ($N$ = 2,322,657).

Cases in this study consisted of all registered individuals in MBRN born during the period 1967–2008 who had been prescribed and dispensed ADHD medications during the years 2004–2012 and were >3 years old at last prescription.

The dispensed and reimbursed ADHD medications methylphenidate (Anatomical Therapeutic Chemical Classification System [ATC] code N06BA04), atomoxetine (ATC code N06BA09), and racemic amphetamine (ATC code N06BA01) were extracted from the NorPD. The use of ADHD medication is restricted in Norway; medical treatment of ADHD is initiated only after thorough assessment of the patient by a specialist in psychiatry or child psychiatry. Dexamphetamine (ATC code N06BA02) was off label in Norway during the study period and is not used as a first-option treatment and therefore was not included in our case definition. Drugs used to treat ADHD may also be used for narcolepsy. Using the reimbursement codes from 2008, we found that 117 individuals (1.4%) were dispensed stimulant medication with the indication narcolepsy, and these were excluded from the case group. Thus, for patients who were dispensed medicine in the period 2004–2008 only, there may be a small number of individuals with narcolepsy left in the case group.

The control group included all registered individuals in MBRN born during the period 1967–2008 and alive at record linkage who had not been dispensed ADHD medication during the period 2004–2012. The 117 individuals who were dispensed stimulant drugs for narcolepsy in the period 2008–2012 were included in the control population ($N$ = 2,274,713). Thus, by design, the control group included people with a diagnosis of ADHD who did not receive ADHD medication or who had used (and stopped using) ADHD medication before 2004 when the NorPD was established.

Maternal educational level was used as a measure for socioeconomic level and grouped in three categories: low (<10 years), medium (10–12 years), and high (>12 years).

### Description of Variables

As potential prenatal risk factors for ADHD, we studied the following maternal chronic somatic diseases, all with inflammatory or immune components of pathologic relevance: multiple sclerosis, asthma, rheumatoid arthritis, hypothyroidism, hyperthyroidism, and pregestational type 1 diabetes. Pregestational type 2 diabetes and chronic hypertension were also included. Because we assumed that immunologic/inflammatory mechanisms are less strongly involved in these conditions, they were included to serve as contrasting chronic diseases in the analyses. We chose the diseases included in the analyses using several criteria. Our focus was immune system diseases, and we selected diseases for which the MBRN registration was previously validated (pregestational type 1 and 2 diabetes, rheumatic arthritis, asthma) (20,22), diseases that were previously described in the literature with data from MBRN (multiple sclerosis) (23–25), diseases for which the MBRN notification form from 1999 had specific check boxes (asthma, diabetes type 1 and 2, rheumatic arthritis and chronic hypertension), and diseases for which the MBRN reported significantly increasing time trends in prevalence and for which associations with ADHD in offspring was previously discussed (thyroid disorders) (26–29). The maternal diseases were diagnosed before or during pregnancy for the target individual. Pregestational diabetes, without subtyping, has been registered in the MBRN from 1967 and specified as type 1 and type 2 since 1988 ($n$ = 32,984 cases, $n$ = 1,113,011 controls).

### Statistical Analyses

Analyses were performed with PASW Statistics 18 (SPSS Hong Kong, Quarry Bay, Hong Kong) and Stata version 13

**Table 1. Sociodemographic Characteristics of Patients With ADHD and Control Subjects in Norway, 1967–2012**

| | ADHD Patients ($N$ = 47,944), $n$ (%) | Control Subjects ($N$ = 2,274,713), $n$ (%) |
|---|---|---|
| Male Sex | 31,514 (65.7) | 1,158,422 (50.9) |
| Year of Birth | | |
| 1967–1978 | 6517 (13.6) | 675,929 (29.7) |
| 1979–1988 | 8443 (17.6) | 485,773 (21.4) |
| 1989–1998 | 23,501 (49.0) | 556,250 (24.5) |
| 1999–2008 | 9483 (19.8) | 556,761 (24.5) |
| Marital Status of Mother | ($n$ = 47,314) | ($n$ = 2,246,177) |
| Single | 7588 (16.0) | 187,218 (8.3) |
| Married/cohabiting/partnership | 38,535 (81.5) | 2,028,282 (90.3) |
| Divorced/separated/widowed | 850 (1.8) | 19,479 (.9) |
| Other/unknown | 341 (.7) | 11,198 (.5) |
| Parity | ($n$ = 47,314) | ($n$ = 2,246,177) |
| Para 0 | 21,015 (44.4) | 925,190 (41.2) |
| Para 1 | 15,886 (33.6) | 784,852 (34.9) |
| Para 2+ | 10,413 (22.0) | 536,135 (23.9) |
| Maternal Age (Years) | ($n$ = 47,314) | ($n$ = 2,246,176) |
| <20 | 4367 (9.2) | 127,279 (5.7) |
| 20–34 | 39,150 (82.8) | 1,882,572 (83.8) |
| ≥35 | 3797 (8.0) | 236,325 (10.5) |
| Paternal Age (Years) | ($n$ = 46,689) | ($n$ = 2,230,886) |
| <20 | 1149 (2.5) | 28,334 (1.3) |
| 20–39 | 42,398 (90.8) | 2,025,111 (90.8) |
| ≥40 | 3142 (6.7) | 177,441 (8.0) |
| Educational Level (Mother)[a] | ($n$ = 46,995) | ($n$ = 2,228,246) |
| Low | 15,528 (33.0) | 529,358 (23.8) |
| Medium | 20,028 (42.6) | 970,395 (43.6) |
| High | 11,439 (24.3) | 728,493 (32.7) |

ADHD, attention-deficit/hyperactivity disorder.
[a]Maternal educational level: high (>12 years of education), medium (10–12 years of education) and low (≤9 years of education).

(StataCorp LP, College Station, Texas). Data were analyzed using descriptive statistics with $\chi^2$ tests, and we calculated relative risks and crude odds ratios (ORs) for categorical variables. We used logistic regression analyses to calculate ORs adjusting for the following factors: maternal age at delivery, parity, time period of birth (5-year categories), maternal marital status, and maternal educational level. All factors were modeled as categorical variables as specified in the footnotes in Tables 1 and 2 and Table S1 in Supplement 1. We further included one model adding maternal and paternal use of ADHD medication from NorPD (2004–2012) as adjustment variables. This information was used as a proxy for maternal and paternal ADHD. In a final model, we included all the studied maternal diseases in addition to infant birth weight and gestational age. We also included maternal smoking in a subanalysis for individuals born after 1998, when smoking information was available. We stratified analyses by sex and compared associations between male and female offspring. Crude and adjusted ORs were reported with 95% confidence intervals (CIs). We also analyzed mothers with more than one birth by calculating OR with robust standard errors using the mother as the cluster variable.

## RESULTS

### Sociodemographic Characteristics

Overall, there was a larger male proportion in the ADHD group (65.7%) (Table 1) compared with the control group (50.9%). Mothers of offspring with ADHD were younger, were more often single, and had lower educational level compared with mothers of control subjects. Similarly, fathers of offspring with ADHD were younger and had lower education compared with fathers of control subjects (data not shown).

### Association Between Maternal Somatic Diseases and ADHD in Offspring

We found higher frequencies of several immune system diseases among mothers of offspring with ADHD compared with mothers of control subjects (Table 2), with significantly higher overall odds for maternal multiple sclerosis, rheumatoid arthritis, type 1 diabetes, asthma, and hypothyroidism. Maternal chronic hypertension, type 2 diabetes, and hyperthyroidism were not associated with ADHD in offspring.

The associations between maternal immune-related disease and ADHD in offspring did not depend on offspring sex. Figure 1 shows that although the point estimates for the maternal disease–offspring ADHD associations to some extent differ between male and female offspring, CIs overlap. However, for maternal asthma, where the point estimate for ADHD in female offspring was 1.7 and for male offspring was 1.5, the CIs around the estimates overlapped only slightly (95% CI = 1.5–1.8 for female offspring and 95% CI = 1.4–1.6 for male offspring). Furthermore, for maternal multiple sclerosis and ADHD in offspring, where the point estimates were 2.2 for female offspring and 1.6 for male offspring, the CIs were broad, and we may have lacked power to detect a possible true sex difference.

We repeated all analyses with data from 1999 to adjust for maternal smoking habits. The results were not altered noticeably. For example, adjusted OR between maternal asthma and ADHD in offspring was 1.5 (95% CI = 1.4–1.6), and when also adjusting for smoking, OR was 1.7 (95% CI = 1.5–2.0) for female offspring and 1.4 (95% CI = 1.3–1.6) for male offspring.

Although we set the level of significance at $p < .05$, all the above-listed significant results had $p$ values $< .01$. The associations with maternal asthma, rheumatoid arthritis, and type 1 diabetes had $p$ values $< .0001$ (Table S1 in Supplement 1).

### Sensitivity Analyses

Because we defined our ADHD cases only on the basis of dispensed ADHD medication, it may be that our cases represent a special subgroup of patients. For the period 2008–2012, we also had available data from the Norwegian Patient Registry. Of the 12,223 individuals registered with an ADHD diagnosis in the Norwegian Patient Registry, only 2040 (17%) individuals did not receive ADHD drugs. Adding these

**Table 2. Maternal Chronic Diseases and ADHD in Offspring: Results From Unadjusted and Different Logistic Regression Models**

| | ADHD Group ($N$ = 47,944), $n$ (%) | Control Group ($N$ = 2,274,713), $n$ (%) | Unadjusted OR (95% CI) | Adjusted OR (95% CI)[a] | Adjusted OR Model Including Maternal and Paternal ADHD[b] | Expanded Model Adjusted OR (95% CI)[c] |
|---|---|---|---|---|---|---|
| Asthma | 1857 (3.9) | 47519 (2.1) | 1.9 (1.8–2.0) | 1.5 (1.4–1.6) | 1.5 (1.4–1.5) | 1.5 (1.5–1.6) |
| Rheumatoid Arthritis | 250 (.5) | 5813 (.3) | 2.0 (1.8–2.3) | 1.7 (1.5–1.9) | 1.7 (1.5–1.9) | 1.6 (1.4–1.9) |
| Hypothyroidism | 235 (.5) | 11,625 (.5) | 1.0 (.8–1.1) | 1.2 (1.1–1.4) | 1.2 (1.0–1.3) | 1.2 (1.0–1.4) |
| Hyperthyroidism | 68 (.1) | 3070 (.1) | 1.1 (.8–1.3) | 1.2 (.9–1.5) | 1.1 (.9–1.4) | 1.2 (.9–1.5) |
| Type 1 Diabetes[d] | 88 (.3) | 2825 (.3) | 1.1 (.9–1.3) | 1.6 (1.3–2.0) | 1.7 (1.3–2.1) | 1.5 (1.2–1.9)[e] |
| Type 2 Diabetes[d] | 19 (.1) | 1135 (.1) | .6 (.4–.9) | 1.1 (.7–1.8) | 1.2 (.7–1.9) | 1.1 (.7–1.8)[e] |
| Multiple Sclerosis | 31 (.1) | 880 (0) | 1.7 (1.2–2.4) | 1.8 (1.2.–2.5) | 1.8 (1.3–2.6) | 1.8 (1.2–2.6) |
| Hypertension, Chronic | 155 (.3) | 6496 (.3) | 1.1 (1.0–1.3) | 1.1 (.9–1.3) | 1.1 (.9–1.3) | 1.1 (.9–1.2) |

ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio.

[a]Adjusted by year of birth (5-year interval 1967–2008), parity (para 0, para 1, para 2+), mother's age at birth (<20, 20–24, 25–29, 30–34, 35–39, >39 years), mother's educational level (low/medium/high), mother's marital status (married/cohabiting/partnership, single, divorced/separated/widowed, other/unknown).

[b]Adjusted by the same covariates listed in *a* adding maternal and paternal use of ADHD medication.

[c]Model including all risk diseases as covariates listed in *a* in addition to birth weight (5 categories [<1500, 1500–1999, 2000–2499, 2500–4499, ≥4500 kg]) and gestational age (5 categories [22–31 weeks, 32–36 weeks, 37–41 weeks, ≥42 weeks]).

[d]Data from 1989 and later.

[e]All variables, including risk diseases, selected from 1989 and later when analyzing diabetes.

2040 individuals to our case population did not change any results (data not shown).

We also ran several additional models. In one model, we included maternal and paternal use of ADHD medication as possible confounding variables. Overall, the associations were unchanged or only slightly weakened (Table 2). We also looked at overall offspring ADHD including all risk diseases as covariates, with additional adjustment for gestational age and infant birth weight. None of the estimates changed much (Table 2). Results also did not change much when calculating ORs with robust standard errors and the mother as cluster variable (data not shown).

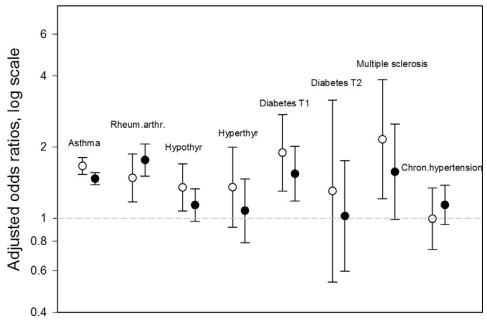


**Figure 1.** Associations (adjusted odds ratios with 95% confidence intervals) between maternal diseases and attention-deficit/hyperactivity disorder (ADHD) in offspring by sex in Norway, 1967–2012. Female patients with ADHD (white circles); male patients with ADHD (black circles).

As shown in Table 2, the OR for type 1 diabetes increased from 1.1 (95% CI = .9–1.3) in the unadjusted model to 1.6 (95% CI = 1.3–2.0) in the adjusted model. To explore this association further, we performed an additional analysis using data after 1998, when a precoded checkbox for type 1 diabetes was introduced in the MBRN registration form. In this analysis, the unadjusted OR (1.5; 95% CI = 1.2–2.0) was similar to the adjusted OR (1.6; 95% CI = 1.2–2.0). Thus, we consider that the low OR for type 1 diabetes association in the early time period may be an artifact caused by insufficient data collection.

## DISCUSSION

This large nationwide register-based study with prospective data showed that several chronic maternal diseases with immune components, including multiple sclerosis, rheumatoid arthritis, asthma, hypothyroidism, and type 1 diabetes were associated with ADHD in offspring. Maternal multiple sclerosis and rheumatoid arthritis were associated with 80% and 70% higher odds of ADHD in offspring, respectively, and maternal asthma was associated with 50% higher odds, independent of maternal smoking. There were no statistically significant sex differences, although we may have lacked power to detect possible true sex differences for some maternal diseases.

This study has several strengths. It is large and includes the entire Norwegian population over a period of 45 years. The genetic homogeneity of the Norwegian population is an advantage when studying other biological risk factors as well as external risk factors. The unique Norwegian personal identity number ensured a valid linkage between the registers involved. The data were prospectively collected with

compulsory notification, minimizing selection and follow-up bias. On one hand, by using the nationwide prescription database to define the case population, thus including only patients who were medicated with reimbursement as cases, we ensured that cases had a valid diagnosis of ADHD. On the other hand, the ADHD cases in this study probably represent the most severely affected patients, as medical treatment is indicated only when substantial loss of function is present. The diagnostic classification system used in Norway is ICD-10. We use data from NorPD during 2004-2012 to define our cases. According to national guidelines published during these years, ADHD should be diagnosed according to ICD-10 criteria, although allowing the inattentive subtype in DSM-IV as sufficient for the diagnosis. Other psychiatric disorders may also be present, as long as the ADHD criteria are fulfilled before the comorbid disorder appears. As some clinicians may have used the more restricted ICD-10 criteria, persons with the inattentive subtype may be underrepresented in our case group. Thus, our results may be most valid for more severe cases of ADHD and the combined subgroup. Moreover, in the Norwegian population, the indications for starting ADHD medication for treating ADHD symptoms could vary slightly from other populations, which may limit to a certain degree the generalizability of our results. Still, our sensitivity analysis showed that only 17% of registered patients during the period 2008–2012 did not receive ADHD medication. Some people included in the control group could have used medication for ADHD before 2004 when NorPD was established; however, this would tend to weaken the associations. Because our control group is very large, the few false-negative ADHD cases should not represent an important source of bias.

We report a robust association between ADHD in offspring and maternal disorders with underlying immune factors, including multiple sclerosis, rheumatoid arthritis, asthma, hypothyroidism, and type 1 diabetes. It has been suggested that maternal diseases with immune components, such as infections, allergy, and autoimmune disease, may cause an exaggerated central nervous system inflammatory response in the fetus (19). Subsequently, this exaggerated inflammatory response could harm the developing brain. Inflammatory mechanisms are believed to play a role in the pathogenesis of psychiatric disorders such as schizophrenia (30) and autism (31), and similar mechanisms may be relevant for the development of ADHD. Altered fetal neurodevelopment has been associated with diverse maternal infections during pregnancy, suggesting the maternal immune response in itself can alter fetal brain development, as shown in a primate model (32).

Ghassabian *et al.* (27) reported that children of mothers with elevated levels of maternal thyroid peroxidase antibodies had more ADHD symptoms. These antibodies could play a part both in the development of autoimmune thyroid disease leading to maternal hypothyroidism and in the fetal neuronal development leading to ADHD.

Patients with ADHD have an increased risk of asthma, the association being highest in female patients (33). However, the present study is the first to show an association between maternal asthma and ADHD in offspring. It was unchanged when adjusting for parental ADHD medication as well as with additional adjustment for maternal smoking and could support shared etiological pathways to ADHD and asthma.

We did not find associations between maternal chronic hypertension or type 2 diabetes and ADHD in offspring. Although it has been proposed that inflammation also may contribute to these disorders (34,35), these chronic conditions are less clearly related to immune system components compared with rheumatoid arthritis and multiple sclerosis, in which the immunopathology is well defined; this indicates that maternal immunological factors could play a role in the pathogenesis of ADHD in offspring.

We controlled for many potential and known confounders. Information on maternal smoking was available only from 1999. However, results using data from 1999 with additional adjustment for smoking were in agreement with the main results. Including maternal and paternal use of ADHD medication in the regression model weakened some of the associations slightly, but they were still in line with the main results.

This study has several limitations. The diagnostic validity of reported diagnosis in the MBRN has not been formally studied for all the studied diseases. The sensitivity of reported rheumatoid arthritis (22) and type 1 diabetes (20) in MBRN is high, estimated to be 88% for rheumatoid arthritis and 90% for type 1 diabetes. For severe asthma, the sensitivity is lower (73%) (20). However, potentially missed maternal cases would most likely attenuate the associations.

The observational design of the study does not allow for definite causal inference. The observed associations could be explained by unmeasured environmental confounding, such as maternal medication use during pregnancy, unmeasured genetic confounding, or an inflammatory response in the fetus; furthermore, these pathways could overlap.

It is known that ADHD is a partially genetic disorder; the heritability has been estimated to .7–.9 (36,37). Environmental factors and the interplay between genetic and environmental factors are also important (38). Analyses of genome-wide genetic markers demonstrated genetic correlations between many traits as well as between somatic and psychiatric disorders (39). Shared genetic susceptibilities could explain some of our findings. For example, the *SLC9A9* gene has been implicated in ADHD and multiple sclerosis (40–42). We did not have data on chronic immune diseases in the fathers in the present data file. However, in a different data set, we had information on prescribed medications of fathers. We used this data set to look at fathers who had been prescribed insulin (2% of the fathers), thyroid replacement drugs (2%), and antiasthmatic drugs (13%) as indications of paternal type 1 diabetes, hypothyroidism, and asthma. Adjusting for the same variables as in the maternal models, we found an adjusted OR for ADHD in offspring related to paternal type 1 diabetes of 1.2 (95% CI = 1.1–1.3), paternal hypothyroidism of 1.1 (95% CI = 1.0–1.2), and paternal asthma of 1.3 (95% CI = 1.3–1.3). In other words, even though there were statistically significant relationships for paternal asthma and type 1 diabetes with ADHD in offspring, the risk estimates were lower than the risk estimates found for maternal chronic immune disease. This finding is an indication that at least some of the relationship between maternal chronic immune disease and ADHD in offspring may be explained by inflammatory mechanisms during pregnancy.

We adjusted for maternal and paternal ADHD, but we had information about parental ADHD only through data registered in the NorPD for parents who had been dispensed ADHD medication during the period 2004–2012. However, before the late 1990s, ADHD was mainly thought of as a childhood disorder, and adults were not given the diagnosis. Therefore, information about parental ADHD is lacking in all data sources until the late 1990s. We cannot exclude residual confounding by shared genetic factors in the present study.

The mechanisms behind our reported findings can also be related to effects of maternal medication use during pregnancy. Acetaminophen used in pregnancy has been associated with an increased risk of hyperkinetic disorder in offspring (43), although the mechanism behind this association is not understood. Acetaminophen may act as a hormone disruptor, interfering with thyroid and reproductive function important for brain development (44). However, it is not completely understood if the association is due to a toxic effect of acetaminophen itself or the underlying causes for women taking these medications during pregnancy. Use of antipsychotics and selective serotonin reuptake inhibitors in pregnancy may affect fetal and infant neurobehavioral development (45,46). It is possible that women with chronic immunological disorders use medications such as acetaminophen and selective serotonin reuptake inhibitors during pregnancy more frequently than women without such disorders. Certain antiasthmatic drugs are associated with an increased risk of birth defects in offspring (47) and could theoretically affect neurodevelopment. However, severe maternal asthma exacerbations are also associated with an increased risk of birth defects in offspring (48). With our data, we could not separate the possible effects of medication taken in pregnancy for the studied diseases from the possible direct effects of the underlying diseases.

Inflammatory response in the fetus can also explain our findings. Abnormal exposure of the fetus to immunomodulatory molecules may play a crucial role in linking adverse pregnancy experiences with altered fetal development. Cytokines are involved in the modulation of the immune system, and elevated cytokine levels resulting from chronic inflammation may affect fetal development in different ways: either directly interfering with neuronal development or by epigenetic mechanisms resulting in altered gene expression (49). This example shows that the activation of the immune system may be a causative agent in the development of neurodevelopmental disorders.

People with chronic illnesses are more frequently in contact with health care services compared with healthy people. Symptoms of ADHD exhibited by their children could be more easily detected and diagnosed than such symptoms in children of mothers without chronic disorders. However, in this case, we would have expected a more uniform increased risk associated with all chronic disorders, including chronic hypertension and type 2 diabetes. In Norway, women of childbearing age with chronic hypertension and type 2 diabetes are closely followed by the family doctor; this would be the natural place to focus on family issues, such as ADHD symptoms in the children.

Besides immunological processes, other disease-related factors may be involved in the association between chronic maternal disease and ADHD in offspring, as ADHD is considered a multifactorial disorder. Although epilepsy is not viewed as an disease with immune components, a clear association was previously reported between maternal epilepsy and ADHD in offspring (8). This association may have several explanations, such as teratogenic effects of antiepileptic medication (49) or fetal hypoxic states caused by maternal seizures. Genetic factors may also be important (50). Thus, different maternal disorders with different pathophysiology may lead to ADHD in the offspring through different underlying pathways.

In conclusion, maternal chronic diseases with immune components as part of the pathogenetic mechanism (multiple sclerosis, type 1 diabetes, hypothyroidism, rheumatoid arthritis, and asthma) were associated with increased risk of ADHD in offspring. The associations did not differ by sex. The etiology of ADHD is probably multifactorial, and the mentioned associations can reflect different causal pathways to ADHD. Maternal disease may impact fetal development through common genetic factors, through environmental factors, or directly through an altered fetal immune response, leading to ADHD in offspring. Further studies are needed to elucidate the mechanisms underlying these relationships, clarifying how genetic vulnerabilities may interact with environmental factors to shape disease risk and clinical presentation. Increased understanding of these pathways could pave the way for new preventive and treatment strategies targeting neurodevelopmental disorders.

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# Attention-Deficit/Hyperactivity Disorder in Offspring of Mothers with Inflammatory and Immune System Diseases

## *Supplemental Information*

**Table S1. Maternal chronic diseases and offspring ADHD; results from adjusted logistic regression model with *P*-values included.**

| | Adjusted OR (95% CI)[a] | *P*-Values |
|---|---|---|
| Asthma | 1.5 (1.4-1.6) | *p*<< 0.0001 |
| Rheumatoid Arthritis | 1.7 (1.5-1.9) | *p*<< 0.0001 |
| Hypothyroidism | 1.2 (1.1-1.4) | 0.006 |
| Hyperthyroidism | 1.2 (0.9-1.5) | 0.237 |
| Diabetes Type 1[b] | 1.6 (1.3-2.0) | *p*< 0.0001 |
| Diabetes Type 2[b] | 1.1 (0.7-1.8) | 0.581 |
| Multiple Sclerosis | 1.8 (1.2.-2.5) | 0.002 |
| Hypertension, Chronic | 1.1 (0.9-1.3) | 0.279 |

[a]Adjusted by year of birth (5 years interval 1967-2008), parity (para 0, para1, para2+), mother's age at birth (<20, 20-24, 25-29, 30-34, 35-39, >39 years), mother´s educational level (low/ medium/high), mother's marital status (married/cohabiting/partnership, single, divorced/ separated/widowed, other/unknown).

[b]Data from ≥ 1989.

# III

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ORIGINAL CONTRIBUTION

# Associations between attention-deficit/hyperactivity disorder and autoimmune diseases are modified by sex: a population-based cross-sectional study

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## Abstract

Several studies have demonstrated associations between neuropsychiatric disorders, such as attention-deficit/hyperactivity disorder (ADHD), and the immune system, including autoimmune diseases. Since ADHD and many autoimmune diseases show sex-specific properties, such associations may also differ by sex. Using Norwegian national registries, we performed a cross-sectional study based on a cohort of 2,500,118 individuals to investigate whether ADHD is associated with common autoimmune diseases. Associations between ADHD and autoimmune diseases in females and males were investigated with logistic regression and effect modification by sex was evaluated. Several subanalyses were performed. The strongest association was found between ADHD and psoriasis in females, adjusted odds ratio (adjOR) = 1.57 (95% confidence interval: 1.46–1.68) and males, adjOR = 1.31 (1.23–1.40); $p$ value for interaction < 0.0001. Furthermore, among females, ADHD was associated with Crohn's disease, adjOR = 1.44 (1.16–1.79) and ulcerative colitis, adjOR = 1.28 (1.06–1.54). In contrast, males with ADHD had lower odds of Crohn's disease, adjOR = 0.71 (0.54–0.92), in addition to a trend for lower odds of ulcerative colitis, adjOR = 0.86 (0.71–1.03); $p$ values for interaction < 0.0001 and 0.0023, respectively. In a group of females where information on smoking and body mass index was available, adjustment for these potential mediators did not substantially alter the associations. Our findings support previously reported associations between ADHD and diseases of the immune system. The associations differ by sex, suggesting that sex-specific immune-mediated neurodevelopmental processes may be involved in the etiology of ADHD.

**Keywords** ADHD · Autoimmunity · Neuropsychiatry · Comorbidity · Psoriasis · Neuroimmunology

## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by the symptoms of inattention, hyperactivity and impulsivity. The symptoms of this childhood onset condition often persist into adulthood [1]. Furthermore, patients often suffer from comorbid

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psychiatric disorders [2, 3] and face socioeconomic hardship [4]. The etiology of ADHD is largely unknown, but in twin studies, the heritability of the disorder has been estimated to be 70–80%, implicating a strong genetic basis [1, 5, 6]. Environmental factors and perinatal factors such as preterm birth and growth restriction have also been shown to influence the development of ADHD [1, 7, 8].

Numerous studies have reported associations between neuropsychiatric disorders and immune system abnormalities [9–16]. However, these associations remain uncertain [17–19]. Likewise, several immune-related disorders, such as atopic dermatitis, asthma, ankylosing spondylitis, ulcerative colitis (UC), juvenile arthritis, autoimmune thyroid disease and celiac disease have been associated with ADHD [20–23]. Additionally, maternal autoimmunity has been associated with offspring ADHD, implying that maternal immune system dysfunction may affect the in utero environment and again fetal neurodevelopment [21, 24]. Despite the genetic architecture of ADHD being relatively unknown, some tentative genetic associations between ADHD and the immune system have been noted. For example, a study on genetic pathways of ADHD, which was based on genome-wide association studies (GWAS), found an increased burden of polymorphisms in and around genes involved in toll-like receptor signaling [25]. These signaling pathways are highly involved in the innate immune responses and have also been shown to regulate hippocampal plasticity and neurogenesis, and memory formation [26]. Furthermore, the single nucleotide polymorphism (SNP) which showed the strongest association signal in a recent ADHD GWAS, which included more than 20,000 ADHD patients and 35,000 controls, is located in the gene *ST3GAL3* [27]. Knockout of the *ST3GAL3* gene affects both eosinophilic immune responses [28] and brain development [29].

ADHD has an approximate male:female ratio of 3:1 during childhood and adolescence, which approaches 1:1 in adults [1]. Moreover, ADHD displays sex-specific manifestations [30]. For example, females are more often primarily affected by inattention, whereas males more often display additional symptoms of hyperactivity and impulsivity [31]. Likewise, autoimmune diseases have prevalence rates and symptom burdens that may differ by sex [32–34]. Interestingly, GWASs have reported SNPs to be associated with an autoimmune disease in one sex, but not the other [35] and genetic effects being in opposite directions depending on sex have been reported [36, 37]. Further, sex hormones are believed to have immune-modulating properties, as exemplified by symptom remission of multiple sclerosis and rheumatoid arthritis during pregnancy [33, 34]. Neural functioning might also be regulated by these hormones, as demonstrated by menstrual cycle-associated seizures of certain types of epilepsy [38]. Besides, behavior may be affected by sex hormones. For instance, females exposed to elevated prenatal androgen levels may develop more aggressive behavior later in life as compared to non-exposed females [39], and moreover, aggressive behavior is associated with ADHD [40].

In sum, if sex-specific genetic pleiotropy, or other sex-specific mechanisms, underlie any associations between ADHD and autoimmunity, these associations may differ substantially by sex. In other words, sex could be an effect measure modifier.

To further explore possible associations between autoimmunity and ADHD, and to evaluate whether these associations vary by sex, we conducted a large cross-sectional study based on Norwegian national registries.

## Materials and methods

### The Medical Birth Registry of Norway (MBRN)

The Medical Birth Registry of Norway (MBRN) was established in 1967 to collect medical and familial information on parents and births in Norway [41]. Registration in the MBRN is mandatory for all pregnancies from 16 completed weeks of gestation, and is based on a standardized notification form. Maternal smoking habits have been included in the registry since December 1998, but is one of few variables where mothers can refuse registration. Still, for approximately 84% of the births smoking information is registered. Since 2006, electronic notification of births to the MBRN has been introduced gradually, based on standardized extraction from medical records at the delivery units, and has included information on maternal height and weight before and at the end of pregnancy. However, it was not until 2014 that electronic notification was in place at all delivery units and in 2013, information on height and weight was still missing for approximately 36% of the pregnancies.

Data for the current study was obtained for all live births in the MBRN from January 1st 1967 to December 31st 2013.

### The Norwegian Prescription Database (NorPD)

The Norwegian Prescription Database (NorPD) was established in 2004 and provides information on all medical prescriptions dispensed to patients from all Norwegian pharmacies, and includes the Anatomical Therapeutic Chemical Classification System (ATC) codes [42]. Information on medication received during hospitalization is not available on an individual basis. From 2008, the NorPD has included information on diagnostic codes for reimbursed medication based on either the International Classification of Primary Care (ICPC) or the International Statistical Classification of Diseases and Related Health Problems 10th version (ICD-10), used in specialist health care. From 2004 to 2008, the NorPD also included diagnostic codes for prescribed

reimbursed medication. However, these diagnostic codes were less specific, and therefore not used in this study.

For the present study, information was obtained for all dispensed drugs between January 1st 2004 and December 31st 2015.

### The National Education Database

The National Education Database holds information on the education of all Norwegian citizens from the age of 16 years. The database covers all levels of education from primary school to PhD-level. For the present study, data on education as registered in 2012 was available.

### The National Registry

The National Registry supplied information on emigration and dates of death.

### Included individuals and record linkage

All individuals registered in the MBRN as born between 1967 and 2011, who were alive and residing in Norway on December 31st 2015, were included in the study. In addition, the mothers of those registered in the MBRN between 1998 and 2013, were identified for supplementary analyses allowing adjustment for body mass index (BMI) and smoking. Mothers who had died or emigrated by December 31st 2015 were excluded from these supplementary analyses (see below).

All Norwegian citizens have a unique personal identification number. This number was used to establish linkage between the registries.

### ADHD case definition

ADHD cases were defined as all individuals, regardless of age, who had been dispensed reimbursed ADHD medication (ATC N06BA) ($n = 63{,}721$), without reimbursement codes for "narcolepsy", G47 in ICD-10 and "sleep disturbance", P06 in ICPC ($n = 407$), during 2004–2015.

The remaining population served as the comparison group ($n = 2{,}436{,}397$).

### Autoimmune diseases

Autoimmune disease cases were defined from reimbursement codes or specific dispensed drugs corresponding to one of several predefined and common autoimmune diseases. The set of diseases was based on a Danish study describing the prevalence of 30 autoimmune diseases [43].

The estimated coverage of the autoimmune disease cases was compared with the reported prevalence rates of the autoimmune diseases in the general population by utilizing Eaton et al. 2010 [43] in addition to Norwegian and Swedish prevalence studies. Autoimmune diseases where the available reimbursement codes were considered too unspecific, that had unlikely prevalence estimates, or with less than 1000 cases in total (< 4 pr 10,000), were excluded. Nine autoimmune diseases passed the inclusion criteria (see Table 1) and were included in the study.

**Table 1** Definitions of ADHD and the autoimmune diseases assessed in the primary analyses

| Disease/disorder | Definition of case |
|---|---|
| ADHD | Prescribed and dispensed at least one reimbursed drug once with ATC-code N06BA excluding those with reimbursement code ICD-10 G47 (narcolepsy) or ICPC P06 (sleep disturbance) |
| Ankylosing spondylitis | Prescribed and dispensed at least one drug once with reimbursement code ICD-10 M45 |
| Crohn's disease | Prescribed and dispensed at least one drug once with reimbursement code ICD-10 K50 |
| Iridocyclitis | Prescribed and dispensed at least one drug once with reimbursement code ICD-10 H20 |
| Multiple sclerosis[a] | Prescribed and dispensed at least one drug once with ATC-code L03AB07, L03AB08, L03AB13, L03AX13, L04AA23, L04AA27, L04AA31, L04AA34, L04AC01, N07XX07 or N07XX09 |
| Psoriasis | Prescribed and dispensed at least one drug once with reimbursement code ICD-10 L40 or ICPC S91 |
| Rheumatoid arthritis | Prescribed and dispensed at least one drug once with reimbursement codes ICD-10 M05 or M06 |
| SLE | Prescribed and dispensed at least one drug once with reimbursement code ICD-10 M32 |
| Type 1 diabetes | Prescribed and dispensed at least one drug once with reimbursement code ICD-10 E10 or ICPC T89, excluding those who have been dispensed at least one drug once with ATC-code A10B |
| Ulcerative colitis | Prescribed and dispensed at least one drug once with reimbursement code ICD-10 K51 |

*ADHD* attention-deficit/hyperactivity disorder, *ATC* Anatomical Therapeutic Chemical Classification System, *ICD-10* International Statistical Classification of Diseases and Related Health Problems 10, *ICPC* International Classification of Primary Care, *SLE* systemic lupus erythematosus

[a] The ICD-10 and ICPC codes for multiple sclerosis are not used in Norway at drug prescribement due to health-regulatory reasons. ATC codes for multiple sclerosis-specific drugs therefore defined multiple sclerosis

### Statistical analysis

Possible associations between ADHD and the autoimmune diseases were estimated as odds ratios (OR) with 95% confidence intervals (CI) using logistic regression. *p* values are presented uncorrected for multiple testing. The threshold for statistical significance was adjusted *ad modum* Bonferroni ($p = 0.05$ divided by the number of autoimmune diseases included in the primary analyses) to $p = 0.0056$. The threshold for nominal significance was defined as $p = 0.05$. Data management and statistical analyses were performed with R [44], RStudio [45] and IBM SPSS [46].

### Primary analyses

In the primary analyses, associations between autoimmune diseases and ADHD were investigated with adjustment for age as a continuous covariate, except for type 1 diabetes where age was categorized into four (years of age in 2015: 4–10; 11–15; 16–20; 21–48). All analyses were stratified by sex [1, 30–34]. Effect modification by sex was evaluated on a multiplicative scale including an interaction term in the logistic regression model, and statistical significance was evaluated by Wald test.

Socioeconomic status as defined by maternal education was adjusted for as a categorical covariate with three categories, low (< 10 years of education), medium (10–12 years) and high (> 12 years).

Statistically significant associations in the primary analyses were further investigated in supplementary analyses concerning potential confounders, mediators and biases.

### Adjustment for smoking and body mass index (mother analyses)

Tobacco smoking and BMI may be mediating factors between ADHD and autoimmune diseases. Smoking is known to be associated with ADHD [47, 48] and has been associated with increased risk of several autoimmune diseases in prospective studies [49–51]. The similar applies to BMI in ADHD [20, 52] and autoimmunity [53–56]. To conduct a sensitivity analysis on whether the associations discovered in the main analyses were mediated mainly through smoking and/or BMI, a new study population including data on smoking and BMI was defined. The MBRN supplied data on smoking for women giving birth from December 1998 to 2013, and these mothers defined the study population when assessing the effect of smoking (from now on referred to as the "mother analyses"). Smoking during pregnancy was used as a proxy for smoking at linkage. As proxy for BMI at linkage, pre-pregnant BMI ($kg/m^2$) of the mothers was used. Mothers with registered height below 130 cm or BMI below 15 or above 60 were set to missing as these values were considered biologically implausible. Socioeconomic status was defined as the education of the mother in 2012 categorized into three: low (< 10 years), medium (10–12 years) and high (> 12 years). For females who had given birth to several children, only data from the last registered birth was included.

Logistic regression was used to investigate associations between ADHD and autoimmune diseases among these mothers with and without adjustment for the mother's smoking habits and with education as covariate. Further, a similar logistic regression was conducted with the inclusion of BMI, modelled as a continuous covariate, in addition to smoking and education. Substantial attenuation of the estimated associations between ADHD and autoimmune diseases when adjusting for smoking and BMI, would indicate that much of the effect of ADHD on these diseases might be mediated through these mediators [57, 58].

Several additional subanalyses were also conducted, when possible, to scrutinize statistically significant associations identified in the primary analyses (see supplemental material).

## Results

### Demographics

We identified a total of 2,500,118 individuals in the MBRN fulfilling our inclusion criteria for the primary analyses, 1,219,669 females and 1,280,449 males.

22,878 (1.9%) of the females had ADHD with the highest prevalence among those born in 1993 (3.5%). Of the males, 40,843 (3.2%) had ADHD, with the highest prevalence among those born in 1996 (6.8%) (supplementary Fig. 1). ADHD was associated with lower socioeconomic status, as defined by maternal educational level (see Table 2).

The total number of patients per autoimmune disease ranged from 1197 (5 per 10,000) for systemic lupus erythematosus (SLE) to 62,418 (250 per 10,000) for psoriasis. The female-to-male ratios varied across the autoimmune diseases, with 42.3% of type 1 diabetes patients being female, to 85.5% of SLE patients. All autoimmune diseases increased in prevalence with age (supplementary Fig. 1). All autoimmune diseases were associated with lower socioeconomic status.

### Primary analyses

ADHD was significantly associated with increased odds of psoriasis in both females, adjusted (adj) OR = 1.57 (95% CI 1.46–1.68) and males, adjOR = 1.31 (95% CI 1.23–1.40). Associations were significantly stronger for females than males, *p* value for interaction by sex = $4.4 \times 10^{-6}$.

**Table 2** Characteristics of the study population in the primary analyses

| Disease/disorder | *n* (per 10 000) | Mean age in 2015 | Females (%) | Maternal education % | | | |
|---|---|---|---|---|---|---|---|
| | | | | Low (< 10 years) | Medium (10–12 years) | High (> 12 years) | Information missing |
| Total study sample | 2,500,118 | 25.8 | 1,219,669 (48.8) | 23.1 | 42.0 | 33.9 | 0.1 |
| ADHD | 63,721 (255) | 23.4 | 22,878 (35.9) | 31.5 | 42.1 | 25.7 | 0.7 |
| Ankylosing spondylitis | 3504 (14) | 37.4 | 1480 (42.2) | 28.9 | 47.6 | 23.0 | 0.5 |
| Crohn's disease | 6292 (25) | 32.1 | 3284 (52.2) | 27.6 | 46.0 | 25.9 | 0.5 |
| Iridocyclitis | 7596 (30) | 34.0 | 3470 (45.7) | 26.3 | 46.7 | 26.6 | 0.4 |
| Multiple sclerosis | 3739 (15) | 38.1 | 2621 (70.1) | 29.6 | 49.6 | 20.5 | 0.4 |
| Psoriasis | 62,418 (250) | 33.8 | 32,190 (51.6) | 29.6 | 46.2 | 23.7 | 0.6 |
| Rheumatoid arthritis | 8560 (34) | 37.2 | 5662 (66.1) | 30.9 | 47.8 | 20.8 | 0.4 |
| SLE | 1197 (5) | 35.9 | 1024 (85.5) | 30.2 | 45.6 | 23.6 | 0.7 |
| Type 1 diabetes | 14,273 (57) | 29.5 | 6041 (42.3) | 23.7 | 46.4 | 29.6 | 0.4 |
| Ulcerative colitis | 10,960 (44) | 34.3 | 5392 (49.2) | 26.3 | 47.3 | 26.0 | 0.4 |

*ADHD* attention-deficit/hyperactivity disorder, *SLE* systemic lupus erythematosus

Sex differences were even larger for Crohn's disease (CD) and UC: Females with ADHD had a significantly higher odds of CD, adjOR 1.44 (95% CI 1.16–1.79), and UC, adjOR = 1.28 (95% CI 1.06–1.54), than females without ADHD. Males with ADHD, on the other hand, seemed protected, with a lower odds of CD than males without ADHD, adjOR = 0.71 (95% CI 0.54–0.92; nominal statistically significant), and a tendency to lower odds of UC, adjOR = 0.86 (95% CI 0.71–1.03). There were significant interaction effects between ADHD and sex on the odds for both CD, $p = 3.6 \times 10^{-5}$, and UC, $p = 0.0023$. Despite not reaching the threshold for statistical significance, UC was taken to supplementary analyses as UC shares many characteristics with CD and displayed statistically significant interaction effects by sex.

ADHD was further associated with lower odds of ankylosing spondylitis among females, but only at nominal statistical significance, adjOR = 0.56 (95% CI 0.32–0.96). No association was found for males, adjOR = 1.16 (95% CI 0.87–1.55). A nominally significant interaction effect between ADHD and sex was noted, $p = 0.021$.

The primary analyses were also adjusted for prematurity, gestational age ≥ 37 weeks or < 37 weeks, with little effect on the results (data and results not presented).

See Table 3 for detailed results and Fig. 1 for graphical representation of the sex-specific associations between ADHD and the autoimmune diseases.

## Adjustment for smoking and BMI (mother analyses)

512,957 females gave their last birth between December 1998 and December 31st 2013 during which time smoking habits were registered in the MBRN. Of these, 373,672 (72.8%) were themselves also registered in the MBRN at their own birth. There was information on educational level for 497,005 (96.9%) of the mothers, and of these, information on smoking for 420,050 (84.5%). Of these 420,050, 73,891 (17.6%) were defined as smokers, and additional information on pre-pregnant BMI for was available for 110,008 (26.2%). The mean and standard deviation of pre-pregnant BMI was 24.4 and 4.8, respectively, and 13,304 (12.1%) of these 110,008 females were defined as smokers. Thus, data on educational level, smoking and BMI was available for 21.4% of all females delivering their last recorded birth since the introduction of smoking information in December 1998 and up to December 31st 2013. See supplementary Fig. 2 for flowchart.

In the mother analyses, ADHD was associated with increased odds of psoriasis, adjOR = 1.62 (95% CI 1.44–1.81) also after additional adjustment for smoking, adjOR = 1.49 (95% CI 1.33–1.67) and BMI, adjOR = 1.29 (95% CI 1.04–1.60).

ADHD was associated with CD, adjOR = 1.77 (95% CI 1.23–2.54) and UC, adjOR = 1.87 (95% CI 1.42–2.46). Adjustment for smoking did not materially change ADHD's association with CD, adjOR = 1.63 (95% CI 1.13–2.34) nor UC, adjOR = 1.90 (95% CI 1.45–2.50). Similarly, additional adjustment for BMI did not alter the ADHD-CD association, adjOR = 2.20 (95% CI 1.24–3.88) nor the ADHD-UC association, adjOR = 2.10 (95% CI 1.30–3.39).

Similar analyses stratified by smoking and overweight, BMI < 25 or ≥ 25, were also conducted. The results were in line with the presented findings (data and results not presented). See Table 4 for detailed results.

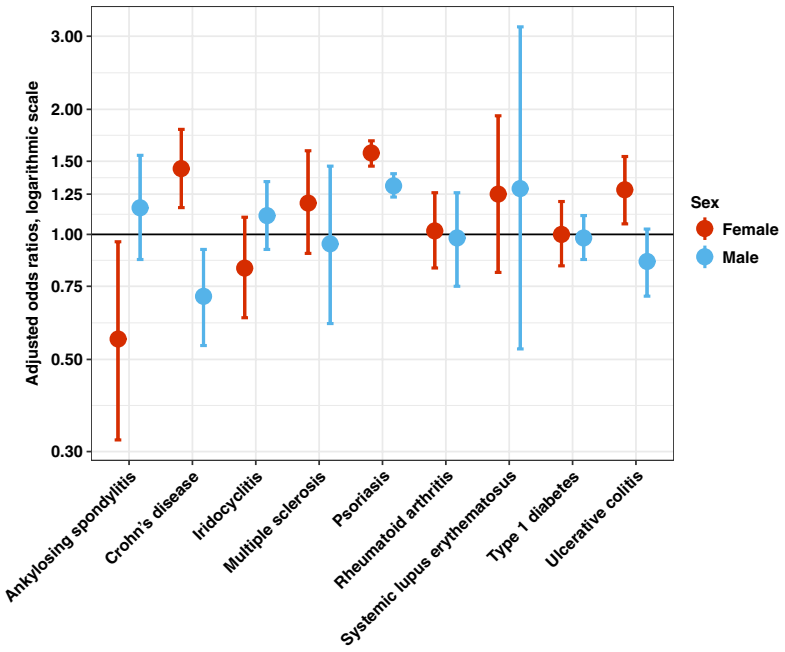


**Fig. 1** Sex-specific associations (odds ratios with 95% confidence intervals adjusted for age and maternal education) between ADHD and the autoimmune diseases investigated in the primary analyses

**Table 3** Associations between ADHD and autoimmune diseases among males and females, and the p-value for the interaction between ADHD and sex, with adjustment for age and maternal education

| Autoimmune disease | Females | | Males | | All |
|---|---|---|---|---|---|
| | Adjusted for age<br>$n$ = 1,219,669<br>ADHD $n$ = 22,878 | Adjusted for age and maternal education<br>$n$ = 1,207,694<br>ADHD $n$ = 22,741 | Adjusted for age<br>$n$ = 1,280,449<br>ADHD $n$ = 40,843 | Adjusted for age and maternal education<br>$n$ = 1,267,647<br>ADHD $n$ = 40,544 | $p$ value of interaction between ADHD and sex adjusted for age and maternal education<br>$n$ = 2,475,341<br>ADHD n = 63,285 |
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | $p$ |
| Ankylosing spondylitis | *0.56 (0.32–0.96)* | *0.56 (0.32–0.96)* | 1.17 (0.88–1.56) | 1.16 (0.87–1.55) | *0.021* |
| Crohn's disease | ***1.47 (1.18–1.82)*** | ***1.44 (1.16–1.79)*** | *0.71 (0.54–0.92)* | *0.71 (0.54–0.92)* | ***$3.6 \times 10^{-5}$*** |
| Iridocyclitis | 0.84 (0.64–1.12) | 0.83 (0.63–1.10) | 1.11 (0.92–1.34) | 1.11 (0.92–1.34) | 0.084 |
| Multiple sclerosis | 1.20 (0.90–1.60) | 1.19 (0.90–1.59) | 0.95 (0.61–1.46) | 0.95 (0.61–1.46) | 0.35 |
| Psoriasis | **1.60 (1.49–1.72)** | **1.57 (1.46–1.68)** | ***1.34 (1.25–1.43)*** | ***1.31 (1.23–1.40)*** | ***$4.4 \times 10^{-6}$*** |
| Rheumatoid arthritis | 1.05 (0.85–1.28) | 1.02 (0.83–1.26) | 1.01 (0.78–1.30) | 0.98 (0.75–1.26) | 0.65 |
| SLE | 1.26 (0.82–1.94) | 1.25 (0.81–1.93) | 1.28 (0.52–3.13) | 1.29 (0.53–3.16) | 0.98 |
| Type 1 diabetes[a] | 1.00 (0.83–1.19) | 1.00 (0.84–1.20) | 0.98 (0.87–1.11) | 0.98 (0.87–1.11) | 0.79 |
| Ulcerative colitis | *1.27 (1.06–1.53)* | *1.28 (1.06–1.54)* | 0.86 (0.71–1.03) | 0.86 (0.71–1.03) | ***0.0023*** |

Italics: $p < 0.05$

Bold and italics: $p < 0.0056$

*ADHD* attention-deficit/hyperactivity disorder, *CI* confidence interval, *OR* odds ratio, *SLE* systemic lupus erythematosus

[a] Age was categorized into four, years of age in 2015: 4–10; 11–15; 16–20; 21–48 and adjusted for as a nominal covariate

**Table 4** Associations between ADHD and Crohn's disease, ulcerative colitis and psoriasis among females with adjustment for education, smoking and body mass index

| Females | Adjusted for education[a] $n = 420{,}050$ ADHD $n = 5636$ | | Adjusted for education and smoking $n = 420{,}050$ ADHD $n = 5636$ | Adjusted for education and smoking[b] $n = 110{,}008$ ADHD $n = 1814$ | | Adjusted for education, smoking and BMI $n = 110{,}008$ ADHD $n = 1814$ |
|---|---|---|---|---|---|---|
| | *n* | OR (95% CI) | OR (95% CI) | *n* | OR (95% CI) | OR (95% CI) |
| Crohn's disease | 1225 | 1.77 (1.23–2.54) | 1.63 (1.13–2.34) | 329 | 2.27 (1.29–4.01) | 2.20 (1.24–3.88) |
| Psoriasis | 14,226 | 1.62 (1.44–1.81) | 1.49 (1.33–1.67) | 3919 | 1.39 (1.12–1.72) | 1.29 (1.04–1.60) |
| Ulcerative colitis | 2479 | 1.87 (1.42–2.46) | 1.90 (1.45–2.50) | 676 | 2.00 (1.24–3.22) | 2.10 (1.30–3.39) |

*ADHD* attention-deficit/hyperactivity disorder, *BMI* body mass index, *CI* confidence interval, *OR* odds ratio

[a] Restricted to females with information on smoking

[b] Restricted to females with information on BMI

### Psoriasis, Crohn's disease and ulcerative colitis

As a robust positive association between psoriasis and ADHD was identified, this association was further examined, both in regards to psoriasis case definition and age- and period effects. The supplementary analyses confirmed the results of the primary analyses (see supplementary material for both specification of analyses and results).

The diagnoses CD and UC partly overlapped as 2334 individuals in the primary analyses were defined as having both conditions (37.1% of the CD patients and 21.3% of the UC patients). Supplementary analyses were conducted after redefining all individuals with both CD and UC as having neither. The results confirmed the positive associations in females, and the interaction by sex, but the negative associations in males were now not present (see supplementary material for both specification of analyses and results). To assess age- and period effects of ADHD on CD and UC, analyses stratified on birth years, 1967–1985 and 1986–2011, were conducted. For CD, the results were in line with the main analyses for both individuals born 1967–1985 and those born 1986–2011, including the sex-effects. However, for UC, the positive association in females, and negative association in males, were only noted in those born 1967–1985. For those born 1986–2011, no associations were noted (see supplementary material for further specification of analyses and results).

## Discussion

In our large cross-sectional study based on population-wide registries, ADHD was clearly and positively associated with psoriasis. This association was present regardless of sex, but with a significantly stronger association in females than males. Furthermore, in females, ADHD was positively associated with CD and UC. In contrast, among males, ADHD showed a negative association with CD, and a similar tendency with UC.

Psoriasis is a skin disorder characterized by red scaly skin plaques, papules or patches and is generally considered an autoimmune disease [43]. The etiology behind psoriasis is complex, including environmental and lifestyle factors [50, 53, 59] and several genetic risk variants have been identified, mainly in and around genes involved in the immune response and skin barrier regulation [60]. In agreement with our findings, a Danish registry-based study noted a possible association between psoriasis and ADHD [21]. However, the association was not statistically significant ($p = 0.09$), which may be due to the study's prospective study design where the autoimmune diseases had to debut prior to ADHD. In contrast, we utilized a cross-sectional design. Moreover, we investigated both children and adults, 4–48 years of age at linkage, whereas the Danish study only examined children and young adults, 5–22 years old at linkage, which lead to a smaller study sample. In addition, many of the individuals in the Danish study were simply too young to have developed psoriasis [59] or to have been diagnosed with ADHD [1].

Several different mechanisms may account for the association between ADHD and psoriasis. A recent family-based epidemiological study reported a significant genetic correlation between ADHD and psoriasis [61], indicating that there could be pleiotropic genetic effects in shared risk pathways. For example, complement factor C3 is highly expressed in both psoriatic lesions [62] and is important for synaptic pruning in the brain [63]. Lifestyle and environmental factors associated with ADHD, such as smoking and high BMI [20, 47, 48, 52], may also provoke psoriasis [50, 53]. However, in our mother analyses, adjustment for these risk factors did not attenuate the association, implying alternative etiological pathways [57, 58]. Furthermore, emotional and social stressors associated with ADHD [4, 64] could perhaps trigger psoriasis in predisposed individuals [65].

CD and UC are both diseases primarily affecting the gastrointestinal system [51]. They are considered separate disease entities, but share many similarities, both clinically and etiologically, and are referred to collectively as inflammatory bowel disease (IBD). More than 150 genetic risk variants have been identified for both, many of which are shared, and environmental factors are highly implicated in the etiology [51, 66, 67]. In a study from Taiwan, ADHD was associated with UC, but not CD [22]. However, the authors did not report sex-specific effects, raising the possibility that the common estimate may be biased, and that the sex-specific effects present in our study, were not identified. Moreover, the prevalence-ratio of CD to UC was > 10:1 among the controls, indicating possible age-effects in addition to ethnic differences.

The increased odds of CD and UC in females with ADHD, with a reverse relation in males is striking. In addition, ADHD females had significantly higher odds of psoriasis than ADHD males. Sex, including both hormonal and non-hormonal influences, is a key determinant of immune system functioning [33, 34], brain development, neural functioning and psychiatric disease [30, 31, 38, 39, 68, 69]. A possible etiology for the sex-specific effects may involve glial cells, which are neuron-and homeostasis-supportive cells of the nervous system with immunomodulatory properties [33, 68, 70]. Glial cells have been shown to modulate sex-determined neurodevelopmental processes, including synaptic patterning and neurite pruning [68, 69]. Further, there are studies suggesting a role for glial cells located along the gut in the etiology of CD and UC, in addition to several other gastrointestinal disorders [70].

Genetically, pleiotropic associations between psychiatric disorders and autoimmune diseases have been reported [16], and so have sex-specific reverse genetic effects [36, 37]. Thus, we might hypothesize that the inverse associations observed in our study could be the result of pleiotropic variants, exhibiting sex-specific associations in opposite directions in either ADHD and/or IBD. Another potential mechanism could be that there is a tendency for more genetic variants positively associated with both ADHD and IBD to be located on the X-chromosome, while on the Y-chromosome, there is a greater burden of variants positively associated with ADHD, but negatively associated with IBD [35]. As the sex chromosomes have been largely ignored in GWASs owing to analytical difficulties, this is an area where further research is warranted.

Alternatively, smoking and BMI may play a role in the sex-discordant associations between ADHD and IBD [20, 47, 48, 52, 56]. However, adjustment for these potential mediators did not affect the associations much in our mother analyses, implying that they are weak mediators. Further, smoking has been shown to protect against UC, but confer risk for CD [51] and can consequently not easily explain our results as we then would have expected a negative association between ADHD and UC in females. Regarding BMI, prospective studies have only associated premorbid BMI with CD and not UC [56], which is not in agreement with our findings.

It could be that living with ADHD as a female gives rise to more stress, for example through social expectations and cultural norms, which again might lead to more autoimmunity [51, 65] and potentially, the sex-specific associations. However, one study showed that even though ADHD symptoms predispose to more stressful life events, female sex has been shown not to predispose to more stressful life events among those with ADHD symptoms [64].

Our study has several strengths. The use of compulsory population-wide registries minimize the risk of selection bias, and may provide the statistical power needed to investigate potential associations between ADHD and different autoimmune diseases. Further, the compulsory registration of prescription data protects against follow-up bias. However, we do not have information on medication given to hospital inpatients and nursing homes. Considering that the individuals in the primary analyses were all under 50 years, and that chronic diseases were investigated, we assume these factors to be of minor importance.

Another strength is the possibility to adjust for smoking and BMI in the mother analyses to assess mediating effects. However, we make the assumption that BMI and smoking at last registered pregnancy is "representative" of lifetime status up to 2015, which is sub-optimal. As the mother analyses were based on females, the generalizability to males could be questioned. Nonetheless, we consider it biologically unlikely that the positive association between psoriasis and ADHD is mediated purely by smoking and BMI in males, but not in females. In addition, several types of bias may occur as the mother analyses were based on only females who had given birth, and many autoimmune diseases are associated with reduced fertility [71], again possibly affecting the generalizability of the study. We are also aware that adjusting for intermediate variables, as we did in the mother analyses, may introduce collider stratification bias due to unmeasured variables affecting both smoking, BMI and the autoimmune diseases [57, 58]. Caution should therefore be exercised in the interpretation of these analyses. Also, we had problems with missing data for both smoking and BMI.

In Norway, the prescription of medication used in the treatment of ADHD is restricted and the drugs are only prescribed after thorough diagnostic evaluation in specialist health care. ADHD patients as defined by dispensed drugs is therefore presumably specific for ADHD. Nonetheless, we have missed patients who used ADHD medication only prior to 2004, and those who have never been prescribed medications due to contraindications, mild symptoms or patients who declined pharmacological treatment. However,

a previous study using similar data from the same period, demonstrated that only 17% of registered ADHD patients had not received ADHD medication [24]. Furthermore, our ADHD case definition includes individuals who in 2004–2008 were prescribed stimulants for treatment of narcolepsy, but as this is a very minor number, it should not influence the results.

Dispensed medication and reimbursement codes (ICD-10 codes and ICPC codes as indications for dispensed medication) were used as proxies for autoimmune diseases. Thus, our definitions of autoimmune diseases may not capture all patients. For example, patients with primary-progressive multiple sclerosis, which constitute 10–15% of multiple sclerosis patients, will often not be identified by our approach as until recently there have been limited pharmacological treatment options for this group [72]. Further, the reimbursement codes may not always be used correctly. Despite the limitations of our disease identification, we believe that a drug prescribed with a reimbursement code, indicates thorough diagnostics, especially considering that many of the drugs may have serious side effects and are not used without due consideration.

We found no robust statistically significant associations between ADHD and the autoimmune diseases iridocyclitis, rheumatoid arthritis, SLE, ankylosing spondylitis, multiple sclerosis or type 1 diabetes. This could be due to a genuine lack of association between these autoimmune diseases and ADHD. Nonetheless, it could be that the low share of individuals born prior to 1990 who have dispensed ADHD-medication (supplementary Fig. 1) as compared to those born later, may reflect ADHD symptom remission before 2004 when the NorPD was established, or historical underdiagnosis and undertreatment of ADHD. Consequently, these ADHD individuals are not identified by our case definition. On the contrary, many autoimmune diseases are diagnosed later in life. Combined, our study may be inadequate for discovering associations between ADHD and autoimmune diseases with late debut. This may also partly explain the absence of any associations between ADHD and UC among individuals born 1985–2011 (supplementary material).

As our study is cross-sectional and we exclude all deceased or emigrated individuals, this may constitute a source of bias as ADHD is associated with increased mortality [73] and so are many of the autoimmune diseases [74, 75]. However, we do not believe that such bias underlies the findings of our study. First, the increased mortality associated with ADHD, mostly accidents, is unlikely to differ by autoimmune diseases nor constitute a large absolute number. Second, our cohort is relatively young with the oldest in the main analyses being 48 years of age at linkage. Therefore, most of the cohort is too young for cardiovascular death, which constitute a large portion of the mortality associated with autoimmune diseases [74–76]. In addition, the findings regarding CD and psoriasis could be identified among younger individuals in the birth year-stratified analyses. On the other hand, not excluding individuals who died or emigrated before the end of study could have lead to bias. Individuals who received ADHD medication after 2004, and thus captured by our study as ADHD patients, but developed autoimmune diseases and died or emigrated before 2008 would be lost.

Another source of bias could be that ADHD patients, already in contact with the health services, may get a diagnosis of comorbid diseases more easily than individuals who do not have an established link with the health services. However, one should then expect increased odds of all autoimmune diseases, and for both females and males, which was not the case. The symptoms of an autoimmune disease could also be mistaken for ADHD symptoms. For example the itch of psoriasis could lead to lower sleep quality and daytime sleepiness [77, 78], which may be mistaken for the impaired attention of ADHD. Yet, one would again expect increased odds of all autoimmune diseases.

In conclusion, our study supports previous reports on associations between ADHD and autoimmune diseases, and adds new knowledge about sex-specific associations and even reverse direction by sex for some associations. Our results also suggest that these associations are not mediated by smoking or BMI. Overall, our study suggests that sex-specific immune-mediated neurodevelopment may play a role in ADHD etiology, warranting further investigation. Future studies investigating the relationship between autoimmunity and neuropsychiatric disorders should be aware of sex-specific effects.

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## Compliance with ethical standards

**Ethical approval** The study was approved by the Regional Committee for Medical and Health Research Ethics of Western Norway (2012/2223/REK vest) and the Norwegian Data Inspectorate. The study has been conducted in accordance with 1964 Decleration of Helsinki and its later amendments.

**Conflict of interest** The authors declare that they have no conflict of interest.

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**Supplementary material**

**Psoriasis**

In the primary analysis, a robust association between attention-deficit/hyperactivity disorder (ADHD) and psoriasis was found. To confirm that this association was not due to an unknown bias affecting our case definition, we applied several stringent psoriasis case definitions. Psoriasis patients were first defined as those who had been dispensed the "topical antipsoriatics" calcipotriol (ATC D05AX02), calcitriol (ATC D05AX03) or calcipotriol combination (ATC D05AX52) which we believe to be specific, though not sensitive, for psoriasis (topical corticosteroids are commonly used in monotherapy) at least once. Secondly, as it is not unreasonable to believe psoriasis is more accurately diagnosed in specialist health care, psoriasis cases were defined as only those who had been prescribed a drug for psoriasis in specialist health care as defined by the ICD-10 code L40, effectively defining all those treated exclusively in general practice since 2008 as non-psoriasis individuals. Thirdly, psoriasis patients were defined as only those who had been dispensed two or more prescriptions for psoriasis based on ICD-10 L40 and/or ICPC S91. Similar analyses as in the primary analyses were then conducted.

All analyses confirmed the results of the primary analyses. See supplementary table 1.

**Supplementary table 1:** Associations between ADHD and psoriasis by different definitions among males and females, and the *p* value for the interaction between ADHD and sex, with adjustment for age and maternal education

| | **Females** | | | **Males** | | | **All** |
|---|---|---|---|---|---|---|---|
| **Psoriasis case definition** | **n pr psoriasis case definition in total material** | **Adjusted for age n = 1 219 669 ADHD n = 22 878** | **Adjusted for age and maternal education n = 1 207 694 ADHD n = 22 741** | **n pr psoriasis case definition in total material** | **Adjusted for age n = 1 280 449 ADHD n = 40 843** | **Adjusted for age and maternal education n = 1 267 647 ADHD n = 40 544** | ***P* value of interaction between ADHD and sex (adjusted for age and maternal education) n = 2 475 341 ADHD n = 63 285** |
| | | OR (95% CI) | OR (95% CI) | | OR (95% CI) | OR (95% CI) | *p* |
| Dispensed specific antipsoriatics[a] | 18 173 | 1.51 (1.37-1.65) | 1.47 (1.34-1.62) | 18 557 | 1.33 (1.22-1.45) | 1.30 (1.20-1.42) | 0.0040 |
| Prescribed drug for psoriasis in specialist health care[b] | 12 500 | 1.44 (1.28-1.61) | 1.42 (1.27-1.59) | 12 341 | 1.18 (1.06-1.31) | 1.17 (1.05-1.30) | 0.0014 |
| Dispensed a drug for psoriasis twice or more[c] | 19 875 | 1.65 (1.51-1.80) | 1.61 (1.47-1.75) | 19 512 | 1.33 (1.22-1.44) | 1.30 (1.19-1.41) | $8.5 \times 10^{-7}$ |

[a] Calcipotriol (ATC D05AX02), calcitriol (ATC D05AX03) and calcipotriol combination (ATC D05AX52)

[b] Only based on reimbursement code ICD-code L40

[c] Based on reimbursement code ICD-10 L40 or ICPC S91

ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio

Further, we assessed whether there were any period effects on the association between psoriasis and ADHD. We grouped all birth years into 5-year categories and performed stratified analyses.

The results suggested that there were no major period effects. See supplementary table 2. For those born years 2002-2006, 9-13 years at time of linkage, there were no associations, for neither females nor males. However, for individuals born 2007-2011, 4-8 years at time of linkage, the association between ADHD and psoriasis was present for both sexes. The associations for 2007-2011 were primarily driven by prescriptions from general practitioners (ICPC) (not shown).

**Supplementary table 2:** Associations between ADHD and psoriasis per 5-year birth year category, 1967-2011**bmi**

| **Females** | | | | | |
|---|---|---|---|---|---|
| **Birth year** | **Total n** | **Psoriasis n** | **Psoriasis specialist n[a]** | **ADHD n** | **Non-adjusted** |
| | | | | | OR (95% CI) |
| 1967-2011 | 1 219 669 | 32 190 | 12 500 | 22 878 | 1.47 (1.37-1.57) |
| 1967-1971 | 151 219 | 6937 | 2746 | 1643 | 1.67 (1.38-2.01) |
| 1972-1976 | 135 848 | 5819 | 2227 | 1784 | 1.65 (1.37-1.99) |
| 1977-1981 | 118 015 | 4478 | 1774 | 1804 | 1.32 (1.07-1.64) |
| 1982-1986 | 117 810 | 4235 | 1578 | 2261 | 1.35 (1.11-1.65) |
| 1987-1991 | 136 399 | 4081 | 1532 | 4129 | 1.61 (1.39-1.87) |

| | | | | | |
|---|---|---|---|---|---|
| 1992-1996 | 141 336 | 3176 | 1203 | 4770 | 1.29 (1.08-1.53) |
| 1997-2001 | 138 641 | 1963 | 804 | 3975 | 1.37 (1.09-1.73) |
| 2002-2006 | 135 761 | 1087 | 467 | 2225 | 1.24 (0.81-1.90) |
| 2007-2011 | 144 640 | 414 | 169 | 287 | 3.70 (1.18-11.59) |
| **Males** | | | | | |
| **Birth year** | **Total n** | **Psoriasis n** | **Psoriasis specialist n[a]** | **ADHD n** | **Non-adjusted** |
| | | | | | OR (95% CI) |
| 1967-2011 | 1 280 449 | 30 228 | 12 341 | 40 843 | 1.00 (0.94-1.07) |
| 1967-1971 | 156 295 | 7305 | 2992 | 1718 | 1.46 (1.20-1.76) |
| 1972-1976 | 140 673 | 6033 | 2545 | 2022 | 1.23 (1.01-1.50) |
| 1977-1981 | 123 417 | 4519 | 1919 | 2168 | 1.61 (1.34-1.94) |
| 1982-1986 | 124 579 | 3759 | 1565 | 2966 | 1.37 (1.14-1.65) |
| 1987-1991 | 143 863 | 3203 | 1220 | 6195 | 1.12 (0.95-1.32) |
| 1992-1996 | 150 394 | 2364 | 883 | 9364 | 1.23 (1.05-1.44) |
| 1997-2001 | 145 859 | 1562 | 611 | 9243 | 1.20 (0.99-1.45) |
| 2002-2006 | 142 557 | 955 | 398 | 6130 | 1.15 (0.86-1.55) |
| 2007-2011 | 152 812 | 528 | 208 | 1037 | 2.55 (1.32-4.95) |

[a] Prescribed drug for psoriasis in specialist health care

ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio

**Crohn's disease and ulcerative colitis**

Sex-specific associations were noted between ADHD and Crohn's disease (CD), and ADHD and ulcerative colitis (UC) in the primary analyses. However, as 2334 individuals had been defined as having both CD and UC (37.1% of the CD patients and 21.3% of the UC patients), we investigated whether these associations were linked to only one of the autoimmune diseases. To define "pure" CD and UC, all individuals with both diagnoses were redefined as having neither CD nor UC. Similar analyses to the primary analyses were then conducted.

The results confirmed the findings of the primary analysis for females, with ADHD being associated with increased risk of both CD, adjusted odds ratio (adjOR) = 1.52 (95%CI: 1.17-1.99), and UC, adjOR = 1.28 (95%CI: 1.03-1.58). However, the negative association between ADHD and CD among males did not pass the threshold for nominal statistical significance, adjOR = 0.79 (95%CI: 0.58-1.08) and no trend for association between ADHD and UC among males was noted. The interaction effects were still present, albeit attenuated. See supplementary table 3 for detailed results.

**Supplementary table 3:** Associations between ADHD and the autoimmune disorders Crohn's disease and ulcerative colitis after redefining those diagnosed with both autoimmune diseases as having neither

| **Autoimmune disease** | **Females** | | | **Males** | | | **All** |
|---|---|---|---|---|---|---|---|
| | **n** | **Adjusted for age n = 1 219 669 ADHD n =22 878** | **Adjusted for age and maternal education n = 1 207 694 ADHD n = 22 741** | **n** | **Adjusted for age n = 1 280 449 ADHD n = 40 843** | **Adjusted for age and maternal education n = 1 267 647 ADHD n = 40 544** | ***P* value of interaction between ADHD and sex (adjusted for age and maternal education) n = 2 475 341 ADHD n = 63 285** |
| | | OR (95% CI) | OR (95% CI) | | OR (95% CI) | OR (95% CI) | *p* |
| Crohn's disease | 2075 | 1.56 (1.20-2.04) | 1.52 (1.17-1.99) | 1883 | 0.80 (0.58-1.09) | 0.79 (0.58-1.08) | 0.0021 |
| Ulcerative colitis | 4183 | 1.27 (1.02-1.57) | 1.28 (1.03-1.58) | 4443 | 0.95 (0.78-1.16) | 0.94 (0.77-1.15) | 0.046 |
| ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio | | | | | | | |

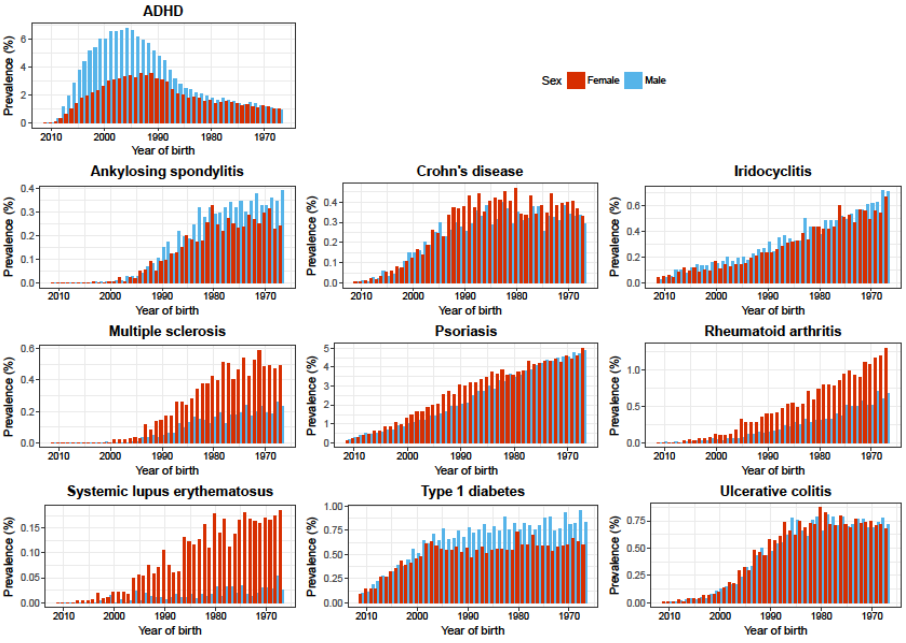
Period and age-effects may play a role in the associations between ADHD and the inflammatory bowel disorders. We therefore stratified the sample into those born in 1985 or earlier, 30 years or older at linkage, and those born after 1985, 29 or younger at linkage. Logistic regression analyses similar to the main analyses were then conducted stratified on the age groups, including adjusting for age as a linear covariate and maternal education.

For CD, the results were largely in line with the main analyses, if to accept non-statistically significant trends. In females, ADHD increased the odds of CD, while male sex lowered the

odds. Age and period effects were of minor importance. However, for UC, only among those born 1967-1985, were the results similar to the main analyses, with ADHD conferring increased odds of UC among females, and decreased odds among males. For individuals born 1986-2011, no association between ADHD and UC was noted in either sex. See supplementary table 4 for detailed results.

**Supplementary table 4:** Associations between ADHD and the autoimmune diseases Crohn's disease and ulcerative colitis after stratification on born in or before 1985, or after 1985.

| **Autoimmune disease** | **Females born 1967-1985** | | **Females born 1986-2011** | | **Males born 1967-1985** | | **Males born 1986-2011** | | **All born 1967-1985** | **All born 1986-2011** |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Adjusted for age and maternal education**<br><br>**n = 497 034 ADHD n = 6942** | | **Adjusted for age and maternal education**<br><br>**n = 710 660 ADHD n = 15 799** | | **Adjusted for age and maternal education**<br><br>**n = 517 374 ADHD n = 8114** | | **Adjusted for age and maternal education**<br><br>**n = 750 273 ADHD n = 32 430** | | ***P* value of interaction between ADHD and sex (adjusted for age and maternal education) n = 1 014 408 ADHD n = 15 056** | ***P* value of interaction between ADHD and sex (adjusted for age and maternal education) n = 1 460 933 ADHD n = 48 229** |
| | n | OR (95% CI) | n | OR (95% CI) | n | OR (95% CI) | n | OR (95% CI) | *p* | *p* |
| Crohn's disease | 1946 | 1.36 (0.98-1.88) | 1321 | 1.25 (0.93-1.68) | 1711 | 0.66 (0.42-1.05) | 1281 | 0.65 (0.47-0.89) | 0.0095 | 0.0025 |
| Ulcerative colitis | 3638 | 1.32 (1.04-1.69) | 1737 | 1.01 (0.76-1.34) | 3773 | 0.67 (0.49-0.92) | 1772 | 0.93 (0.74-1.17) | $7.2 \times 10^{-4}$ | 0.68 |
| ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio | | | | | | | | | | |


ADHD
Sex
Female
Male
Ankylosing spondylitis
Crohn's disease
Iridocyclitis
Multiple sclerosis
Psoriasis
Rheumatoid arthritis
Systemic lupus erythematosus
Type 1 diabetes
Ulcerative colitis
Prevalence (%)
Year of birth
2010
2000
1990
1980
1970

# IV

*Article*

# Adult ADHD and Comorbid Somatic Disease: A Systematic Literature Review

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**Abstract**

**Objective:** To systematically review, synthesize, and appraise available evidence, connecting adult ADHD (aADHD) with somatic disease. **Method:** Embase, Psychinfo, and Medline databases were searched for studies published from 1994 to 2015 addressing aADHD and somatic comorbidity. Somatic conditions were classified according to International Classification of Diseases (ICD-10) codes. Levels of evidence were graded as inconclusive, tentative, or well documented. **Results:** Most of the 126 studies included in the qualitative synthesis were small and of modest quality. Obesity, sleep disorders, and asthma were well-documented comorbidities in aADHD. Tentative evidence was found for an association between aADHD and migraine and celiac disease. In a large health registry study, cardiovascular disease was not associated with aADHD. **Conclusion:** There are few large systematic studies using standardized diagnostic criteria evaluating aADHD and somatic comorbidities. Significant associations are found between aADHD and several somatic diseases, and these are important to consider when assessing and treating either aADHD or the somatic diseases. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

**Keywords**

adult ADHD, asthma, migraine, sleep disorders, review

ADHD is a common neuropsychiatric disorder defined by a persistent pattern of inattention and/or hyperactivity/impulsivity that interferes with functioning or development (American Psychiatric Association [APA], 2013). The first systematic studies of ADHD focused on school-aged boys (Still, 1902). Later, it was recognized that many girls have similar problems, and that symptoms persist into adulthood in the majority of cases, with worldwide prevalence estimates of ADHD around 2.5% to 3% in the adult population (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Simon, Czobor, Balint, Meszaros, & Bitter, 2009).

In addition to the core clinical symptoms of ADHD, psychiatric and non-psychiatric coexisting problems and clinical conditions have been described in ADHD patients (Angold, Costello, & Erkanli, 1999). In particular, psychiatric comorbid conditions are recognized in both children and adults, and pose considerable clinical and public health challenges (Angold et al., 1999; Halmoy et al., 2010).

Recognition of medical/somatic conditions is also a key component in the routine clinical assessment of psychiatric patients. Failure to diagnose medical conditions can lead to misdiagnosis or incorrect treatment, with potentially serious consequences. According to the current diagnostic criteria for ADHD in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; APA, 2013), the diagnosis of ADHD is only considered appropriate if the disturbance is not judged to be the direct pathophysiological consequence of a specific medical condition (e.g., multiple sclerosis, stroke, hypothyroidism). However, in the most recent version of the International Classification of Diseases and Related Health Problems (ICD-10; World Health Organization, 1992), it is also emphasized that psychiatric syndromes may be causally related to cerebral and systemic diseases, and that proper diagnosis will require two codes:

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one for the psychopathological syndrome and the other for the underlying disorder.

Compared with the extensive descriptions of psychiatric comorbidity, somatic comorbidity in ADHD has received less attention in the research literature, particularly among adults. This discrepancy is obvious in the recent diagnostic definition of ADHD (APA, 2013), where many psychiatric disorders are listed either as possible differential diagnoses or as comorbid conditions. The only non-psychiatric disorder specifically mentioned is medication-induced symptoms of ADHD. Associated medical conditions have been studied more in other psychiatric disorders, where they are also considered to contribute to a lower quality of life and reduced life expectancy. In schizophrenia, it is known that weight gain, diabetes, metabolic syndrome, and cardiovascular disease are common, and it is speculated that a shared vulnerability for psychosis and medical conditions can explain some of this comorbidity (Ringen, Engh, Birkenaes, Dieset, & Andreassen, 2014). Population-based prospective studies have documented an increased risk of premature death and reduced life expectancy also for ADHD patients (Dalsgaard, Ostergaard, Leckman, Mortensen, & Pedersen, 2015), but it is unclear if this risk is mediated by coexisting medical diseases.

The primary objective of this review was to obtain an overview of, and evaluate, the literature covering this topic during the past 20 years. Secondary objectives were to inform clinicians on the most common somatic comorbid conditions to enhance optimal patient evaluation and treatment, and to identify particular areas of research that should be further investigated.

## Method

### *Literature Search Strategies and Data Sources*

We performed a systematic review of the literature addressing aADHD and somatic comorbidity. The search strategy was developed in collaboration with a university librarian experienced in systematic medical literature searches. The electronic databases Embase, Psychinfo, and Medline were searched in December 2014 and January 2015, limiting the search to study participants above 18 years of age. The search was finalized on January 26, 2015, retrieving 4,091 papers. The detailed electronic search strategy is provided in Supplementary 1.

After removing duplicates and studies published prior to 1994 when the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; APA, 1994) was introduced, J.T.I. screened title and abstract in the remaining studies, excluding papers that clearly did not fulfill the inclusion criteria listed below. Furthermore, reference lists of the retrieved papers were hand searched to identify additional relevant articles. Other papers of interest found in manual search published January 2015 to February 2016 were also included. In total, 208 papers were assessed in full text by at least one of the authors, depending on their experience and fields of expertise, and all papers were discussed by at least two. Extraction of data was checked and harmonized by two authors (J.T.I. and K.K). Of the 208 papers, 82 were excluded using the criteria listed below. Of the 126 remaining papers, 98 contained original data, 26 were classified as reviews, one a letter to the editor and one an annotation.

The specific number of included and excluded papers at each step is provided in a PRISMA flow chart (Figure 1).

All the 126 studies, both the individual studies and reviews, are referred to in the text. Sources of bias in the 98 individual studies were considered to be mainly related to study design, the selection of participants, the size of the study, and the methods used to define ADHD and the comorbid disorders. All these characteristics were therefore assessed and are tabulated in a supplementary table (Supplementary 2). Reviews are omitted from this table (Supplementary 4 for list). Some additional studies not fulfilling the inclusion criteria have been mentioned as part of the discussion.

### *Study Selection Criteria*

*Inclusion criteria.* Studies focusing on the comorbidity between somatic disease and ADHD in adults (i.e. 18 years or older) were included. ADHD was defined according to ICD or DSM criteria (ICD-9/ICD-10/DSM-III/DSM-IV/DSM-5). As indicated in a supplementary table (Supplementary 2), different protocols have been used to classify individuals as having aADHD, that is, either (a) aADHD clinically diagnosed, included the use of semi-structured interviews; (b) ADHD medication used as a proxy for ADHD diagnosis; (c) symptoms of ADHD measured by a validated ADHD Symptom Rating scale; (d) information on ADHD cases from clinical databases. The properties and utility of some aADHD instruments have been reviewed (Haavik, Halmoy, Lundervold, & Fasmer, 2010) and are summarized in Supplementary 3.

For all studies, the reported diagnoses of somatic disease/comorbidity were fit into broad disease categories as defined in the ICD-10. In the cited studies, these diagnoses were obtained either after clinical evaluation or from self-reports. Due to the large number of somatic comorbidities studied and the different protocols involved, it was not feasible to systematically describe the inclusion criteria for each of the individual somatic comorbidities, but an overview of how the somatic diseases are defined, is summarized in Supplementary 2.

Instruments used for ADHD assessment and the most commonly used methods to assess for comorbid disorders described in the included studies are briefly described and listed in Supplementary 3.

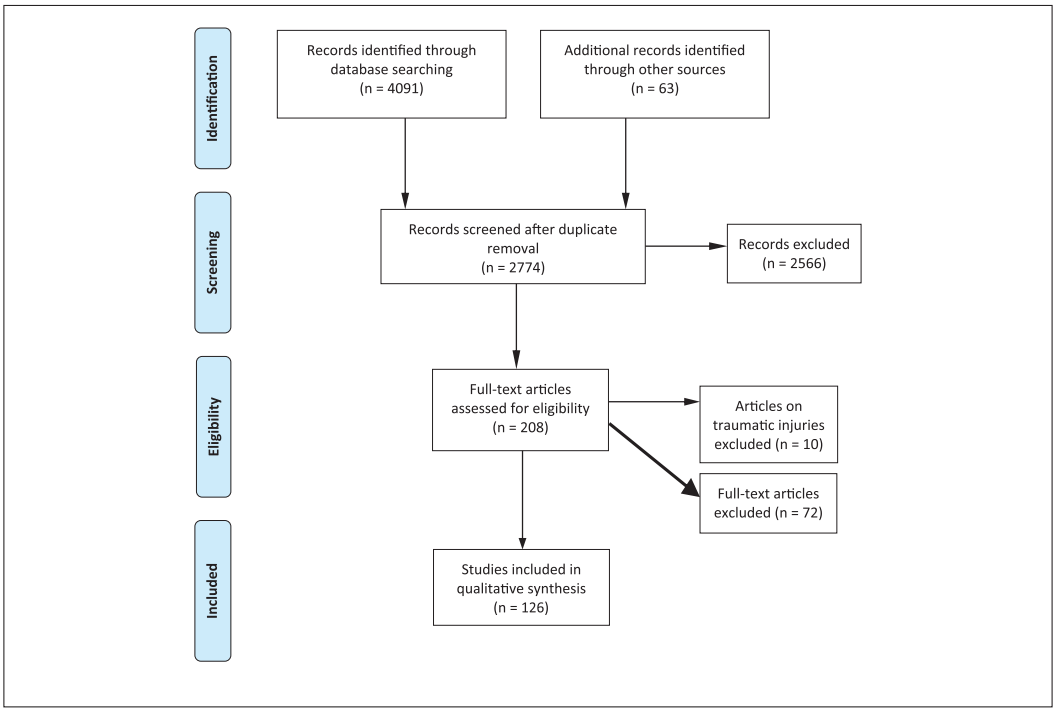


**Figure 1.** Flow diagram (from PRISME).
*Source.* Moher, Liberati, Tetzlaff, and Altman (2009).

*Exclusion criteria.* The following exclusion criteria were applied: (a) studies not including ADHD as described under inclusion criteria, (b) studies including *only* children and adolescents, (c) publications not subject to peer review, (d) non-English papers, (e) single case studies, (f) studies describing only psychiatric comorbidities as classified in *ICD-10* Chapter V: Mental and behavioral disorders, and (g) pharmacological trials, for example, focusing on specific treatment options and not on the comorbid disorder itself. We also excluded studies on traumatic incidents, as we consider these to be outside our main focus which is somatic diseases comorbid with aADHD.

## Classification of Studies

Based on available evidence, the 98 individual studies were classified into three categories (Table 1). Category 1 includes conditions where the association between ADHD and somatic disease is well established and described in meta-analysis or systematic reviews. Category 2 includes conditions where there is tentative evidence for an association, the associations being described in cohort or case-control studies with clinically diagnosed ADHD and the somatic diseases not only being based on self-report questionnaires. Comorbidities shown in large population-based studies with diagnoses retrieved from clinical databases were also included in this category. Category 3 includes conditions where the evidence was considered too weak to make conclusions, including associations described only in studies where ADHD and/or somatic comorbidities are not clinically diagnosed (i.e., based on self-report questionnaires only) or where the evidence is limited. This category also includes conditions where the combined results clearly showed conflicting results. Studies on conditions lacking information on diagnostic protocols or the age distribution of the ADHD participants were also categorized in Category 3.

The somatic diseases included in the present review have been broadly grouped using ICD-10 codes, although this classification in some instances may be arbitrary (e.g. classifications of sleep problems), due to the application of various diagnostic criteria.

## Measurements

*ADHD scales.* The Adult ADHD Self-Report Scale (ASRS) was developed in conjunction with the World Health Organization and is designed to measure current ADHD

**Table 1.** Name of Disease Category, ICD-10 Code, and Number of Individual Studies Investigating the Association Between Adult ADHD and Somatic Disease.

| Diagnosis | ICD-10 code | Number of individual studies | Association and quality of evidence[a] |
|---|---|---|---|
| In general | | 4 | |
| Resistance to thyroid hormone | E07.8 | 1 | Association (3) |
| Hypothyroidism | E00-E03 | 1 | Association (3) |
| Diabetes | E10-E14 | 3 | No/negative association (3) |
| Nutritional diseases | | | |
| Obesity | E66 | 22 | **Association (1)** |
| Metabolic disorders | E70-E90 | | |
| In general | | 1 | Association (3) |
| Albinism | E70.3 | 1 | Association (3) |
| Maple syrup urine disease | E71.0 | 1 | Association (3) |
| Diseases of the nervous system | | | |
| Restless legs | G25 | 6 | Association (3) |
| Dementia with Lewy bodies | G31.83 | 1 | Association (3) |
| Epilepsy | G40 | 3 | Association (3) |
| Migraine | G43 | 2 | **Association (2)** |
| Sleep disorders | G47 | 25 | **Association (1)** |
| Myotonic dystrophy | G71.1 | 2 | Association (3) |
| Chronic fatigue syndrome | G93.3 | 2 | Association (3) |
| Diseases of the circulatory system | Chapter IX | 4 | **No association (2)** |
| Allergic diseases | | | |
| In general | | 2 | Association (3) |
| Allergic rhinitis | J30 | 1 | Association (3) |
| Respiratory disorders | Chapter X | | |
| In general | | 2 | Association (3) |
| Asthma | J46 | 7 | **Association (1)** |
| Diseases of the digestive system | Chapter K | | |
| In general | | 1 | Association (3) |
| Irritable bowel syndrome | K58 | 2 | Association?[b] (3) |
| Celiac disease | K90.9 | 3 | **Association (2)** |
| Skin disorders | Chapter XII | | |
| In general | | 1 | No association (3) |
| Atopic dermatitis | L20 | 1 | Association (3) |
| Alopecia areata | L63 | 1 | No association (3) |
| Acne (ICD-10: L70) | L70 | 1 | Association (3) |
| Musculoskeletal disorders | Chapter XIII | | |
| In general | | 3 | Association (3) |
| Rheumatoid arthritis | M05-M06 | 1 | No association (3) |
| Systemic lupus erythematosus | M32 | 2 | Association (3) |
| Fibromyalgia | M79.7 | 2 | Association (3) |
| Calvé-Legg-Perthes | M91.1 | 1 | Association (3) |
| Congenital syndromes and anomalies | Chapter XVII | 12 | |
| Symptoms/signs involving the urinary system | **R30-R39** | | |
| In general | | 1 | No association (3) |
| Enuresis | R32 | 3 | Association?[b] (3) |

*Note.* ICD-10 = International Classification of Diseases; Conditions classified in (1) or ( 2) in bold.
[a]The reported studies were classified into conditions (1) where the association between ADHD and the somatic disease is well established, (2) where there is tentative evidence for an association, and (3) where evidence is still too weak to make conclusions.
[b]Conflicting evidence. One study shows no association, another study/studies show association. See text for more information.

symptoms. A high symptom score on ASRS is not sufficient to clinically diagnose ADHD in adults but is frequently used in research literature to define study populations with possible ADHD (Kessler et al., 2005). The Wender Utah Rating

Scale (WURS) retrospectively assesses symptoms of ADHD in childhood (Ward, Wender, & Reimherr, 1993). For additional measurements, see Supplement 3.

*Measure of obesity.* Body mass index (BMI) is defined as weight in kilograms divided by height in meters squared. In adults, <18.5 kg/m$^2$ is defined as underweight, 18.5 to <25 kg/m$^2$ is defined as normal, 25.0 to <30 kg/m$^2$ is defined as overweight, and a BMI of ≥30 kg/m$^2$ is defined as obese (WHO, 1995). BMI is as simple and easy way to evaluate obesity and is useful to evaluate obesity trends in the general population. However, BMI does not provide an accurate measurement of body fat, nor does it take sex, age, and ethnicity into account (Bhurosy & Jeewon, 2013). For additional measurements, see Supplement 3.

*Sleep measurements.* Polysomnography is used to record several physiologic parameters relevant to sleep, such as electroencephalography (EEG), electrooculography (EOG), electrocardiography (ECG), chin- and anterio tibialis electromyography (EMG), respiratory effort, airflow, and oximetry (Chesson et al., 1997). Polysomnography is used in assessing a number of different sleep-related disorders, such as restless legs syndrome periodic limb movements during sleep, central hypersomnias, circadian rhythm sleep disorder, and sleep-disordered breathing (Kushida et al., 2005). For additional measurements, see Supplement 3.

## Results

### Literature Search and Selection of Papers

A range of different medical conditions have been studied in connection with ADHD in adults, as shown in Table 1. Most studies represent small clinical samples of ADHD patients assessed for a limited number of comorbid conditions, or clinical studies of somatic diseases where comorbid aADHD or ADHD symptoms also were diagnosed. A limited number of population-based cohort studies have also been published during this 20-year period.

The diagnostic protocols and quality of the clinical assessments of ADHD varied between studies, as was the case for the somatic/medical comorbid conditions. However, for the purpose of this literature study, we did not consider it appropriate to limit this overview to a specific diagnostic protocol or classification system. Thus, the cited prevalences are not directly comparable.

ADHD comorbidity with sleep disorders or obesity has previously been reviewed. However, for the majority of conditions mentioned, the differences in research designs, the limited number of cases, and the fact that most conditions were only described in few studies made it unfeasible to perform meaningful meta-analyses of prevalences.

### Somatic Health in General

ADHD is associated with generally impaired somatic health (Nigg, 2013) and increased medical costs (Secnik, Swensen, & Lage, 2005) when compared with unaffected sex- and age-matched controls, even when no differences in health habits were identified (Spencer, Faraone, Tarko, McDermott, & Biederman, 2014). In a prospective U.S. study including 72 ADHD cases and 479 controls, ADHD was diagnosed through clinical interviews in adolescence. When reassessed at >10 years, having ADHD was significantly associated with impaired general physical health (Brook, Brook, Zhang, Seltzer, & Finch, 2013). When retrospectively investigating U.S. health care claims for 2006, matching adults with ADHD ($n$ = 31,752) to non-ADHD ($n$ = 95,256), adults with ADHD had more physical comorbidities and were more likely to use non-psychiatric health care compared with controls (Hodgkins, Montejano, Sasane, & Huse, 2011).

### Obesity (ICD-10: E66)

*Clinical samples.* Obesity is one of the most frequently reported comorbid medical conditions in aADHD. The prevalences of clinically diagnosed ADHD and suspected ADHD based on rating scales have been reported to be 10% to 32% in studies exploring adults with obesity or obesity treatment, mainly including female participants (Alfonsson, Parling, & Ghaderi, 2012; Altfas, 2002; Docet, Larranaga, Fernandez Sastre, & García-Mayor, 2010; Fleming, Levy, & Levitan, 2005; Levy, Fleming, & Klar, 2009; Pagoto et al., 2010; Vogel et al., 2015). Similarly, in a Dutch study with 202 clinically assessed aADHD patients and 189 controls, 16.8% of the ADHD patients had BMI 30 to 39, compared with only 3.7% of the controls ($p$ < .001; Bijlenga, van der Heijden, et al., 2013). In contrast, a small U.S. study (137 ADHD participants, 124 controls) found no significant differences between participants in age-corrected BMI (Biederman, Spencer, Monuteaux, & Faraone, 2010).

It is unclear whether the association between ADHD and obesity is dependent on ADHD subtypes (Davis et al., 2009), but there are indications of higher proportions of inattentive symptoms/subtypes (Altfas, 2002; Fleming et al., 2005).

*Non-clinical samples.* The above studies were conducted in clinical settings. When examining population-based, non-clinical samples, results have been less consistent. In a population-based U.S. study, Pagoto et al. assessed 6,735 participants between 18 and 44 years (52% females; Pagoto et al., 2009). A diagnosis of aADHD was associated with increased risk of overweight and obesity, also when adjusting for demographic characteristics and major depressive disorder, but not when controlling for binge eating disorder

in the past year. In a French study using ASRS to assess aADHD symptoms, the prevalence of being overweight and obese was approximately doubled for persons reporting ADHD symptoms (Caci, Morin, & Tran, 2014). In a German cross-sectional study including 1,622 residents between 18 and 64 years, the prevalence of ADHD based on self-reported symptoms in obese participants was 9.7% (de Zwaan et al., 2011). Similar to findings of Altfas and Pagoto et al. (Pagoto et al., 2009), the prevalence increased with the degree of obesity. The associations between estimated ADHD and obesity were significant when adjusting for sociodemographic characteristics, symptoms of anxiety and depression and also purging behaviors, indicating that the relationship between obesity and ADHD in adulthood is not fully explained by binge eating. A small non-clinical Canadian study also found associations between ADHD symptoms and overweight/obesity, independent of binge eating (Davis, Levitan, Smith, Tweed, & Curtis, 2006).

A population-based U.S. study included 34,653 participants who were asked about ADHD symptoms (Cortese, Faraone, Bernardi, Wang, & Blanco, 2013). In this study, remittent ADHD was not significantly associated with obesity, whereas there was an association in adults with persistent ADHD. However, after adjusting for mood and anxiety disorders, the association was no longer significant. In contrast, a 33-year follow-up study including 111 males, remittent, but not persistent ADHD was associated with obesity, also after adjusting for sociodemographic characteristics and lifetime mental disorders (Cortese, Ramos-Olazagasti, et al., 2013).

The prevalence and comorbidity of ADHD in older adults have generally been little explored. In a Dutch study including 231 random older participants from the population registries ($Mean_{age}$ = 71.6 years), 23 of the participants were clinically diagnosed with ADHD (Semeijn et al., 2013). In this age group, there was no association between ADHD and BMI or waist circumference.

*Meta-analyses*. In a meta-analysis by Cortese et al., on the association between aADHD and obesity, 11 data sets with a total of 2,046 aADHD participants and 63,747 controls were analyzed, including previously unpublished studies (Cortese et al., 2015). Studies of individuals in bariatric clinics were excluded. The pooled prevalence of obesity was 28.2% (95% confidence interval [CI] = [22.8%, 34.4%]) in adults with ADHD relative to 16.4% [13.4%, 19.9%] in those without ADHD. When analyzing all age groups, age did not influence the association between ADHD and obesity, indicating that the relationship may be present from childhood (Cortese et al., 2016). This was supported by two prospective cohort studies from the United States (Anderson, Cohen, Naumova, & Must, 2006; Cortese, Ramos-Olazagasti, et al., 2013). The association between ADHD and obesity found in the meta-analysis by Cortese et al. remained significant when limiting to studies where ADHD was diagnosed by direct interview, using directly measured height and weight and after adjusting for confounding factors.

In a meta-analysis conducted by Nigg et al., a total of 43 population-based samples or case-control studies including 703,937 participants in all age groups were included (Nigg et al., 2016). The pooled effect size expressed as odds ratio (OR) was 1.22 [1.11, 1.34], increasing to 1.37 [1.19, 1.58] when limiting data to adults of 18 years or more, and was not significant for children.

*Combined ADHD and obesity comorbid with other conditions*. The combination of obesity and ADHD also shows comorbidity with other psychiatric disorders, for instance mood and anxiety disorders (Cortese, Faraone, et al., 2013), and disturbed eating behavior/binge eating (Alfonsson et al., 2012; Davis et al., 2006; Nazar et al., 2014; Strimas et al., 2008). Compared with obese adults without ADHD, obese people with ADHD symptoms are three times more likely to suffer from abnormal eating behaviors (Docet, Larranaga, Perez Mendez, & Garcia-Mayor, 2012). Obesity is also associated with excessive sleepiness, which may produce ADHD symptoms (Cortese, Konofal, & Lecendreux, 2008). A mediation analysis conducted as part of a clinical study, including 114 patients with obesity, 202 aADHD patients, and 154 controls, showed that both sleep duration and unstable eating patterns mediated the association between BMI and ADHD symptoms. A link between ADHD, obesity, and iron deficiency has also been discussed (Cortese & Angriman, 2014).

*Implications for treatment.* Several of the cited studies have emphasized the importance of recognizing comorbid conditions for planning optimal treatment of either ADHD or obesity. Treatment for obesity in people with ADHD may be less successful compared with obese people without ADHD (Altfas, 2002; Pagoto et al., 2010), and treatment of comorbid ADHD in obese individuals may improve the treatment for obesity (Cortese & Castellanos, 2014). Clinicians should also consider abnormal eating behaviors as contributing to obesity in ADHD patients (Cortese & Morcillo-Peñalver, 2010; Nazar et al., 2014).

Treating ADHD successfully might help people with obesity and ADHD to better manage overeating ( Davis, 2009), reduce self-blame, and facilitate the process of regaining control for persons with abnormal eating behaviors (Cortese, Bernardina, & Mouren, 2007). Behavioral treatment may contribute to weight reduction, but this has not yet been investigated in well-controlled studies (Cortese & Morcillo-Peñalver, 2010). ADHD medication may act on brain pathways involving both ADHD and mediating abnormal eating behaviors (Cortese, Angriman, et al., 2008). It has been hypothesized that stimulant treatment may

decrease impulsiveness and thus improve abnormal eating behaviors (Cortese & Morcillo-Peñalver, 2010). Treatment of comorbid ADHD in obese individuals may improve the otherwise poor effects of standard treatment strategies for obesity (Cortese & Angriman, 2014). This is supported by a small Canadian study where ADHD patients treated with stimulant medication had a significant weight reduction, whereas the weight increased in the non-medicated group (Levy et al., 2009). Furthermore, a meta-analysis by Cortese et al. limited to studies on unmedicated patients only showed a pooled estimate for obesity of OR = 1.43 [1.23, 1.67], compared with OR = 1.00 [0.87, 1.15] when limiting to medicated patients only (Cortese et al., 2016).

Finally, clinicians should be aware that comorbid anxiety and mood disorders may be more directly linked to obesity than to ADHD itself, and also take these disorders into account when planning treatment (Cortese, Faraone, et al., 2013).

### *Restless Legs Syndrome (RLS; ICD-10: G25)*

RLS is a neurological disorder which makes it difficult to fall asleep. RLS has a reported population prevalence of 3% to 34%, generally increasing by age and highest in women (Allen et al., 2005; Milligan & Chesson, 2002; Rijsman, Neven, Graffelman, Kemp, & de Weerd, 2004). It is characterized by an unpleasant feeling in the feet or other limbs, combined with an urge to move the limb to relieve the discomfort. The symptoms primarily occur when a person is relaxed or trying to sleep, and is often combined with paresthesias or dysesthesias. Poor quality of sleep associated with RLS can lead to hyperactivity and lack of concentration, and dopaminergic agents are used to treat the condition.

Two small studies showed that the prevalence of RLS is higher in persons with ADHD compared with controls (Schredl, Alm, & Sobanski, 2007; Zak, Fisher, Couvadelli, Moss, & Walters, 2009), and another small study showed that ADHD is also more common among patients with RLS compared with controls (Wagner, Walters, & Fisher, 2004). People with combined ADHD and RLS had more severe ADHD symptoms compared with those with ADHD without restless legs symptoms (Zak et al., 2009). In a German population- based sample (Roy et al., 2015), crude analysis showed that aADHD was associated with RLS. However, this association was no longer significant when adjusting for sleep disturbances. Pearson et al. reported a non-significant increase in the use ADHD medication (amphetamines) in 110 restless legs patients ($M_{age}$ 61 years; $p = .09$) compared with 54 age- and race-matched controls (Pearson et al., 2008). Steinlechner (Steinlechner et al., 2011) found that parents of children with ADHD had an increased risk of RLS compared with the population prevalence. There is also evidence of increased psychiatric comorbidity and RLS in families with ADHD (Steinlechner et al., 2011), and that symptoms of restless legs are related to depressive symptoms among ADHD patients (Schredl et al., 2007). Appropriate management of RLS can in some cases cause improvement of the comorbid disorder (Becker & Novak, 2014).

### *Epilepsy (ICD-10: G 40)*

Epilepsy is a common neurological brain disorder defined as "an enduring predisposition to generate epileptic seizures" and "the neurobiologic, cognitive, psychological, and social consequences of this condition" (Fisher et al., p. 471, 2005).

The cognitive dysfunction and behavioral disturbances associated with epilepsy have similarities with both the core symptoms and adjunctive features of ADHD. The cognitive deficits may be a consequence of recurrent seizure activity in the brain, adverse effects of anti-epileptic drugs, or it could represent an inherent part of the syndrome.

The prevalence of epilepsy in the general population is estimated to be around 0.4% to 1% (Forsgren, Beghi, Oun, & Sillanpaa, 2005; Russ, Larson, & Halfon, 2012), with decreasing prevalence and incidence with age. Thus, like for ADHD, the majority of cases with childhood-onset epilepsy will remit over time, although accompanying symptoms, comorbidity, and impairment may remain (Sillanpaa et al., 2015).

A reciprocal comorbidity between ADHD and epilepsy is well known in pediatric populations (Davis et al., 2010; Socanski, Aurlien, Herigstad, Thomsen, & Larsen, 2013); however, less is known about the comorbidity between the two disorders in adults. We found only two studies investigating the prevalence and co-occurrence of ADHD in adult patients with epilepsy (from both the same group and survey [Ettinger et al., 2015; Ottman et al., 2011]) and no published study investigating the prevalence of epilepsy in adult patients with ADHD. In their population-based, longitudinal health survey including more than 172,000 adults aged 18 years or more, Ottman et al. (2011) found a prevalence ratio of ADHD of 2.4 (2.0-2.8) among adults with epilepsy relative to a control group without epilepsy. Both the diagnoses of epilepsy and ADHD were based on self-reported lifetime occurrence of the disorders. In a follow-up of these data, Ettinger et al. (2015) investigated the presence and impact of ADHD symptoms in adults with self-reported epilepsy (Ettinger et al., 2015). Using ASRS, they found that 18.4% of adults with epilepsy screened positive for ADHD. A positive screen for ADHD was associated with greater severity of epilepsy (frequency of seizures, more use of anti-epileptic drugs), more comorbidity with anxiety and depression, lower quality of life, and worse functioning/more disabilities in work and social life. A Dutch study found that 2.4% of patients with epilepsy

admitted to a special clinic for epilepsy were diagnosed with ADHD (van der Feltz-Cornelis & Aldenkamp, 2006), compared with a 1% prevalence of ADHD in the Dutch population (Kooij et al., 2005).

The comorbidity between ADHD and epilepsy may have diagnostic, prognostic, and treatment implications for both disorders. Central stimulants may theoretically increase seizure susceptibility, although the documentation for this in patients with epilepsy is limited and shows conflicting results (Brown, Becker, Pollard, & Anderson, 2013; Gonzalez-Heydrich et al., 2010). We found only two small studies of methylphenidate (MPH) treatment in adults with epilepsy (Moore, McAuley, Long, & Bornstein, 2002; van der Feltz-Cornelis & Aldenkamp, 2006); none of these demonstrated adverse effects of this treatment.

## *Migraine (ICD-10: G43)*

Migraine is an episodic headache disorder, with attacks of pain and time-limited neurological dysfunction. Migraine is common in the general population and usually starts in adolescence or early adulthood. The prevalence is approximately 10% to 15%, and females are more often affected than males (Fasmer, Halmoy, Oedegaard, & Haavik, 2011). Thus, compared with ADHD, migraine has a very different profile regarding its prevalence, gender distribution, and age of onset. Both migraine and ADHD have a strong genetic basis, and a similar well-established comorbid connection with both mood and anxiety disorders is found in clinical and epidemiological studies (Fasmer et al., 2012). Cognitive dysfunction is not usually thought to be associated with migraine, apart from changes occurring during acute attacks.

Two large Norwegian studies showed an association between ADHD and migraine. Using data from the Norwegian Prescription Database, a positive and significant association between prescription of anti-migraine and ADHD medication was found for all age groups between 20 and 50 years and for both genders, with ORs ranging from 1.8 to 2.8 (Fasmer et al., 2012).

In a cross-sectional study of aADHD patients ($n$ = 572) and community controls ($n$ = 675), the prevalence of migraine was higher in the patient group compared with the controls (28.3% vs. 19.2%, $p$ = .001) (Fasmer, Halmoy, Oedegaard, & Haavik, 2011). The difference from controls was more marked for men (22.5% vs. 10.7%, OR = 2.43, CI = [1.51, 3.90]) than for women (34.4% vs. 24.9%, OR = 1.58, CI = [1.13, 2.21], although not significanlty so. Among the controls, the presence of migraine was associated with higher scores on both ASRS and WURS.

## *Sleep Disorders (ICD-10: G47)*

ADHD and ADHD symptoms in adults are related to a variety of sleep problems and sleep-related disturbances, both in clinical and non-clinical samples (Boonstra et al., 2007; Fargason, Hollar, White, & Gamble, 2013; Gau et al., 2007; Kass, Wallace, & Vodanovich, 2003; Oosterloo, Lammers, Overeem, de Noord, & Kooij, 2006; Schredl et al., 2007; Surman et al., 2009; Vogel et al., 2015; Walters, Silvestri, Zucconi, Chandrashekariah, & Konofal, 2008; Yoon, Jain, & Shapiro, 2012). Fisher et al. (2014) found that 80% of adults with ADHD reported sleep problems, regardless of sex and ADHD subtype. Sleep problems were more common in aADHD than in controls, also when taking psychiatric comorbidity and psychotropic medication into account (Schredl et al., 2007; Surman et al., 2009). Furthermore, persons with sleep problems performed worse on neuropsychological testing for attention (Fisher et al., 2014). Subjectively, patients with ADHD (without current psychiatric comorbidity or ADHD pharmacotherapy) reported worse sleep quality than controls (Philipsen et al., 2005), with more insomnia and problems with the sleep–wake pattern (Schredl et al., 2007). In a clinical sample of ADHD patients without psychiatric comorbidity and denying having insomnia symptoms, the ADHD sample reported more sleep quality problems compared with controls (Fargason et al., 2013). Measured objectively by polysomnography, adults with ADHD showed increased nocturnal activity compared with controls (Kooij, Middelkoop, van Gils, & Buitelaar, 2001; Middelkoop, Van Gils, & Kooij, 1997; Philipsen et al., 2005; Sobanski, Schredl, Kettler, & Alm, 2008), although one study found no difference between the groups (Boonstra et al., 2007). Several studies show that people with ADHD have longer sleep latency than controls (Boonstra et al., 2007; Sobanski et al., 2008), but the results are conflicting (three studies showing no difference between ADHD patients and controls: Kooij et al., 2001; Middelkoop et al., 1997; Philipsen et al., 2005).

Excessive daytime sleepiness affects 37% of adults with ADHD (Oosterloo et al., 2006), and appears to be a predictor of academic and overall functional impairment among students with ADHD (Langberg, Dvorsky, Becker, & Molitor, 2014). Furthermore, sleepiness and inattention can correlate in ADHD patients (Oosterloo et al., 2006). However, a small study by Sangal and Sangal (2004) showed no correlation between self-reported sleepiness and current inattentive symptoms, concluding that sleepiness is not a major contributor to inattention in aADHD individuals. It is important to be aware of the possible diagnostic confusion between aADHD and hypersomnia or narcolepsy using self-report questionnaires, as there is a high degree of symptom overlap (Oosterloo et al., 2006).

*Sleep and ADHD subtype.* Studies investigating the association between ADHD and comorbid sleep disorders with respect to ADHD subtypes show diverging results. Both inattentive and hyperactive-impulsive ADHD symptoms

have been associated with delayed sleep timing (Gamble, May, Besing, Tankersly, & Fargason, 2013). In a study of 62 students diagnosed with ADHD, students with the inattentive subtype did not differ from those with combined subtype on self-ratings of daytime sleepiness (Langberg et al., 2014). However, in two studies with a total of 62 non-medicated patients with ADHD, sleep problems were associated with having the combined ADHD subtype and symptoms of hyperactivity/impulsivity (Mahajan, Hong, Wigal, & Gehricke, 2010; Van Veen, Kooij, Boonstra, Gordijn, & Van Someren, 2010), and hyperactivity alone has been associated with decreased sleep duration (Gau et al., 2007). No significant associations were found between inattention and sleep quality, suggesting that sleep problems are connected with hyperactive-impulsive but not inattentive symptoms (Mahajan et al., 2010). In contrast to these results, which were based on small samples, other studies found that symptoms of inattention were most evidently associated with disturbed sleep, delayed circadian rhythm, and greater sleep need (Bae et al., 2010; Caci, Bouchez, & Bayle, 2009; Gau et al., 2007; Rybak, McNeely, Mackenzie, Jain, & Levitan, 2007; Voinescu, Szentagotai, & David, 2012).

*Symptom severity.* The severity of sleep problems is positively correlated with the number of ADHD symptoms, both among ADHD patients and in the general population (Gau et al., 2007; Mahajan et al., 2010; Schredl et al., 2007), also when taking ADHD comorbidity and medication into account (Schredl et al., 2007). The severity of daytime ADHD symptoms was also associated with the level of sleep problems (Schredl et al., 2007). Daytime sleepiness is associated with increased ADHD severity (Gamble et al., 2013), and is a predictor of academic and overall functional impairment among students with ADHD (Langberg et al., 2014).

*Insomnia (ICD-10: G47.0).* Insomnia implies dissatisfaction with sleep quantity or quality due to difficulty initiating sleep, maintaining sleep or early-morning awakenings. The symptoms impair daily functioning and affect about 6% to 12% of the adult population when ascertained according to formal diagnostic systems (Pallesen, Sivertsen, Nordhus, & Bjorvatn, 2014). Insomnia is common in people with ADHD; one study showed that 78% of the 40 non-medicated ADHD participants included suffered from sleep-onset insomnia (Van Veen et al., 2010), another study showed that the higher reports of insomnia among ADHD patients compared with controls may be related to the presence of depressive symptoms (Schredl et al., 2007). Sleep-onset insomnia, defined as difficulty getting to sleep at the desired bedtime, is the most problematic sleep problem reported in ADHD (Fisher et al., 2014), and is also a prominent initial side effect of stimulant medication.

*Circadian rhythm sleep disorder, delayed sleep phase type (ICD-10: G47.21).* Delayed sleep phase syndrome implies a disturbance in the normal circadian rhythm. It is characterized by a preference for late sleep and late rising, with sleep-onset insomnia when trying to get to sleep early and high activity in the late evening/night. The prevalence in the adult general population is estimated at 0.13% to 3.1% (Ando, Kripke, & Ancoli-Israel, 2002; Schrader, Bovim, & Sand, 1993). In a Dutch study by Bijlenga et al., including 202 adults with clinically diagnosed ADHD (18-65 years) and 189 controls, delayed sleep phase syndrome was more prevalent among aADHD patients (26%) than among controls (2%; Bijlenga, van der Heijden, et al., 2013). Adults with comorbid ADHD and insomnia were found to have significant circadian rhythm delay, the severity of ADHD symptoms and neuropsychological deficits correlating with the delay (Gamble et al., 2013; Rybak et al., 2007). In contrast to the controls, the patients with aADHD had the same prevalence of delayed sleep phase syndrome independent of age, the authors suggesting that delayed sleep phase syndrome in ADHD is not age related (Bijlenga, Van Someren, et al., 2013).

*Hypersomnia (ICD-10: G47.1 and G47.4).* Central hypersomnias such as idiopathic hypersomnia (G47.1) and narcolepsy (G47.4) cause excessive daytime sleepiness not caused by disturbances in nocturnal sleep or circadian rhythm. In a study including 74 patients with narcolepsy (G47.4) or idiopathic hypersomnia (G47.1), 19% of the affected patients fulfilled the criteria for aADHD when using self-report measures (Oosterloo et al., 2006). The overlap between symptoms of hypersomnia and ADHD might lead to misdiagnosis of both diagnoses (Oosterloo et al., 2006). However, both ADHD and hypersomnias are treated using psychostimulant medication, indicating a relation between these disorders (Oosterloo et al., 2006).

*Sleep-disordered breathing (ICD-10: G47.3 and G47.8).* Sleep-disordered breathing includes a spectrum of sleep-related abnormalities such as upper airway resistance syndrome (G47.8) and obstructive sleep hypopnea syndrome (G47.3), with symptoms such as snoring, episodes of breathing cessation during sleep, and excessive daytime sleepiness. Approximately 13% of men and 6% of women suffer from moderate to severe sleep-disordered breathing (Peppard et al., 2013). Of 78 severely obese adults with ADHD, 56% had sleep apnea (Levy et al., 2009). The cognitive and behavioral symptoms of obstructive sleep apnea such as inattention, poor planning, and restlessness, are similar to symptoms of ADHD (Ball, Wooten, & Crowell, 1999), and treatment may have a positive effect on ADHD symptoms (Youssef, Ege, Angly, Strauss, & Marx, 2011). In a case report of six adults with clinically diagnosed ADHD and impaired sleep quality, all had polysomnographic evidence of sleep-disordered

breathing (Surman, Thomas, Aleardi, Pagano, & Biederman, 2006). One study indicated that sleep-disordered breathing symptoms are mainly associated with increased BMI and smoking, and not ADHD symptomatology as such (Schredl et al., 2007). In a Turkish study of 81 treatment-naïve obstructive sleep apnea patients and 32 controls, the prevalence of ADHD symptoms was similar in patients with obstructive sleep apnea and controls (Oguzturk, Ekici, Cimen, Ekici, & Senturk, 2013). One study found a correlation between low oxygen saturation and hyperactivity in patients with sleep-disordered breathing (Sangal & Sangal, 2004). In two small case studies with a total of nine aADHD patients, it was observed that treatment for sleep apnea relieved their ADHD symptoms, and some were rediagnosed as having sleep apnea instead of ADHD (Ball et al., 1999; Naseem, Chaudhary, & Collop, 2001). According to these results, sleep apnea may actually be misdiagnosed as ADHD.

*Periodic limb movements during sleep (ICD-10: G47.61).* In the disorder called periodic limb movements during sleep, contractions of muscles during sleep causes periodic episodes of repetitive limb movements. Unmedicated patients with ADHD show increased periodic limb movements during sleep compared with controls (Philipsen et al., 2005; Sobanski et al., 2008).

*Impact of stimulant medication.* Sleep problems are present in unmedicated adults with ADHD, but stimulant treatment is also associated with dysregulation of sleep. Common initial side effect of stimulant medication is insomnia or delayed sleep-onset latency (Kirov & Brand, 2014; Kooij & Bijlenga, 2013). Atomoxetine may also cause insomnia as an adverse effect (Adler, Liebowitz, et al., 2009). It varies between individuals whether stimulants cause insomnia or not, and sleep problems such as sleep-onset latency may decrease with time as the medication is finished titrated and ADHD symptoms improve (Stein, Weiss, & Hlavaty, 2012). If ADHD medication affects the circadian rhythm, the effect on sleep may be less obvious and appear later (Stein et al., 2012).

Subjectively measured, ADHD participants using methylphenidatereported an improvement in sleep quality (Kooij et al., 2001). A study of the central stimulant lisdexamphetamine including 420 participants showed no difference in global sleep quality among aADHD patients receiving lisdexamphetamine compared with placebo, and daytime functioning in the stimulant treatment group improved compared with the aADHD group receiving placebo (study not included in the literature search, as it is not a study primarily on comorbidity; Adler, Goodman, Weisler, Hamdani, & Roth, 2009). A clinical study including 80 aADHD patients all denying insomnia symptoms (treated with stimulants, $n = 39$; with non-stimulants, $n = 15$ and with no medication, $n = 26$), showed significantly more sleep disturbance and prolonged sleep latency compared with controls ($n = 25$). This result indicated that medical treatment, including stimulant treatment, did not account for the sleep quality problems in the aADHD group (Fargason et al., 2013).

Objectively measured, sleep-onset latency increased (Boonstra et al., 2007) and sleep duration (Gamble et al., 2013) was reduced in patients treated with stimulant medication compared with those without such medication, although no change (Kooij et al., 2001) and less sleep latency were also reported (Sobanski et al., 2008). Objectively measured, sleep quality and efficiency improved (Boonstra et al., 2007; Sobanski et al., 2008) in ADHD participants using MPH compared with placebo (Boonstra et al., 2007) or compared with a premedication baseline (Sobanski et al., 2008). Also when adjusted for depression and anxiety symptoms, sleep was more consolidated with less interrupted sleep (Boonstra et al., 2007). Regarding the impact of MPH treatment on nocturnal activity, the results are conflicting: Sobanski et al. (2008) found unchanged number of periodic limb movements during sleep in contrast to Kooij et al. (2001) who found reduced nocturnal activity. Improvements in sleep quality may, however, not be directly related to stimulant medication, as the same proportion (one third) of a total of 831 ADHD participants ($n = 831$) experienced sleep improvement independent of receiving stimulant treatment or placebo (Surman & Roth, 2011).

*Treatment.* ADHD is a 24-hr disease, with symptoms appearing both at day- and nighttime (Stein et al., 2012). Before starting treatment for ADHD, patients should be screened for sleep disorders and sleep patterns, to more easily track changes in sleep associated with stimulant treatment (Stein et al., 2012). Sleep disorders are associated with cognitive impairment, thus ADHD symptomatology may improve if comorbid sleep disorders are adequately treated in addition to specific treatment for ADHD (Schredl et al., 2007). If the patient is using medical treatment for ADHD and has sleep problems, give advice on sleep hygiene and consider reducing the stimulant treatment in the late afternoon, add a small dose of stimulant treatment earlier in the evening or switch to non-stimulant medication (Brown & McMullen, 2001; Hvolby, 2015; Lecendreux & Cortese, 2007). Usually, insomnia as a side effect of stimulant treatment attenuates after 1 to 2 months treatment (Lecendreux & Cortese, 2007). When treating aADHD with delayed sleep phase syndrome, one can combine stimulant treatment with exogenous melatonin together with bright light therapy and good sleep hygiene; Kooij et al. describe this treatment in detail (Kooij & Bijlenga, 2013).

## *Other Neurological Disorders (ICD-10: Chapter XI)*

*Dementia with Lewy bodies (ICD-10: G31.83).* Symptoms of dementia with Lewy bodies include mental decline,

Parkinson-like motor symptoms, sleep disturbances, and hallucinations. In a study from Argentina including patients with Lewy body dementia ($n = 109$), Alzheimer's disease ($n = 251$), and sex-, age-, and education-matched controls ($n = 149$), previous symptoms of aADHD were associated with risk of Lewy body dementia (Golimstok et al., 2011). The prevalence of previous ADHD symptoms was significantly higher than in both the Alzheimer group (OR = 4.9 [2.8, 8.4]) and the control group (OR = 5.1 [2.7, 9.6]). ADHD symptoms were tested according to *DSM-IV* criteria using WURS and ASRS, and in patients with cognitive impairment information was obtained from an informant knowing the patient for at least 10 years. Both ADHD and Lewy body dementia are related to a hypodopaminergic state; this being a possible explanation for the association (Golimstok et al., 2011).

*Myotonic dystrophy 1 (DM1; ICD-10: G71.1).* Douniol and coauthors described the psychiatric phenotype of the juvenile form of DM1(Douniol et al., 2009), the most common inherited neuromuscular disease, with autosomal dominant transmission. The study included 28 people with juvenile DM1 from 7 to 24 years of age. In the total sample, including both children and adults, 28.6% had ADHD, all inattentive subtypes. ADHD was measured by ASRS in the adults. A study by Echenne et al. describes adult cases with comorbid ADHD and myotonic dystrophy, but it is not known how ADHD was diagnosed or if the participants were tested for ADHD as adults (Echenne et al., 2008).

*Chronic fatigue syndrome (CFS; ICD-10: G93.3).* CFS is characterized by a combination of prolonged and severe fatigue with non-specific somatic manifestations and cognitive symptoms, including difficulties in concentration, short-term memory and thinking, impaired attention and slow processing speed (Valdizán Usón & Idiazábal Alecha, 2008). These cognitive symptoms may mimic symptoms of ADHD and possibly share some underlying pathophysiological mechanisms (Bellanti et al., 2005). Fatigue symptoms are also commonly reported in aADHD and may affect neuropsychological functioning (Fisher et al., 2014).

We found only one study on prevalence of aADHD in CFS patients (Sáez-Francàs et al., 2012). In their clinical sample of 158 adults with CFS, 97% women, Sáez-Francàs et al. found that 47 patients (29.7%) fulfilled diagnostic criteria for childhood ADHD assessed retrospectively, and 33 patients (20.9%) were found to still meet criteria for ADHD in adulthood. We found no studies on the prevalence of CFS in samples of adults with ADHD, nor any population-based studies on CFS and aADHD; thus, the possible relationship between these conditions and the magnitude of the problem is not clear. Young et al. (2013a) described three female cases with CFS (38-58 years), who were also found to fulfill criteria for ADHD dating back to childhood (Young, 2013a). In all three cases, symptoms of chronic fatigue and/or pain, and general and occupational functioning, improved after treatment with central stimulants.

Despite the limited amount of literature, the suggested association between ADHD and CFS is clinically interesting, as central stimulants, the first-line pharmacological treatment of ADHD, have shown positive effects on both the core symptom of CSF, that is, chronic fatigue (Blockmans, Persoons, Van Houdenhove, & Bobbaers, 2006), and the associated cognitive symptoms, such as executive dysfunction (Young, 2013b).

## *Endocrine Diseases (ICD-10: E00-E35)*

*Resistance to thyroid hormone (RTH; ICD-10: E07.8).* RTH usually involves mutations in the thyroid hormone receptor β gene and is often transmitted as an autosomal dominant trait. Classical features include ADHD, tachycardia, and growth delay. Brucker-Davis et al. (1995) described 104 RTH patients and 114 unaffected participants, both children and adults. ADHD was found to be common among the RTH patients; more common in males (72%) than in females (43%). Among adults, 42% had ADHD in the RTH group compared with 4% in the non-RTH group. Full-scale IQ was lower among RTH patients than among controls, and 38% of the patients had IQ less than 1 standard deviation (*SD*) below the mean; however, there was no correlation between IQ and ADHD in the RTH patients.

*Hypothyroidism (ICD-10: E00-E03).* Hypothyroidism is an endocrine disorder in which the thyroid gland does not produce enough thyroid hormone, leading to a large range of symptoms, including weight gain, fatigue, and poor ability to tolerate cold. In the previously mentioned study by Hodgkins et al., investigating U.S. health care claims for 2006 (aADHD: 31,752; non-ADHD: 95,256), hypothyroidism was significantly more common in adults with ADHD compared with those without ($p \leq .0001$; Hodgkins et al., 2011).

*Diabetes (ICD-10: E10-E14).* Pancreas insulin cells diabetes mellitus is a heterogeneous group of metabolic diseases characterized by high blood glucose levels over prolonged periods of time. Interestingly, diabetes (ICD-10: E10-E14) was significantly higher in the non-ADHD group compared with the ADHD group in the above-mentioned study investigating U.S. health care claims ($p \leq .0001$; Hodgkins et al., 2011). However, a Dutch study including older adults with ADHD ($n = 23$) and controls ($n = 208$) found no difference in self-reported diabetes between the individuals with ADHD and controls (Semeijn et al., 2013). Furthermore, a U.S. study including adult patients with ADHD ($n = 98$) and controls ($n = 100$) showed no significant differences in the number of self-reported diabetes (Spencer et al., 2014).

## Metabolic Disorders (ICD-10: E70-E90)

Bijlenga et al. have reported a significantly increased frequency of self-reported metabolic disorders among adults with ADHD compared with controls (Bijlenga, van der Heijden, et al., 2013). We also identified studies describing the co-occurrence of aADHD or ADHD symptoms with several different inborn metabolic diseases:

*Albinism (ICD-10: E70.3).* Albinism is an inherited disorder causing an absence or reduction of melanin in the hair, skin, and/or eyes. The prevalence of albinism worldwide is estimated to 1/17,000 (0.006%), although it varies considerably over different continents (Gronskov, Ek, & Brondum-Nielsen, 2007). In their study of albinism and comorbid ADHD, Kutzbach et al. found that 17 of 75 children (22.7%) and 3 of 44 adults (6.8%) met criteria for ADHD, and that the majority of these had the hyperactive/impulsive subtype (Kutzbach, Summers, Holleschau, King, & MacDonald, 2007).

*Maple syrup urine disease (MSUD; ICD-10: E71.0).* MSUD is an inborn error of metabolism, with clinical features including neuropsychiatric disturbances and neurologic deterioration. Muelly et al. (2013) studied neuropsychiatric symptoms in 37 patients with MSUD aged 5 to 35 years; 26 treated with diet and 11 with liver transplantation. They found the cumulative lifetime incidence of ADHD to be 54% among MSUD patients on dietary therapy and 82% among patients with liver transplants. They concluded that neurochemical deficiencies correlated with neuropsychiatric morbidity (Muelly et al., 2013).

## Diseases of the Circulatory System (ICD-10: Chapter IX)

Possible increased risk of cardiovascular events due to stimulant treatment of ADHD is an important clinical issue. Long-term (≥12 months) stimulant treatment is associated with increased heart rate and increased blood pressure, but no evidence has so far indicated elevated risk of serious cardiovascular events (Hammerness, Karampahtsis, Babalola, & Alexander, 2015). Although this is a debated issue, only a few studies have investigated the comorbidity of ADHD and cardiovascular disorders per se; none of them focusing on cardiovascular disease alone.

The study by Bijlenga et al. on sleep patterns (202 aADHD patients, 189 controls) reported a significantly increased frequency of self-reported cardiovascular disease among adults with ADHD compared with controls (Bijlenga, van der Heijden, et al., 2013). In contrast to this, another Dutch study including older ($M_{age}$ = 71.6) adults with ADHD ($n$ = 23) and controls ($n$ = 208) found no difference in self-reported hypertension and cardiovascular disease between the ADHD individuals and controls (Semeijn et al., 2013). In line with this result, no significant differences between adults with ADHD and controls were found concerning hypertension and other cardiovascular diseases in the previously mentioned study investigating U.S. health care claims for 2006 (31,752 aADHD matched with 95,256 non-ADHD individuals; Hodgkins et al., 2011). Furthermore, a U.S. study including adult patients with ADHD ($n$ = 98) and controls ($n$ = 100) showed no significant difference in the number of self-reported heart attacks (Spencer et al., 2014).

## Atopic Diseases/Allergic Diseases (Primarily ICD-10: Chapter X and Chapter XII)

The results from a systematic review including mainly studies on children concluded that atopic disease in general was not associated with ADHD, but that atopic eczema specifically appears to be independently associated with ADHD (Schmitt, Buske-Kirschbaum, & Roessner, 2010). For further information on atopic eczema, we refer to the paragraph describing skin disorders. Information on the allergic disorders asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis was collected in a study using data from the Taiwan National Health Insurance Research Database from 1996 to 2010. Patients with ADHD ($n$ = 5,811; ICD-9-CM diagnosis), patients with tic disorder, patients with comorbid ADHD and tic disorder ($n$ = 349), and age/gender-matched controls were retrieved (Chen et al., 2013). Most of the ADHD patients included were adolescents and young adults. Compared with the control group, the ADHD group showed a significantly increased risk of having allergic comorbidities after adjusting for age, gender, and comorbid psychiatric disorders. The comorbid ADHD and tic disorders group showed the highest prevalence of allergic disease. The results pointed to an additive effect of ADHD and tic disorder on the association with allergic comorbidities.

*Allergic Rhinitis (ICD-10: J 30).* A German study focused on allergic rhinitis, and by collecting information from the German National Health Insurance beneficiaries, 111,394 patients with allergic rhinitis in 2005/2006 were retrieved (Schmitt, Stadler, Kuster, & Wustenberg, 2016). In addition, information on different comorbid disorders was collected, including hyperkinetic disorder (F 90). The results showed that ADHD was more prevalent among those with allergic rhinitis compared with those without, RR = 1.21 [1.13, 1.29]; however, specific information on adults with ADHD was not given.

## Respiratory Disorders ICD-10: Chapter X

*Asthma (ICD-10: J 46).* Two studies reported an association between unspecific lung diseases and aADHD (Bijlenga, van der Heijden, et al., 2013; Semeijn et al., 2013), while

there are several studies on aADHD and comorbid asthma (Chen et al., 2013; Fasmer, Halmoy, Eagan, Oedegaard, & Haavik, 2011; Fasmer, Riise, et al., 2011; Hodgkins et al., 2011; Karlstad, Nafstad, Tverdal, Skurtveit, & Furu, 2012; Secnik et al., 2005; Spencer et al., 2014). Asthma is an inflammatory disorder of the airways, following a chronic course, but with episodic worsening. Common symptoms are wheezing and coughing, caused by reversible airflow obstruction and bronchospasm (Handoyo & Rosenwasser, 2009). As is the case with ADHD, the disorder usually starts in childhood, and also similar to ADHD, psychiatric disorders, in particular mood and anxiety disorders, are often comorbid problems (Goodwin, Jacobi, & Thefeld, 2003). Tobacco smoking may be another factor that is common to these conditions (Thomson, Chaudhuri, & Livingston, 2004). ADHD patients have a higher smoking prevalence than the general population. It is uncertain if smoking is a cause of asthma, but it aggravates symptoms among people prone to asthma, and passive smoking in childhood and prenatal exposure are associated with an increased risk of asthma (Fasmer, Halmoy, Eagan, et al., 2011).

The relationship between aADHD and asthma has been investigated both in clinical samples and using registry data. In a U.S. database search, adults with ADHD were significantly more likely to have a comorbid diagnosis of asthma compared to controls ($p < .01$ (Secnik et al., 2005). Data from the Norwegian Prescription Database showed a higher-than-expected occurrence of ADHD in 20- to 29-year-olds treated for asthma compared with the general population (Karlstad et al., 2012). Similarly, another study using the Norwegian Prescription Database showed that patients prescribed central stimulants were also prescribed anti-asthmatic drugs more often than the remaining population (Fasmer, Riise, et al., 2011). In this study, a weaker relationship between ADHD and asthma was found in the younger age groups (<20 years) than in the older age groups (>20 years), although the associations were significant across all ages. In a cross-sectional questionnaire-based study of 594 aADHD patients compared with 719 persons from the general Norwegian population, the prevalence of self-reported asthma was significantly higher in the ADHD group than in controls (24.4% vs. 11.3%). In addition, controls with asthma had higher scores on ratings of ADHD symptoms (Fasmer, Halmoy, Eagan, et al., 2011). These studies point to a comorbidity of ADHD and asthma, apparently most pronounced for adult patients, although none of these four studies adjusted for smoking as a possible confounder.

## *Diseases of the Digestive System (ICD-10: Chapter K)*

*Irritable bowel syndrome (IBS; ICD-10: K58).* IBS causes abdominal pain and bloating, and can lead to both diarrhea and constipation. In the previously mentioned U.S. database search by Secnik et al. (2005), 2,252 adults diagnosed with ADHD did not differ significantly from the corresponding large control group in the prevalence of IBS (Secnik et al., 2005). However, the study by Hodgkins et al. (2011), based on U.S. health care claims for 2006 (aADHD: 31,752; non-ADHD: 95,256), found that adults with ADHD reported significantly more IBS compared with those without ($p \leq .0001$; Hodgkins et al., 2011).

*Celiac disease (CD; ICD-10: K90.9).* CD is an autoimmune disease where the ingestion of the wheat protein gluten leads to damage and subsequent atrophy of the intestinal villi, and thus may compromise nutrient absorption. The primary symptoms are diarrhea, abdominal pain, or discomfort, with weight loss and anemia being common complications. CD is estimated to affect 1% to 2% of the population, with increasing prevalence in later years due to new screening methods and the detection of asymptomatic patients.

Zelnik, Pacht, Obeid, and Lerner (2004) studied the prevalence of several neurological disorders in a sample of 111 young patients with CD ($M_{age}$ = 20 years, 42% men), and found that 23 patients (20.7%) had a learning disability (LD) and/or ADHD, compared with 10.5% in a control group without CD, recruited from the same pediatric gastroenterological clinic (Zelnik et al., 2004). Interestingly, the gender distribution of LD/ADHD was very even in the CD group (20.3% females and 21.2% males), whereas male participants were more affected in the control group (12.9% vs. 8.7%), as expected in the general population.

Niederhofer & Pittschieler (2006) found an overrepresentation of ADHD symptoms in patients with CD and investigated possible effects of a gluten-free diet on ADHD symptoms in a sample of patients with CD consisting of both children and adults ($n$ = 78, age = 3-57 years [$M$ = 19.3]; (Niederhofer & Pittschieler, 2006). Interestingly, although results should be interpreted with caution due to the small sample size and open study design, they found a significant reduction of ADHD-like symptomatology after at least 6 months of gluten-free diet. The reduction of ADHD symptoms further correlated with pain reduction. The same authors also investigated the presence of CD in a primary sample of patients with ADHD ($n$ = 67, 52 males, age = 7-42 years [$M$ = 11.4]), and found that 10 of the 67 patients were positive for CD (seven males, 13.5%, and three females, 20.0%), defined by the presence of CD-specific antibodies (antigliadine and antiendomysium) in blood serum. A gluten-free diet of at least 6 months was associated with improvement of ADHD symptoms also in this patient sample (Niederhofer, 2011).

## *Skin Disorders (ICD-10: Chapter XII)*

For unspecific skin disorders, the study by Bijlenga et al. on ADHD and sleep patterns showed no differences in

self-reported skin disorders between 202 aADHD patients and 189 controls (Bijlenga, van der Heijden, et al., 2013).

*Atopic dermatitis (ICD-10: L 20).* Atopic dermatitis is a chronic, pruritic inflammatory skin condition characterized by pruritus and red swollen skin. Several studies, mainly on children, have shown a positive association between atopic dermatitis and ADHD symptoms (Gee & Bigby, 2011). For adults, a Turkish study investigating 60 adult patients with atopic dermatitis and 50 non-atopic control participants found significantly more ADHD symptoms in patients with atopic dermatitis than in controls, the association being strongest in females (Cicek et al., 2009). A self-report scale showed that features of inattention, hyperactivity, and impulsivity were all associated with atopic dermatitis, and the authors concluded that co-occurrence of ADHD should be taken into consideration when treating patients with atopic dermatitis.

*Alopecia areata (AA; ICD-10: L 63).* AA is a likely autoimmune disorder causing hair loss. A register-based study from Taiwan ($n$ = 5,117 patients with AA and $n$ = 20,468 controls) investigated psychiatric comorbidity in patients with AA and found no association with AA and aADHD (Chu et al., 2012).

*Acne (ICD-10: L70).* Acne is a skin disorder characterized by inflammation of the pilo sebaceous follicle. A registry-based U.S. study including both children and adults showed that ADHD was twice as likely to be associated with acne relative to all other dermatological disorders (Gupta, Gupta, & Vujcic, 2014), also when adjusting for age, sex, atopic dermatitis, anxiety, depression, and stimulant medication. However, there were few participants >18 years.

## *Musculoskeletal Disorders (ICD-10: Chapter XIII)*

Adults with ADHD report chronic musculoskeletal and skeletal complaints, including fibromyalgia (FMS), more frequently than controls without ADHD (Bijlenga, van der Heijden, et al., 2013; Spencer et al., 2014). Stray and coauthors (2013) investigated motor regulation problems and reported musculoskeletal pain in 25 adults with ADHD (all responders to treatment with MPH) and 23 control individuals. The adults with ADHD scored higher on tests indicating more motor problems than control individuals. As much as 80% of the ADHD patients reported widespread pain; pain level was more severe and more often widespread than in the control individuals. The authors concluded that motor inhibition problems and heightened muscle tone are, as in children with ADHD, increased in adults with ADHD, and that the more widespread and higher pain levels may represent long-term secondary effects of these muscular problems.

*Rheumatoid arthritis (ICD-10: M05-M06).* In the Dutch study including older adults with ADHD ($n$ = 23) and controls ($n$ = 208), no difference in self-reported rheumatoid arthritis (ICD-10: M05-M06) was found between the ADHD patients and controls (Semeijn et al., 2013).

*Systemic lupus erythematosus (SLE; ICD-10: M32).* SLE (ICD-10: M32) is an autoimmune connective tissue disorder where many internal organs in the body, as well as the nervous system, may be affected. Neuropsychiatric symptoms are common, as described in a systematic review by Meszaros and coauthors in 2012 (Meszaros, Perl, & Faraone, 2012). In a recent Chinese study, Gao and coworkers investigated whether SLE patients ($n$ = 117) had more ADHD symptoms than healthy age- and sex-matched controls ($n$ = 64; Gao, Lo, & Mok, 2015). ADHD symptoms were assessed by the ASRS. Possible ADHD was found in 7.7% of SLE patients and 6.3% of controls ($p$ = 1.0); however, SLE patients had more clinically significant items in the inattention domain of the ASRS than the controls ($p$ = .006), especially if they had previous cerebral involvement ($p$ = .004). Anxiety and depressive symptoms correlated with ADHD symptoms.

N-acetylcysteine (NAC) has been reported to improve psychiatric symptoms in various disorders (Berk et al., 2008; Bernardo et al., 2009). In a randomized- controlled trial, Garcia and coworkers (2013) investigated whether ADHD might serve as a marker for neuropsychiatric disease in SLE patients and as a target for treatment with NAC. They included 49 SLE patients and 46 matched healthy controls, and randomized 24 of the SLE patients to receive placebo or NAC in two dosages. The authors concluded that increased scores on the ASRS indicate previously unrecognized and clinically significant ADHD symptoms that respond to NAC treatment in SLE patients.

*Fibromyalgic syndrome (FMS; ICD-10: M79.7).* Studies focusing on the comorbidity between aADHD and FMS are few, small, and still exploratory in nature. In a sample of 201 women with FMS, 32.3% fulfilled criteria of childhood ADHD, compared with 2.5% in an aged-matched control group of healthy women (Reyero et al., 2011).

Based on clinical reports of aADHD with co-occurring fibromyalgic complaints, who experienced relief of their complaints after medication for ADHD, Krause et al. conducted a German pilot study to investigate the comorbidity between ADHD and FMS. Twelve patients with FMS were compared with 12 patients with pain of other origin. The FMS patients had significantly higher symptom scores of ADHD (both past and present) than the other pain patients (Krause et al., 1998).

In a Dutch study including 44 patients with FMS, 11 (25%) of the patients met the criteria for ADHD after being clinically interviewed (Derksen, Vreeling, & Tchetverikov, 2015).

*Legg-Calve-Perthes disease (LCPD; ICD-10: M91.1).* LCPD is a disease which leads to deformation of the femoral head, is diagnosed in children, and is associated with early hip dysfunction and osteoarthritis of the hip. Hailer and coauthors studied health-related quality of life, physical activity, and behavior patterns in 116 adult patients with LCPD, who had been treated at Uppsala University Hospital between 1978 and 1995 (Hailer, Haag, & Nilsson, 2014). The patients answered self-report questionnaires by interview using ASRS to assess ADHD symptoms. A total of 28% had ASRS scores corresponding to a likely ADHD diagnosis, and a higher ASRS score was associated with a lower score on quality of life questionnaires.

## *Congenital Syndromes and Anomalies (Mainly ICD-10: Chapter XVII)*

This is a heterogeneous disease entity where various organ systems are affected, either as isolated anomalies with largely unknown etiology occurring sporadically or as multiple anomalies which may or may not be part of known syndromes or associations. The anomalies may be associated with environmental exposures or have well-defined genetic causes. In all instances, ADHD symptoms may be an important feature of the condition, for some genetic syndromes even the presenting feature. If all the clinical criteria of ADHD are fulfilled, it is recommended to separately diagnose this as ADHD, irrespective of its association with other well defined and perhaps underlying illnesses (APA, 2013). Most of the research on syndromes and associated neuropsychiatric disorders such as ADHD and autism is based on children, while we focus on studies where adults are included.

*Tuberous sclerosis (ICD-10: Q85.1)* is an autosomal dominant genetic syndrome associated with neuropsychiatric manifestations such as mental retardation, autism spectrum disorders (ASD), and ADHD (de Vries et al., 2005). ADHD is assumed to be associated with brain lesions due to this disorder (Hunt, 1998). Muzykewicz et al. (2007) reported that 30% of 241 children and adults (average 20 years, range = 8 months - 63.4 years) with tuberous sclerosis had ADHD symptoms (Muzykewicz et al., (2007). A similar fraction of patients had anxiety or depression.

*Chromosomal aberrations* may also be associated with ADHD, as well as with other psychiatric disorders. The *22q11.2 deletion syndrome* (ICD-10: D82.1; velo-cardio-facial [VCFS] or DiGeorge syndrome) is among the most studied genetic syndromes in psychiatry. Whereas high rates of ADHD have been reported in children, psychotic disorders may be the most prominent psychiatric disorders in adulthood (Murphy, 2005); however, psychiatric morbidity in adults is not yet adequately documented (Baker & Vorstman, 2012). The clinical phenotype of this relatively common syndrome (1/2,000-1/4,000 live births) is highly variable. In their comprehensive review of 1,402 participants with VCFS (age = 6-68 years), Schneider et al. (2014) reported that ADHD was the most frequent psychiatric disorder in children (37.1%) and among the most common in adults (15.6%). In contrast to the general population, where the combined type of ADHD is the most common, most cases of VCFS had the inattentive form of ADHD. A similar prevalence of ADHD was found in a smaller study by Tang et al. (2014), where 31% of 112 cases with VCFS (age = 8-45 years, 37% ≥18 years) had ADHD, and 11% had psychosis. There was no significant effect of age on the prevalence of ADHD in this group nor in a study by Niklasson et al. where in-depth neuropsychiatric assessments were done on 100 consecutive patients with VCFS (16% ≥17 years; Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2009). ADHD was diagnosed in 30 individuals; nine of these also had ASD. Gothelf et al. assessed 51 consecutive patients with VCFS, aged 16 to 30 years (Gothelf et al., 2004). Twenty-one patients (41.2%) were diagnosed with ADHD ($M_{age}$ [*SD*] = 11.1 [6.9]), and this group also had a significantly greater prevalence of ADHD among their first-degree relatives. The authors concluded that ADHD in VCFS may have a genetic contribution, and that the VCFS-related developmental factors might play a lesser role.

Both children and adults with *trisomy 21* (Down's syndrome; ICD-10: Q 90; Capone, Goyal, Ares, & Lannigan, 2006; Edvardson et al., 2014) and *fragile X syndrome* (FXS; ICD-10: Q 99.2; Dorn, Mazzocco, & Hagerman, 1994; Tranfaglia, 2011) have an increased prevalence of behavioral problems and comorbid diagnoses, including ADHD. FXS is the most common hereditary cause of intellectual disability in men and also affects women. Hyperactivity symptoms in FXS usually decline with age (Tranfaglia, 2011). Unlike conventional X-linked disorders, men can be carriers of the syndrome. These carriers (FXS premutation) may have normal intelligence but differ in response inhibition and selective attention, neuropsychiatric symptoms also found in ADHD (Cornish et al., 2008; Dorn et al., 1994). With age, individuals with FXS premutation may develop more severe problems with inhibitory control. A small study from 1994 using a family informant method on 24 daughters of FXS carrier fathers and 32 daughters of control fathers found a significantly higher proportion of aADHD as well as other psychopathology among FXS carrier fathers (Dorn et al., 1994). It has been proposed to screen for FXS carrier status in ADHD individuals whose male family members have intellectual disability (Hay, 2008).

As opposed to the mentioned chromosomal aberrations, only hyperactivity symptoms associated with ADHD were found more frequently in *Angelman syndrome (ICD-10: Q93.5)* when compared with a similar control group of individuals with intellectual disability (Berry, Leitner, Clarke, & Einfeld, 2005). *Cornelia de Lange syndrome* (CdLS;

**Table 2.** Other Comorbid Disorders With Limited Information on the Association With aADHD.

| Comorbid disorder | Reference | Design | Study population | Result |
|---|---|---|---|---|
| STD | Hosain, Berenson, Tennen, Bauer, & Wu (2012) | Cross-sectional | 462 females (between 18 and 30 years). ASRS to assess ADHD symptoms. Self-reported lifetime diagnosis of STD. | [a]No significant association |
| Cancer | Bijlenga, van der Heijden, et al. (2013) | Case control | 202 clinically assessed aADHD patients ($M_{age}$ = 34.9), 189 controls ($M_{age}$ = 33.0). | No significant association |
| Cancer | Semeijn et al. (2013) | Case control | 23 participants with aADHD assessed by semistructured diagnostic interview (mean age 72.0), 208 controls (mean age 68.0). | No significant association |
| Congenitalesotropia | Olson, Louwagie, Diehl, & Mohney, (2012) | Case control | 42 congenitalesotropia patients, 20 controls. Age at ADHD diagnosis not specified | No significant association |
| Photophobia | Kooij & Bijlenga, (2014) | Online survey | 231 people with self-reported ADHD diagnosis/ADHD symptoms (mean age 36.7), 263 controls (mean age 38.4). | Significant association |

*Note.* aADHD = Adult ADHD; STD = sexually transmitted diseases.
[a]10% increased risk of being diagnosed with STD when comparing the ADHD symptom group with the control group, no longer statistically significant when adjusting for sociodemographic covariates.

*ICD-10: Q87.1*) is a very rare genetic disorder usually caused by de novo mutations. In their study of 69 CdLS patients, Kline et al. (2007) have described their physical and psychiatric disturbances, among which ADHD is one of several psychiatric diagnoses where the symptoms often worsen with age.

Regarding ADHD and comorbid anatomical anomalies that are not part of a well-known syndrome, there are few studies in adults. A large registry-based study from 2012 found an increased risk of ADHD persisting to adulthood in individuals born with oral clefts (ICD-10: Q 35-37; Halmoy, Klungsoyr, Skjaerven, & Haavik, 2012). Another study describing 447 adults with Fallot's tetralogy (TOF) found an increased prevalence of ADHD among TOF patients who had at least two additional "syndromic" features such as dysmorphic facies, learning disabilities, or voice abnormalities (Piran et al., 2011).

### *Enuresis (ICD-10: R32)*

The previously described study by Bijlenga et al. showed no differences in self-reported urinary symptoms in people with aADHD and controls (Bijlenga, van der Heijden, et al., 2013).

The diagnosis of enuresis in aADHD compared with controls is reported in two studies using information from U.S. claim databases. One study included 2,252 individuals diagnosed with ADHD according to ICD-9 during 1999-2001 matched with a similar number of controls (Secnik et al., 2005). Based on ICD-9 codes, there was no significant difference in the prevalence of enuresis between the groups. In a study investigating U.S. health care claims for 2006 (aADHD: 31,752; non-ADHD: 95,256), adults with ADHD were significantly more often diagnosed with enuresis compared with adults without ADHD ($p < .05$; Hodgkins et al., 2011).

In a French study including 1,171 adults, ASRS was used to measure aADHD. aADHD was significantly related to lifetime self-reported enuresis regardless of sex, OR = 5.8 [2.4, 14.1] (Caci et al., 2014).

### *Other Disorders*

Our search also identified some papers describing various other disorders, summarized in Table 2. For most of these disorders, no significant association with aADHD was reported. The exception was for photophobia, where 69% of the ADHD participants reported photophobia compared with 28% in the control group ($p = .001$; Kooij & Bijlenga, 2014).

## Discussion

In our systematic review, we have included 126 papers over the past 20 years mentioning aADHD in connection with somatic disease. We found a consistent association between aADHD and increased risk of obesity, sleep disorders, and asthma. Associations were also consistent for migraine and celiac disease. Less robust associations have been reported for a number of different disorders such as enuresis, irritable bowel syndrome, restless legs, epilepsy, chronic fatigue syndrome, , fibromyalgic syndrome, systemic lupus erythematosus and atopic dermatitis. One large population-based study (aADHD: $n$ = 31,752) and two smaller studies showed no association between aADHD and diseases of the circulatory system (Hodgkins et al., 2011; Semeijn et al., 2013; Spencer et al., 2014). In contrast, a small study by Bijlenga et al. showed an increased risk of self-reported cardiovascular disorder in

aADHD. Many rare congenital syndromes/malformations, including tuberous sclerosis and FXS, are reported to increase the risk of ADHD. However, under such conditions the ADHD symptoms may also be considered part of the syndrome itself and not a proper comorbid disorder.

We noticed several methodological limitations in the evaluated studies. Most studies were small. Many studies compared a case group with a control/comparison group. However, while the case group might be well defined and characterized, the control group was often less well defined, often based on self-selection and from a different source population than the cases. Information on recruitment and participation rates was sparse, and selection bias was difficult to assess. While the diagnosis of ADHD was often based on clinical interviews or validated self-report questionnaires, the comorbid conditions were sometimes based entirely on a single question to the individual about the condition being present or not. An example is the study by Bijlenga et al., which includes 202 clinically diagnosed ADHD patients and 189 controls non-randomly recruited from students and their acquaintances, and self-selected by posters in libraries and municipal buildings (Bijlenga, van der Heijden, et al., 2013). The numerous somatic diseases described were based solely on self-report from a general health questionnaire.

The larger studies were often based entirely on self-report questionnaires or on registries and databases. Large population-based disease registries may be more suitable to study comorbidity across many different diagnoses, in particular for less prevalent conditions. However, such registries can also be subject to systematic bias, depending on the diagnostic traditions in different countries (Polanczyk et al., 2007) and the covered population.

For details on characteristics of the individual studies with their associated sources of bias, see table in Supplementary 2.

Many studies on psychiatric comorbidity in somatic conditions have explicitly excluded "childhood" psychiatric conditions such as ADHD, as they are not included in commonly used structured psychiatric diagnostic interviews, such as The Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I; First, Spitzer, Gibbon, & Williams, 2002) or The Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). This systematic bias could give the false impression that ADHD is not a relevant psychiatric comorbidity in somatic disease among adults.

As mentioned in many of the cited articles, there are many reasons to systematically search for psychiatric disorders in somatic conditions and to screen for somatic diseases among psychiatric patients. For the individual patient, it is important to detect potentially treatable somatic diseases masking as a psychiatric disorder. The utility of this approach was illustrated in a recent report, showing that metabolic screening of individuals with psychosis revealed treatable metabolic disorders in a significant number of cases (Demily & Sedel, 2014).

ADHD is a prevalent condition, and patients with many different somatic conditions may exhibit ADHD symptoms either as a comorbid condition or as part of the somatic disease. Likewise, the lifestyle of ADHD patients may make them more vulnerable to certain somatic diseases. Thus, the identification of other treatable and possibly underlying conditions should be addressed in every diagnostic workup.

The presence of a known co-occurring somatic condition has important implications for ADHD treatment. For instance, stimulant therapy may be contraindicated or need careful monitoring in the presence of cardiac disease, hypertension, glaucoma, or liver failure (Kooij, 2012). However, stimulant therapy may have positive effects on the treatment of obesity, sleep disorders, CFS, and restless legs.

## *Pathophysiology*

Conditions classically thought to be disorders of the nervous system may also include alterations in other physiological systems, for example, involving immunological or endocrine signaling mechanisms (Qureshi & Mehler, 2013). Classical quantitative genetic studies, such as twin studies, and more recently genome-wide association studies with polygenic analyses have revealed genetic correlations between many different psychiatric and somatic disorders and traits. Elucidation of such shared genetic mechanism could lead to new therapies or diagnostic procedures. There is increasing evidence for inflammatory and autoimmune mechanisms in psychiatric disorders, including ADHD. In a recent epidemiological study of 48,000 Norwegian ADHD patients, a strong connection between immunological diseases in the mothers and ADHD in the offspring was observed (Instanes et al., 2015).

Different hypotheses regarding underlying pathophysiological mechanisms are further elaborated for some of the most commonly associated diseases.

Several mechanisms may account for the reported association between ADHD and obesity. Shared neurobiological or genetic mechanisms may be common to both ADHD and obesity (Nigg, 2013); ADHD and obesity being facets of the same underlying condition (Odent, 2010). Both ADHD and obesity are related to the dopamine system, and dopamine-related genes may affect body weight, eating patterns, and ADHD (Davis, 2009). It has been hypothesized that the urge for food intake can share the same mechanisms as ADHD-drug abuse (Cortese et al., 2007; Davis, 2010). Low tonic dopamine levels in the prefrontal cortex may lead to overeating as a kind of self-medication to increase the dopamine levels (Campbell & Eisenberg, 2007). Hypersensitivity to reward contributes to overeating because of an increased motivation in engaging in pleasurable activities (Davis,

2009). Other possible mechanisms involve the Brain Derived Neurotrophic Factor (Cortese & Morcillo-Peñalver, 2010), immune or inflammatory response (Nigg, 2013), and the melatonin system (Cortese & Morcillo-Peñalver, 2010; Kirov & Brand, 2014). A mediation analysis conducted in a clinical sample including 114 obese people, 202 aADHD patients, and 154 controls showed that both sleep duration and unstable eating patterns mediated the association between BMI and ADHD after controlling for current anxiety/depression and sociodemographics (Vogel et al., 2015).

Obesity and disorders related to obesity could also create symptoms resembling ADHD symptoms, such as sleep-disordered breathing, which can lead to inattentive symptoms during the day (Cortese & Morcillo-Peñalver, 2010). ADHD itself can lead to obesity rather than the other way around (Cortese, Ramos-Olazagasti, et al., 2013). The behavior associated with ADHD can lead to bad eating habits due to poor planning of the meals (Davis, 2009), or deficient inhibitory control or aversion to delay leading to increased consumption of palatable fast food (Cortese, Angriman, et al., 2008; Davis et al., 2006). Impulsivity associated with binge eating may contribute to impulsivity as a symptom of ADHD in obese patients, and abnormal eating behaviors may lead to symptoms of inattention and hyperactivity (Cortese, Angriman, et al., 2008). ADHD may also be characterized by motor clumsiness and poor energy regulation, resulting in periods of overactivity interspersed with underactivity, making it difficult for persons with ADHD to be a part of activities promoting fitness and weight loss that requires planning and sustained effort (Nigg, 2013). Positive correlations between symptoms of aADHD measured by ASRS, depression, anxiety, and disordered eating pattern have been shown (Alfonsson et al., 2012).

The cause of sleep problems in ADHD appears to be multifactorial and complex (Kirov & Brand, 2014), and the association between ADHD and sleep problems may be caused by different underlying pathways. It is not fully understood how obstructive sleep apnea, periodic limb movements during sleep, and RLS are connected to ADHD pathophysiology, or whether they can be viewed as comorbid sleep disorders in ADHD (Kirov & Brand, 2014). RLS share features with ADHD, and RLS and ADHD may be a part of the same symptom complex and share a central nervous dopaminergic dysfunction (Philipsen, Hornyak, & Riemann, 2006). As for ADHD, altered dopaminergic signaling and iron deficiency have been hypothesized to contribute to the pathophysiology of RLS (Cortese et al., 2005; Cortese, Lecendreux, et al., 2008). Hyperactive symptoms may directly cause sleep problems (Hvolby, 2015), and persons with ADHD can be more vulnerable to the effects of sleep disturbances (Hvolby, 2015). In itself, sleep problems may mimic ADHD symptomatology (Hvolby, 2015) and may also exacerbate underlying ADHD symptoms (Owens, 2005). Insomnia may cause inattention, a core symptom of ADHD (Voinescu et al., 2012). Without a thorough assessment, persons with sleep problems could be misdiagnosed as having ADHD (Gau et al., 2007). Furthermore, the stimulant treatment used for ADHD may result in sleep problems as a side effect (Owens, 2005). Common pathophysiology can lead to both ADHD and sleep disturbance (Brown & McMullen, 2001; Hvolby, 2015). Furthermore, a person with a delayed circadian rhythm may compensate being tired by binge eating during the day, which again leads to obesity (. Kooij & Bijlenga, 2013). A delayed sleep phase and sleep deficit can be risk factors for several disorders such as obesity, diabetes, and cardiovascular disorders (Kooij & Bijlenga, 2013).

As for ADHD, the dopaminergic system has also been suggested as a possible factor involved in the pathophysiology of asthma, as dopaminergic receptors are present in sensory nerves in the airways, and inhaled dopamine may induce bronchodilation during asthma attacks (Birrell et al., 2002; Cabezas, Lezama, & Velasco, 2001). Other common pathophysiological factors for these disorders may be inflammatory mechanisms (Barrios, Kheradmand, Batts, & Corry, 2006) and obesity (Cortese, Angriman, et al., 2008; Delgado, Barranco, & Quirce, 2008), as obesity leads to a proinflammatory state (Bazar, Yun, Lee, Daniel, & Doux, 2006).

There is substantial evidence that dopaminergic mechanisms are involved in migraine. It is therefore possible that changes in dopaminergic systems may represent common etiological factors for ADHD and migraine (Fasmer, Akiskal, Kelsoe, & Oedegaard, 2009).

## *Suggestions for Further Research*

A number of shortcomings have been identified in the literature cited in this review.

1. Different research designs have been utilized to explore the relationship between ADHD and somatic health. As each of these designs has their inherent limitations, there is a need to establish the prevalence of somatic diseases in representative samples of ADHD.
2. In many studies, the patients were simply screened for ADHD symptoms. We need to know what proportion of these patients has the full clinical syndrome, including impairment criteria. Harmonization of diagnostic protocols should increase reliability of such data.
3. It is suspected that many of the reported associated conditions are due to recognized or previously unknown confounders. Future research should investigate how much of the comorbidities are actually due to confounding factors, for example, that

headache or sleep disorders may be confounding factors for the association between obesity and ADHD (Cortese & Angriman, 2014; Gau et al., 2007), or that iron deficiency in ADHD is explained by, at least partly, the elevated presence of obesity (Cortese & Angriman, 2014).

4. Many of the existing studies are small. To be able to reveal a true association between ADHD and comorbid somatic diseases with adequate control for potential confounders, large studies are needed. The possibilities of combining the use of population-based registries and common diagnostic protocols should be investigated.
5. From a practical perspective, we need to know how current diagnostic and treatment algorithms should be optimized to account for coexisting conditions.
6. Access to biomarkers from large samples of ADHD cases and its comorbid conditions will allow systematic studies of their shared pathophysiology. This information should also inform future decisions regarding diagnoses and treatment.
7. Even for the best documented conditions, the literature was dominated by a few authors, research groups, and study populations. More research should be conducted in different geographical areas and ethnic groups.

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## Author Biographies

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**Anne Halmøy**, MD, PhD, is an associate professor at the Department of Biomedicine in the University of Bergen and a psychiatrist at Haukeland University Hospital. She is interested in neuropsychiatry and issues related to developmental aspects, comorbidity, and diagnostic assessments of psychiatric disorders.

**Ole Bernt Fasmer** is a professor of adult psychiatry at the University of Bergen and a psychiatrist at Haukeland University Hospital. His main interests are biological aspects of bipolar disorder and ADHD.

**Jan Haavik**, MD, PhD, is a professor of biomedicine at the University of Bergen and a psychiatrist at Haukeland University Hospital. He is interested in molecular mechanisms of the nervous system and clinical aspects of brain disorders, including ADHD.

SUPPLEMENTARY 1.

Search strategies.

Search Strategy MEDLINE 8.12.2014:

1 Attention Deficit Disorder with Hyperactivity/ (21710)

2 (adhd or addh or attention deficit disorder or hyperkinetic disorder).tw. (17126)

3 1 or 2 (25533)

4 exp "diseases (non mesh)"/ (12226658)

5 Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ (1604084)

6 Case control.tw. (85883)

7 (cohort adj (study or studies)).tw. (100884)

8 Cohort analy$.tw. (4268)

9 ((follow up or follow-up or followup) adj (study or studies)).tw. (40272)

10 (observational adj (study or studies)).tw. (51544)

11 (Longitudinal or retrospective or cross sectional).tw. (626298)

12 Cross-sectional studies/ (193902)

13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (2045054)

14 3 and 4 and 13 (2566)

15 limit 14 to "all adult (19 plus years)" (834)

16 limit 14 to "all child (0 to 18 years)" (2263)

17 15 and 16 (603)

18 16 not 17 (1660)

19 14 not 18 (906)

20 "review"/ (1985863)

21 review.tw. (994783)

22 20 or 21 (2395613)

23 19 and 22 (120)

24 3 and 4 and 22 (1922)

25 limit 24 to "all adult (19 plus years)" (356)

26 limit 24 to "all child (0 to 18 years)" (1210)

27 25 and 26 (280)

28 26 not 27 (930)

29 24 not 28 (992)

Search Strategy PsycINFO 8.12.2014:

1 exp attention deficit disorder/ (19335)

2 (adhd or addh or attention deficit disorder or hyperkinetic disorder).tw. (20785)

3 1 or 2 (23135)

4 exp congenital disorders/ or exp feeding disorders/ or exp physical disorders/ (404949)

5 exp symptoms/ (173417)

6 4 or 5 (507138)

7 3 and 6 (7838)

8 limit 7 to "300 adulthood <age 18 yrs and older>" (2144)

9 limit 7 to (100 childhood <birth to age 12 yrs> or 200 adolescence <age 13 to 17 yrs>) (5309)

10 8 and 9 (1112)

11 9 not 10 (4197)

12 7 not 11 (3641)

13 limit 12 to ("0430 followup study" or "0450 longitudinal study" or "0451 prospective study" or "0453 retrospective study") (238)

14 clinical trials/ (8138)

15 longitudinal studies/ (14979)

16 retrospective studies/ (347)

17 cohort analysis/ (1061)

18 Prospective Studies/ (438)

19 (Cohort adj (study or studies)).mp. (10998)

20 (Case control adj (study or studies)).mp. (4806)

21 followup studies/ (12314)

22 ((follow up or follow-up or followup) adj (study or studies)).tw. (11745)

23 (Family adj (study or studies)).mp. (2806)

24 (observational adj (study or studies)).tw. (5761)

25 (epidemiologic$ adj (study or studies)).tw. (10301)

26 (cross sectional adj (study or studies)).tw. (13481)

27 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (90626)

28 12 and 27 (166)

29 13 or 28 (343)

30 limit 29 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract") (35)

31 29 not 30 (308)

32 review.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] (303998)

33 12 and 32 (420)

34 33 not 30 (418)

35 limit 34 to yr="1994 -Current" (366)

Search Strategy EMBASE 26.01.2015:

1 attention deficit disorder/ (38493)

2 (adhd or addh or attention deficit disorder or hyperkinetic disorder).tw. (21522)

3 1 or 2 (40160)

4 exp physical disease/ (15651306)

5 3 and 4 (24757)

6 limit 5 to (adult <18 to 64 years> or aged <65+ years>) (5041)

7 limit 5 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (12157)

8 6 and 7 (2191)

9 7 not 8 (9966)

10 5 not 9 (14791)

11 Clinical study/ or Case control study/ or Family study/ or Longitudinal study/ or Retrospective study/ (633963)

12 Prospective study/ (271121)

13 Randomized controlled trials/ (63501)

14 12 not 13 (269332)

15 Cohort analysis/ (186105)

16 (Cohort adj (study or studies)).mp. (127928)

17 (Case control adj (study or studies)).tw. (79630)

18 ((follow up or follow-up or followup) adj (study or studies)).tw. (48562)

19 (observational adj (study or studies)).tw. (70739)

20 (epidemiologic$ adj (study or studies)).tw. (77107)

21 (cross sectional adj (study or studies)).tw. (93580)

22 cross-sectional study/ (128813)

23 11 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (1346755)

24 10 and 23 (1274)

25 limit 24 to (book or book series or conference abstract) (187)

26 24 not 25 (1087)

27 review.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2770704)

28 10 and 27 (5006)

29 limit 28 to (book or book series or conference abstract) (228)

30 28 not 29 (4778)

31 limit 30 to yr="1994 -Current" (4668)

32 *attention deficit disorder/ (21353)

33 (th or dt).fs. (3887116)

34 31 and 32 (1384)

35 34 not 33 (443)

**Supplementary 2.**
**Study characteristics of individual studies included in the systematic review. The table only describes somatic and psychiatric comorbidities relevant for the present review-article, i.e. the individual studies may include more outcomes.**

**For abbreviations on assessment tools (*) see supplementary 3.**

| Ref. | Country | Study design & selection | Total number | Somatic comorbid disorder | Adult ADHD | | Age<br><br>Mean (SD) | Males (%) |
|---|---|---|---|---|---|---|---|---|
| | | | N | Diagnosis | N | Diagnosis | | |
| **Brook et al., 2013 (Brook, Brook, Zhang, Seltzer, & Finch, 2013)** | **USA** | **Prospective, community based cohort study following adolescents into adulthood.**<br><br>**Participation rate for original invitation not given. Adolescents assessed: 756; where 72.9% were followed to adulthood and had ADHD information** | **551** | **General physical health: assessed with self-report questionnaire.** | **72** | **Baseline: Assessment of ADHD in adolescence by structured interview.**<br><br>***DSM-III* criteria for ADHD.** | **Total cohort:**<br><br>**Baseline: Mean: 14-16 years.**<br><br>**Follow up: 36.8 years.** | **Total cohort: 45%** |
| Hodgkins et al., 2011 (Hodgkins, Montejano, Sasane, & Huse, 2011) | USA | Retrospective analysis of health care claims and employer-rated health and productivity management databases in 2006. Adult individuals with ADHD were matched with non-ADHD controls and a group of patients with depression. | 156,973 | **General physical health:**<br><br>Annual direct health care cost assessed by the utilization and expenditure data.<br><br>Indirect costs:<br><br>Absence from work, short-term disability and and workers' compensation.<br><br>"Comorbidity burden" (Charlson Comorbidity Index) based on diagnosed medical/physical conditions and<br><br>non-diagnostic claims during 2006 for obesity, diabetes, hypothyroidism, hypertension, other cardiovascular disease, asthma, enuresis and irritable bowel syndrome. | 31,752 | Criteria: At least 1 evaluation & management or psychiatry claim with an ADHD diagnosis in 2002-2007; at least 1 confirmatory ADHD diagnosis within next 12 months; evidence of continuing treatment for ADHD in 2006; and continuous enrollment in a health plan with pharmacy benefits in 2006. Diagnosis based on *ICD-9-CM*. | Both in ADHD and control group: 32.1 (13.2). | Both in ADHD and control group: 55% |
| Secnik et al., 2005(Secnik, Swensen, & Lage, 2005) | USA | Registry based matched case control study based on linked data from medical claims databases providing information on medical history and work. | Comorb-idity: 4504.<br><br>Work and costs: 708 | **General physical health:**<br><br>Direct medical costs and productivity costs related to missed work days.<br><br>Asthma; enuresis; irritable bowel syndrome. Based on registered ICD-9 diagnoses. | Co-morbidity: 2252<br>Work and costs: 354 | Registered ICD-9 code in the medical claims database. | Total population: All individuals 18 -64 years,<br><br>44% were 18-24 years | Total pop: 64.3% |
| Spencer et al., 2014 (Spencer, Faraone, Tarko, McDermott, & | USA | Case control study. Selection of potential cases through referrals to authors' clinical programs, - participation rate not given. | 198 | **General physical health:**<br><br>Health status based on self-reported history of diabetes, heart attacks, | 98 | Structured clinical interview for *DSM-IV* by trained lay interviewers, blind for ADHD status. | ADHD cases: 32 (12).<br>Controls: | ADHD cases: 44%.<br>Controls: 47%. |

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| Biederman, 2014) | | Self-selection of controls through advertisements in the greater Boston area. | | asthma, musculoskeletal complaints including fibromyalgia, and others. Health risk indicators based on self-report and clinical measurements. "Bad health habits" as measured by the Behavioral Risk Factor Surveillance System. | | ASRS*. | 30 (10). | |
| Hosain et al., 2012 (Hosain, Berenson, Tennen, Bauer, & Wu, 2012) | USA | Cross sectional study based on baseline interviews of an ongoing longitudinal study among low-income women from family planning clinics. Eligible women: 885; Included: 462 (52%) without drug and alcohol abuse | 462 | **Sexually transmitted infections (A50-A64):** Interview assessment, using Sexual Risk Behavior Assessment Schedule. | N/A | ASRS* | Total group: 23.9 (3.7) | 0% |
| Brucker-Davis et al., 1995) (Brucker-Davis et al., 1995) | USA | Case-control study.<br><br>Cases:104 hospitalized patients with resistance to thyroid hormone (RTH) from 42 unrelated families .<br><br>Controls: 114 unaffected relatives, including 29 persons married into families with RTH. | 218 including 113 adults | **Resistance to thyroid hormone (E07.8):** Diagnosed by blood sample, and confirmed by DNA analysis. | Number not specified. Among adults with RTH: 42% Among adults without RTH: 4% | Diagnosed by psychiatrist blind to the RTH diagnosis, using appropriate psychiatric interviews. | Adults with RTH: 34.5 (1.6),<br><br>Adults without RTH: 36.3 (1.7). | Adults with RTH: 45%<br><br>Adults without RTH: 54% |
| Hodgkins et al., 2011 (Hodgkins et al., 2011) | USA | Retrospective analysis of health care claims and employer-rated health and productivity management database in 2006; see above. | 156,973 | **Hypothyroidism (E00-E03) and**<br><br>**Diabetes (E10-E14):**<br>Information from databases, see above. | 31,752 | Diagnosis based on *ICD-9-CM*; see above. | See above. | See above. |
| Semeijn et al.,2013 (Semeijn et al., 2013) | The Nether-lands | Case control study based on an ongoing longitudinal study with randomly selected samples from population registries.<br><br>Response rates varying over phases. N=1494 screened for ADHD, 271 randomly selected for interview, 231 included in study. | 231 | **Diabetes (E10-E14):**<br><br>Respondents asked about current diseases e.g.: cardiac diseases, hypertension, diabetes mellitus, chronic nonspecific lung disease, rheumatoid<br><br>arthritis, cancer.<br><br>If positive response, more detailed questions from a general health questionnaire. Information on chronic diseases also from general practitioners. | 23 | Hyperactivity disorder (ADHD) Screening List for screening ADHD in older adults Aged 60-94 years.<br><br>DIVA* | ADHD:68.0 (4.9)<br><br>Controls:72.0 (72.8) | ADHD: 48%.<br><br>Controls: 40.0% |
| Spencer et al., 2014 (Spencer et al., 2014) | USA | Case control study; see above | 198 | **Diabetes (E10-E14):**<br><br>Self-reported history of diabetes; see above. | 98 | Structured clinical interview for *DSM-IV*, and ASRS*; see above | See above | See above |
| Alfonsson et al., 2012 (Alfonsson, Parling, & Ghaderi, 2012) | Sweden | Study based on self-report questionnaires. Patients referred to bariatric clinic invited. Participation rate 86%. | 187 | **Obesity (E66):**<br><br>Measured height and weight. | 19 (10.2%) with likely ADHD | ASRS-S* | Total : 41.04 (11.07). | Total pop: 26.7%. |

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| Altfas et al., 2002 (Altfas, 2002) | USA | Retrospective, systematic review of clinical records of all patients treated for obesity at one bariatric clinic in 2000. | 215 | **Obesity (E66):**<br><br>All patients were referred to bariatric clinic. Measured height and weight, grouped in BMI categories | ADHD:<br><br>59 (27.4%), all inattentive type.<br>ADHD symptoms:<br><br>72 (33.5%) | Semi-structured clinical interview according to *DSM-IV* criteria | Overall: 43.4 (10.9)<br><br>ADHD: 44.6 (11.4)<br><br>ADHD symptoms: 42.7 (11)<br><br>NonADHD: 43.2 (10.7) | Overall: 10.2%<br><br>ADHD: 15.3%<br><br>ADHD symptoms: 8.3%<br><br>NonADHD: 8.3% |
| Anderson, 2006 (Anderson, Cohen, Naumova, & Must, 2006) | USA | Prospective, community based cohort study (Children in the Community Study), following children (age 9.1-16.6 years) to adulthood (age 27.7-38.3 years).<br>Participation rate not given. | 655 | **Obesity (E66):**<br><br>BMI from reported weight and height at each evaluation point. Standardized to BMI Z-scores. | 466 (71.1%) | In-home structured, diagnostic interview by trained lay interviewers at ages < 16.6 years, consistent with *DSM IV* criteria for ADHD, oppositional defiant disorder and conduct disorder. No specific information on adult ADHD. | Total cohort at baseline: Girls 13.0 (9.1-16.6);<br><br>Boys 12.8 (9.2-16.6) | Total cohort: 50.7% |
| Biederman, 2010 (Biederman, Spencer, Monuteaux, & Faraone, 2010) | USA | Two longitudinal case-control studies, (boys and girls). Cases (ADHD patients) selected 1) from consecutive referrals to pediatric psycho-pharmacology unit, and 2) consecutive pediatric outpatients where patient records ascertained ADHD.<br><br>Controls were from outpatients receiving routine physical check- ups. Participation rates not given. | Baseline: 522,<br>At 10 years follow up: 404 (77.4%)<br><br>At follow up with growth data: 261 (50%) | **Obesity (E66):**<br><br>BMI: Measured weight and height at each wave.<br><br>Converted to standardized weight, height and BMI Z-scores | Baseline: 280 | Consecutive children referred for ADHD to outpatient clinics. Diagnosis confirmed by telephone questionnaires to mother, then structured interview by trained interviewers, using K-SADS-E* and SCID*. Diagnosis based on *DSM-IV*. Diagnostic uncertainties resolved by psychiatrist.<br><br>Persistent ADHD if full or subthreshold *DSM-IV* criteria met at last month before 10 year follow up. | At 10-11 year follow up:<br><br>ADHD boys: 21.5 (3.5) ¨<br><br>Control boys: 22.3 (4.1)<br><br>ADHD girls: 21.1 (3.3) ¨<br><br>Control boys: 22.2 (2.8) | Baseline:<br><br>50%<br><br>At 10-11 years: 53.7% |
| Bijlenga et al., 2013 (Bijlenga, van der Heijden, et al., 2013) | The Nether-lands | Cross sectional analysis comparing ADHD patients with a control group.<br><br>ADHD cases recruited from an out-patient clinic for adult ADHD individuals. Controls mainly self-selected from public institutions, and a group of students “and one of their acquaintances”. Participation rate not given. | 391 | **Obesity (E66):**<br><br>BMI based on reported height and weight.<br><br>Self-report questionnaires and checklists covering: Sleep, metabolic disorder, cardiovascular disorder,respiratory disorder, digestive system disorder, immune system disorder, skin disorder, skeletal disorder, urinary system disorder, cancer. | 202 | Diagnosed by trained psychologist/ psychiatrist at outpatient clinic for adult ADHD, using DIVA*. All met *DSM-IV* criteria.<br>ADHD combined type: 83.2%<br>ADHD inattentive type: 16.3%<br>ADHD hyperactive/impulsive type: 0.5% | ADHD: 34.9 (10.6) Controls: 33.0 (13.6) | ADHD: 53%<br>Controls 34.9% |

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| Caci et al., 2014 (Caci, Morin, & Tran, 2014) | France | Parents of youths participating in a large study on ADHD symptoms in the community were asked to fill in questionnaires, response rate not given. | 1171 | **Obesity (E66):**<br><br>BMI based on reported height and weight. | ADHD defined by the 2-phase method: 2.99% | ASRS* filled in and scored in three ways: 6-item screener, all 18 items and the screener followed by the 12 remaining items (2-phase). The 2-phase method used to define an ADHD group. | Women:<br><br>40.7 (5.6)<br><br>Men:<br><br>43.2 (6.3) | 43.6% |
| Cortese et al., 2014 (Cortese, Faraone, Bernardi, Wang, & Blanco, 2013) | USA | Cross sectional survey data from the National Epidemiologic Study on Alcohol and Related Conditions, a survey from a large, representative sample of the US population. | 34,653 | **Obesity (E66):**<br><br>BMI based on reported height and weight. | Persistent: 340<br><br>Remitted: 275 | Face-to-face interviews by experienced lay interviewers with extensive training and supervision; using the Alcohol Use Disorder and Associated Disabilities Interview Schedule - *DSM-IV* Version. ADHD diagnosed after *DSM-IV* criteria, but with symptoms debut < 12 years of age.<br><br>Remittent, persistent and lifetime ADHD assessed. | Age group 18-29: 30.5%<br>Age group 30-44: 35.6%<br>Age group 45-64: 31.8%<br>Age group 65+: 4.1% | Non-ADHD: 48%<br><br>Persistent ADHD:53%<br><br>Remitted ADHD: 62% |
| Cortese et al., 2013 (Cortese, Ramos Olazagasti, et al., 2013) | USA | Longitudinal study. Cases: boys diagnosed at research clinic with ADHD, combined type, without comorbid behavior problems.<br><br>Matched controls without ADHD and conduct disorder from same clinic.<br><br>Reassessed as adults, included when height and weight measures present. | 222 | **Obesity (E66):**<br><br>BMI based on reported height and weight. | Persistent: 24<br><br>Remitted: 87 | Childhood ADHD meeting the *DSM-IV- TR* criteria, all combined type.<br><br>Adult ADHD defined as meeting the *DSM-IV-TR* criteria using The Assessment of Adult Attention Deficit Hyperactivity Disorder, SCID 1* and PRISM*, by clinicians blind to childhood diagnosis. | At inclusion: Mean age 8.3<br><br>At reassessment: Cases:<br><br>41 years, Controls:<br><br>42 years | 100% |
| Cortese et al., 2015 (Cortese et al., 2015) | | A systematic review including 42 studies describing the degree of association between overweight/obesity and ADHD, 41 of these included in a meta-analysis describing an association between obesity and ADHD. | 728,136 | **Obesity (E66):**<br><br>Obesity defined either by 1) self-report or medical record diagnosis, 2) BMI based on reported or measured height and weight. | Total: 48161<br>Adults: 2046 | 1) ADHD as defined by *DSM* or hyperkinetic disorder as defined by *ICD*, 2) scores above a symptom threshold on a validated ADHD rating scale, 3) a positive answer to the question: "did your doctor ever tell you that you had ADHD? 4) a medical record diagnoses of ADHD. | N/A | N/A |
| Davis et al., 2009 (Davis et al., 2009) | Canada | Case control study where cases with binge eating disorder BED) and controls were self-selected through posters in public institutions and newspaper ads. All were screened by telephone interview. Participation rate not given. | 181 | **Obesity (E66):**<br><br>BMI based on measured height and weight.<br><br>Binge eating disorder based on modified *DSM-IV-TR* criteria. Telephone and structural clinical interview. | N/A | CAARS*, WURS*. | BED:<br>34.5 (6.5).<br><br>Normal weight controls:<br>33.3 (7.5).<br><br>Obese controls: | BED: 21.7 %<br><br>Normal weight controls: 11.5%<br><br>Obese controls: 25% |

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| | | | | | | | 37.0 (6.7) | |
| de Zwaan et al., 2011(de Zwaan et al., 2011) | Germany | Cross-sectional study with a representative sample of the general population. Cases with self-reported ADHD symptoms compared with a control group.<br><br>Response rate 61.9%. | 1633 | **Obesity (E66):**<br><br>BMI based on reported height and weight. | 77 | Self-reported: WURS* (short version) and ADHD-SR*. | 19-64 years<br>43.2 (12.7) | Total: 46.4%<br><br>Non- ADHD: 46.4%<br><br>ADHD: 45.5% |
| Docet et al., 2010 (Maria F Docet, Larranaga, Fernandez Sastre, & García-Mayor, 2010) | Spain | Case-control study. Cases: obese attending a nutrition clinic.<br><br>Controls: normal weight adults attending a pharmacy.<br><br>Refused participation: 1.2% obesity group and 3.9% in the normal weight group. | 243 | **Obesity (E66):**<br><br>BMI based on measured height and weight. | 40 | A symptom questionnaire based on the *DSM-IV* criteria and ASRS*, screener and if positive full version. | Obese:<br><br>51 (13.4)<br><br>Normal weight:<br><br>41.4 (12.8) | Obese: 24.1%<br><br>Normal weight: 28.8% |
| Docet et al., 2012 (M. F. Docet, Larranaga, Perez Mendez, & Garcia-Mayor, 2012) | Spain | Case-control study. Participants attending a nutrition clinic. Cases: positive screening for ADHD. Controls: negative screening for ADHD.<br><br>Refused participation: 1.9% for ADHD and 0.5% for nonADHD. | 230 | **Obesity (E66):**<br><br>Abnormal eating behaviors assessed by an eating pattern questionnaire during a clinical interview. | 51 | ASRS* administered during a clinical interview. | ADHD:<br><br>42.3 (15.5)<br><br>nonADHD 50.9 (12.4) | ADHD: 12%<br>nonADHD 23% |
| Fleming et al., 2005 (Fleming, Levy, & Levitan, 2005) | Canada | Prospective study of consecutive obese women referred to an obesity clinic.<br><br>33% drop-out. | 75 | **Obesity (E66):**<br><br>BMI ≥35. Details on assessment not given. | 20 | WURS*, CAARS*, BADDS* | 40.4 (10.8) | 0 |
| Levy et al., 2009(Levy, Fleming, & Klar, 2009) | Canada | Longitudinal clinical intervention study over 466 days. A consecutive sample of severely obese patients referred to a medical specialist to treat refractory obesity, all evaluated for ADHD. The ADHD group divided into those using ADHD medication and those not. | 242 | **Obesity (E66):**<br><br>BMI based on measured height and weight, self-reported for 11 controls.<br><br>**Sleep apnea:** chart records and overnight sleep. | 78 | WURS*, ASRS*, clinical interview. | Treated for ADHD:<br>41.3 (12.1)<br>Untreated for ADHD<br>38.8 (9.4) | Total ADHD group: 7.7% |
| Nazar et al., 2014 (Nazar et al., 2014) | Brazil | Cross-sectional study. Clinical sample of obese women with eating disorder, both with and without ADHD. 22.8% were excluded from the sample of 171 | 132 | **Obesity (E66):**<br><br>No information on measured or self-reported height and weight.<br><br>Eating disorders diagnosed by the Eating Disorders Module of the SCID-P.<br><br>Binge Eating Scale, BIS, Beck Depression Inventory | 40 | K-SADS* module for ADHD, adapted to adults. | Overall:<br><br>38.3 (10.6)<br><br>ADHD:<br><br>37.5 (11.3) | 0 |
| Nigg et al., 2016 (Nigg et al., 2016) | USA | Meta-analysis of 43 population based or case-control studies investigating an association between obesity and ADHD. | 703,937 | **Obesity (E66):** | Total: 69,669<br>Adult ADHD | Based on *DSM* criteria, or a measure of ADHD symptoms using a validated ADHD symptom rating scale, or in epidemiological studies, | Range 3-65 | N/A |

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| | | | | Overweight and obesity defined by BMI. | ≥ 18 years: no info. | identification of ADHD using a diagnostic-specific question, or by a chart review. | | |
| Pagoto et al., 2009 (Pagoto et al., 2009) | USA | Cross-sectional analysis of data (2001-03) from two population based national representative surveys comparing cases (childhood or current ADHD) with controls (non- ADHD).<br><br>Response rate: Survey 1:71%, survey 2: 72%. | 6735 | **Obesity (E66):**<br><br>BMI based on reported height and weight.<br><br>Binge eating disorder: CIDI* (*DSM-IV* criteria with adjustments). | Childhood ADHD: 492<br><br>Adult ADHD: 243 | Retrospective assessment of childhood ADHD: retrospective version of *DSM-IV*.<br><br>Those with childhood symptoms assessed for aADHD by clinical interviews using ACDS*, ADHDRS–IV* and an adaptation ADHDRS–IV*.<br><br>Major depressive disorder: CIDI* (*DSM-IV* criteria), SCID* for clinical reappraisal. | Total: Range 18-44<br><br>Mean age 31.0 (0.25) | Total: 48.4 |
| Pagoto et al., 2010 (Pagoto et al., 2010) | USA | Cohort study. All patients completing a 16-week behavioral weight loss program at a medical center invited to fill out questionnaires on ADHD and eating habits. Chart review pre- and post-treatment.<br><br>Response rate: 40.6% | 63 | **Obesity (E66):**<br><br>Information on height and weight pre- and post- treatment was retrospectively collected from medical charts. | 19 | ASRS | Overall:<br><br>49 (10.3) | Overall: 25% |
| Semeijn et al.,2013 (Semeijn et al., 2013) | The Nether-lands | Case control study; see above. | 231 | **Obesity (E66):**<br><br>BMI based on measured height and weight. | 23 | Screening list and DIVA*; see above | See above | See above |
| Strimas et al., 2008 (Strimas et al., 2008) | Canada | Self-report questionnaires and height and weight measurements from a group of healthy adult males. No information on how or from where participants were recruited. Response rate not given. | 145 | **Obesity (E66):**<br><br>BMI based on measured height and weight.<br><br>Overeating assessed by questionnaires: the Depression subscale of the Emotional Eating Scale, the Emotional Eating and External Eating subscales of the Dutch Eating Behavior Questionnaire and the Bingeing subscale of the Binge Eating Questionnaire. | N/A | WURS*, CAARS*, BIS* | 34.4 (7.7) | 100 |
| Vogel et al., 2015(Vogel et al., 2015) | The Netherlands | Case control study. Obese patients recruited from outpatient clinics for obesity and eating disorder, and from a lifestyle event for obese persons. Selection of ADHD patients and control group not described detailed in present paper. From reference: ADHD patients recruited from out-patient clinics, controls self-selected, recruited from posters on public | Total: 470; Obese group:<br><br>114; Control group:<br><br>154 | **Obesity (E66):**<br><br>BMI based on reported height and weight.<br><br>**Circadian rhythm disturbance (G47;** see below) defined by manifestations of sleep problems and unstable eating patterns. | 202 | Not described in detail, but they were included "after extensive diagnostic assessment at the PsyQ outpatient clinic". | Obese group: 43.8 (11.2)<br>ADHD group: 34.9 (10.6)<br>Controls: 35.9 (13.5) | Obese group: 13.3%<br>ADHD group: 53%<br>Controls: 34.4% |

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| | | institutions and among college students and their acquaintances. | | | | | | |
| Bijlenga et al., 2013 (Bijlenga, van der Heijden, et al., 2013) | The Nether-lands | Cross sectional analysis; see above. | 391 | **Metabolic disorders in general (E70-E90):**<br><br>Self-report questionnaires; see above. | 202 | Diagnosed by trained psychologist/ psychiatrist at outpatient clinic for adult ADHD; see above | See above | See above |
| Kutzbach et al., 2007 (Kutzbach, Summers, Holleschau, King, & MacDonald, 2007) | USA | Case study of children and adults diagnosed with albinism. Participants recruited at a conference of the National Organization for Albinism and Hypopigmentation in Minneapolis and from the University of Minnesota International Albinism Center. Self-selection | Total: 122<br><br>Adults: 44 | **Albinism (E70.3):**<br><br>Diagnosed by ophthalmologist using clinical criteria. In 78% also grouped by type of albinism. | Total: 20<br><br>Adults:<br><br>3 (6.8%) | Adults: self-report questionnaire. Adult ADHD diagnosed by positive response to the Utah criteria for ADHD when supported by the history and the physician interview. | Not given | Not given |
| Muelly et al., 2013 (Muelly et al., 2013) | USA | Case control study. No information on how or from where participants were recruited, or on participation rate. | 63.<br><br>Maple syrup urine disease (MSUD) cases:37, of which 26 treated with diet, 11 liver transplant. Controls: 26 | **Maple syrup urine disease (E71.0):**<br><br>No information on how or where cases were diagnosed | No clear information on number of adult ADHD patients. Lifetime cumulative incidence: MUSD diet: 13 (54%) MUSD transplant: 9 (82%) Controls: 7 (27%) | No clear information. Conner's Parent Rating *DSM-IV* Sub scores are tabulated, but otherwise no info on diagnosis of ADHD. | Overall:<br><br>18.7 (8) | Overall:<br><br>54% |
| Pearson et al., 2008 (Pearson et al., 2008) | USA | Matched case control study. Cases were RLS patients diagnosed at sleep- or medical centers, controls recruited through the media, from same local community as cases. Participation rates not given. | 164:<br><br>110 RLS patients and 54 controls. | **Restless legs (G25):**<br><br>Diagnosis based on clinical interview by neurologist. | Not given | ADHD diagnosis: Based on medication use | RLS patients: 60.7 (12.9) | RLS patients: 30% |
| Roy et al., 2015 (Roy et al., 2015) | Germany | Self-report questionnaires from a randomly selected community-based sample. Invited: 4069; agreed: 2520 (61.9%); final sample of adults: 1632 (40.1%) | 1632 | **Restless legs (G25):**<br><br>Restless legs (RLS) based on validated self- report questionnaires. Overweight and sleep disturbance also assessed. | Adult ADHD:76, of which 9 also had RLS | A German ADHD self-rating scale | Not given | Not given |
| Schredl et al., 2007 (Schredl, Alm, & Sobanski, 2007) | Germany | Case-control study.<br><br>Cases: ADHD patients from an out-patient clinic. | 564 | **Restless legs (G25):**<br><br>Sleep disorders (see below). | Total:120<br><br>Free of medication and without | All cases met *DSM-IV* diagnoses of ADHD. BADDS*. | Controls: 23.5 (5.7)<br><br>Total ADHD group: | Controls: 15.3%<br><br>Total ADHD group: 46.7% |

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| | | Controls: No information on recruitment. Participation rate not given. | | Restless legs based on the LISST sleep questionnaire, where "movement disorders" make up one group (5 items) | comorbidity: 61 | | 34.8 (10.0) | |
| Steinlechner et al., 2011 (Steinlechner et al., 2011) | Germany | Interview and self- report questionnaires from 37 parents of 26 children diagnosed with ADHD. Recruited from pediatric department, participation rate not given. | 37 | **Restless legs (G25):**<br><br>RLS (N=11) diagnosed by neurologist. Lifetime clinical psychiatric (Axis I) and personality (Axis II) disorders assessed by the Structured clinical interview for *DSM-IV* by psychiatrists. | ADHD: 6. With concurrent RLS: 5. | Structured clinical interview for *DSM-IV* by psychiatrists | Mean age mothers: 43.4 (5.09)<br><br>Mean age fathers: 46.67 (5.2) | 32.4% (fathers) |
| Wagner et al., 2004 (Wagner, Walters, & Fisher, 2004) | USA | Comparison between restless leg syndrome (RLS) patients, patients with insomnia and controls with respect to occurrence of ADHD. Patients with RLS or insomnia included sequentially from neurology clinic.<br><br>Healthy controls (N=77) recruited through advertisement in hospital newsletter.<br><br>Initially included 195 individuals, 171 (87.7%) remained after exclusions. | 171 | **Restless legs (G25):**<br><br>Patients were diagnosed with RLS by one of the authors using<br><br>criteria developed by the International Restless Legs<br><br>Syndrome Study Group (IRLSSG).<br><br>The IRLSSG Rating Scale (self-report questionnaire) used for severity score. | Inattention and hyper-activity (*DSM-IV* sympt score): RLS: N=16 (26%); Insomnia: N=2 (6%); Healthy control:<br><br>N=4 (5%) | *DSM-IV* criteria for ADHD. The BADDS* questionnaire (self-report). For patients with scores indicating probable ADHD, also structured interview and neuropsychiatric test battery by neuropsychologist | RLS:<br><br>60.8 (13.1) Insomnia:<br><br>62.8 (11.1) Healthy controls:<br><br>62.3 (11.4) | RLS: 38%; Insomnia: 31%; Healthy controls: 34% |
| Zak et al., 2009(Zak, Fisher, Couvadelli, Moss, & Walters, 2009) | USA | Pilot study on prevalence of Restless leg syndrome (RLS) in 30 adult ADHD patients.<br>Recruitment from a psychological service specialized in treating adult ADHD, and from a sleep clinic (patients referred for RLS not included). | 30 | **Restless legs (G25):**<br><br>Diagnosis by John Hopkins Telephone Diagnostic Interview for RLS | 30,<br><br>all inattentive type | Screened for ADHD according to *DSM-IV-TR* criteria through interview by a neuropsychologist, following neuro-psychological testing to confirm diagnosis. Conners' Adult ADHD Rating Scale (self-report) for symptoms severity. | 43.5<br><br>(19-65) | 66% |
| Golimstok et al., 2011 (Golimstok et al., 2011) | Argen-tina | Matched case control study. Patients with Dementia with Lewy bodies (DLB), with Alzheimer and controls without neurological diseases, consecutively selected from record database at the Italian Hospital Medical Care Program in Buenos Aires. Case selection in 2000-2005. | 509 | **Dementia with Lewy bodies (G31.83):**<br><br>Diagnosis by trained neurologist, consensus criteria used for DLB diagnosis, Dementia Rating Scale and Mini Mental Status Exam-ination for severity. | Preceding ADHD in DLB: 47.8%, in Alzheimer 15.2%, in controls: 15.1% | Two trained neurologists, blind to the study objective, diagnosed the participants using WURS* and applying *DSM-IV* criteria for aADHD. If discordant diagnosis, a third (blind) neurologist assessed the patient. Information collected from a direct informant for patients with dementia. | DLB:<br><br>75.1 (7.4) Alzheimer: 74.2 (7.1) Controls:<br><br>74.1 (8) | DLB: 32.6% Alzheimer: 31.9% Controls: 33.3% |
| Ettinger et al., 2015 (Ettinger et al., 2015) | USA | Community-based cross sectional survey, as part of the Epilepsy Comorbidity and Health Study (EPIC) study. 11-item screening survey sent to a random 340 000 individuals' population sample. Return rate 51%. Follow-up postal survey to 7500 | 1361 | **Epilepsy (G40):**<br><br>Answering "yes" to: "Have you ever been told by a health care professional that you have epilepsy/seizure disorder", | 251 screen positive on ASRS | Adult ADHD Self-Report Scale (ASRS-6). | ASRS screen positive:<br><br>47.3 (14.1); ASRS screen negative: | ASRS screen positive: 51%; ASRS screen negative: 47.4% |

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| | | persons with self-reported epilepsy, return rate 68%. | | in addition to self-reported use of anitepileptic medicine.<br><br>Additional scales assessing general health, mental health, quality of life. | | | 50.3 (14.8) | |
| Ottman et al., 2011 (Ottman et al., 2011) | USA | Community-based cross sectional survey, as part of the Epilepsy Comorbidity and Health Study (EPIC) study. 11-item screening survey sent to a general population sample, returned from 172, 959 (51%). | 172, 959 | **Epilepsy (G40):**<br><br>Answering "yes" to: "Have you ever been told by a health care professional that you have… [list of 16 disorders]?'' including epilepsy/seizure disorder. | 13.2% | Answering ''yes'' to: "Have you ever been told by a health professional<br>that you have… [list of 16 disorders]?'' including ADHD | Total group: All above 18 years, largest group was 60 years and above (29.5%) | Total group: 39.8% |
| van der Feltz-Cornelis (2006) (van der Feltz-Cornelis & Aldenkamp, 2006) | The Nether-lands | Consecutive patients with new seizures, referred to a tertiary care epilepsy clinic, subjected to standardized psychiatric interview. Six ADHD patients included in an open treatment trial of methylphenidate. | 156, of which 126 had epilepsy | **Epilepsy (G40):**<br><br>Diagnosed at a tertiary epilepsy clinic, with EEG and video registration. | 6, of which 3 had epilepsy and 3 Psycho-genic non-epileptic seizures | Standardized psychiatric interview to establish *DSM-IV* diagnostic classification | Among the 6 ADHD cases:<br><br>25 (19-30) | Among the 6 ADHD cases:<br><br>50% |
| Fasmer et al., 2011 (Fasmer, Halmoy, Oedegaard, & Haavik, 2011) | Norway | Cross sectional study comparing a case and a control group. ADHD cases collected from a national registry of adults with ADHD in 1997–2005, after 2005 also from psychiatrists/ psychologists nationwide. Participation rate not given.<br><br>Controls randomly selected from a nationwide population based registry. | 1247 | **Migraine (G43):**<br><br>Self-report questionnaire. Diagnosis based on answering yes to the question: "Have you ever had migraine?" | 572 | ADHD diagnoses from the national registry of adult ADHD patients were all verified by 1 of 3 national expert committees. Additional patients diagnosed by psychiatrists/ psychologists. *ICD-10* research criteria used, but allowing the inattentive subtype as sufficient for diagnosis. Self-report questionnaires, including ASRS*, WURS* and MDQ* | Cases:<br>Males:<br>33.9 years;<br>Females:<br>34.4 years;<br><br>Controls:<br>Males:<br>30.3 years;<br>Females:<br>29.0 years; | Cases: 50.7%<br>Controls: 40.1% |
| Fasmer et al., 2012 (Fasmer et al., 2012) | Norway | Cross sectional analysis of prescription data covering the entire country during one year | Total:<br><br>4,640,219 | **Migraine (G43):**<br><br>Number and percent of Norwegian population being dispensed anti-migraine drugs at least once during 2006. | 18,481 | Number and percent of Norwegian population being dispensed ADHD drugs at least once during 2006. | 20-49 years:<br>Migraine:<br>58.6%;<br>ADHD 26.9%<br>50+ years:<br>Migraine:<br>34.8%,<br>ADHD: 2.3% | Male/ female ratio<br>ADHD: varying from 1.93 (age 20-29) to 0.83 (age 70-79); for migraine: from 0.25 to 0.28 |
| Ball et al., 1999 (Ball, Wooten, & Crowell, 1999) | USA | Review of literature and case report of six patients with Obstructive Sleep Apnea (OSA) recruited from a sleep disorder center. | 6 | **Sleep disorders (G47):**<br><br>OSA diagnosed with polysomnograms, severity by Respiratory Disturbance Index | 6 | Patients previously diagnosed with ADHD, diagnostic criteria not given. WURS* (completed for 5) to assess whether ADHD symptoms present from childhood | 38.5<br><br>(20-50) | 100 % |
| Bijlenga et al., 2013 (Bijlenga, van der Heijden, et al., 2013) | The Nether-lands | Cross sectional analysis; see above. | 391 | **Sleep disorders (G47):**<br><br>Dutch questionnaires based on MEQ*, Munich Chronotype Questionnaire and the Seasonal Pattern Assessment Questionnaire–Global Seasonality Score. | 202 | Diagnosed by trained psychologist/ psychiatrist at outpatient clinic for adult ADHD;<br><br>see above | See above | See above |

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| Bijlenga et al., 2013 (Bijlenga, Van Someren, et al., 2013) | The Nether-lands | Case control study.<br><br>Cases: adult ADHD patients with delayed sleep phase syndrome (DLPS), recruited from an outpatient adult ADHD clinic. Matched, healthy controls recruited by e-mail invitations. Participation rates not given. | 24 | **Sleep disorders (G47):**<br><br>DLPS based on self- report questionnaires on sleep hygiene, actigraphy, measurements of core body and skin temperature, melatonin measurements from saliva, sleep logs. | 12 | Diagnosed by trained psychologist/psychiatrist at outpatient clinic for adult ADHD, using DIVA 2.0 (semi-structured diagnostic interview based on *DSM-IV* criteria). | ADHD-patients: 32.5 (9.9)<br><br>Controls: 32.4 (10.8) | ADHD-patients: 50%<br>Controls: 50% |
| Boonstra et al., 2007 (Boonstra et al., 2007) | The Nether-lands | 1) Case control comparison,<br><br>Cases: adults with ADHD, self-referred or referred by other clinicians to outpatient clinic for assessment of ADHD. Matched controls without ADHD or other psychiatric disorders, no information on how they were recruited. Participation rates not given.<br><br>2) Double blind, placebo-controlled, cross-over medication trial among 31 of the 33 ADHD cases | 1) 72 (33 ADHD patients, 39 controls<br><br>2) 31 ADHD patients | **Sleep disorders (G47):**<br><br>1) Comparison of circadian rhythm disturbances. Measured by actigraphy, sleep and activity logs.<br><br>2) Assessing effect of methylphenidate on circadian rhythm and sleep quality in ADHD patients | 1) 33<br><br>2) 31 | Diagnosed by trained psychiatrist at outpatient clinic for adult ADHD, using semistructured diagnostic interviews and self-report questionnaire.<br><br>*DSM-IV* criteria applied. | ADHD-patients:<br><br>1) 37.9 (10.3);<br><br>2) 37.8 (10.6)<br><br>Controls: 37.8 (9.5) | ADHD-patients: 48.5%<br><br>Controls: 46.2% |
| Fargason et al., 2013 (Fargason, Hollar, White, & Gamble, 2013) | USA | Case-control study. Cases: sample of all new referrals and established patients seen in an ADHD clinic over a 6-week period who met the inclusion criteria (ADHD but not active psychiatric symptoms, insomnia or circadian rhythm sleep disorder). Healthy, matched controls without ADHD and sleep disorders. No information on how controls were recruited, or participation rates. | 105 | **Sleep disorders (G47):**<br><br>Sleep quality and rhythm. PSQI*. Separate questionnaire with questions on sleep timing and medication. Hamilton Depression Scale and Hamilton Anxiety Scale to exclude people with residual anxiety and depression. | 80<br>ADHD + stimulants: 39;<br>ADHD + non-stimulants: 15;<br>ADHD + no medicine: 26; | Clinical interview, MINI* and ASRS*. All established clinical participants were on medication and all new referrals were unmedicated awaiting psychopharmacological treatment. | Two thirds under 40 years<br>Range:<br><br>19-65. | 53% |
| Fisher et al., 2014 (Fisher et al., 2014) | Canada | Chart review over 20 years of patients with ADHD from one outpatient clinic, with respect to neuropsychological tests, sleep disorders and health symptoms | 1828, of which 1163 adults | **Sleep disorders (G47):**<br><br>Sleep, cognitive function, fatigue. Neuropsychological test battery with standard tests used over time. Self-report questionnaires: Personal Problems Checklist for Adults, Personal History Checklist for Adults, Patient Behavior Checklist for ADHD Adults, Physical Complaints Checklist for ADHD Adults | 1163 adults;<br>877 inattentive type;<br><br>286 hyper-active/ impulsive and comorbid disorders | Clinical assessment by trained neuropsychologist using same neuropsychological test battery over 20 years, in addition to self-report questionnaires with respect to sleep, attention, psychiatric and somatic health symptoms | Adult ADHD inattentive: 35 (11)<br>Adult ADHD hyper-active/ impulsive and comorbid disorders: 38 (13) | Adult ADHD inattentive: 39%<br><br>Adult ADHD hyper-active/ impulsive and comorbid disorders: 31% |
| Gamble et al., 2013 (Gamble, May, Besing, Tankersly, & Fargason, 2013) | USA | Analysis of a 2-week baseline phase of a randomized, placebo controlled crossover trial on effect of ramelteon on sleep problems in ADHD adults. Matched controls without ADHD, psychiatric disorders or sleep problems. Recruitment by newspaper ads and from outpatient | 38 | **Sleep disorders (G47):**<br><br>Insomnia or Delayed Sleep Phase Disorder assessed by clinical interview, meeting *DSM-IV-TR* criteria. | 24;<br>Combined type:<br>10 (42%);<br>Inattentive type:<br>5 (21%); | ADHD according to *DSM-IV-TR* criteria. Clinical interview by experienced psychiatrist. ADHD Rating Scale, MINI*, Hamilton Depression and Hamilton Anxiety Scales. | ADHD-patients: 39.7 (12.8)<br>Controls: 39.6 (14.8) | ADHD-patients: 54%<br>Controls: 50% |

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| | | psychiatry clinic. Participation rates not given. | | | Hyper-active-impulsive type: 3 (13%); Symptoms controlled: 6 (25%) | | | |
| Gau et al., 2007 (Gau et al., 2007) | Taiwan | Cross sectional survey using self-report questionnaires among college students.<br><br>60.8% response rate. | 2284 | **Sleep disorders (G47):**<br><br>Various sleep problems (current and lifetime) by self-report questionnaires, based on the Sleep Habit Questionnaire.<br><br>Definitions of sleep problems according to *DSM-IV* criteria. | Highly likely ADHD: 64 (2.8%) Probable ADHD: 74 (3.2%) Possible ADHD: 447 (19.6%) | Chinese version of ASRS*, after 2-way translation. | Total group: 19.3 (2.7) | Total group: 50.6% |
| Kass et al., 2003 (Kass, Wallace, & Vodanovich, 2003) | USA | Cross sectional survey using self-report questionnaires among a sample of students. No information on response rate. | 148 | **Sleep disorders (G47):** Epworth Sleepiness Scale, the Athens Insomnia Scale and The Boredom Proneness Scale. | 12 | Attention deficit scores on the ABC* indicating ADHD | Total group: 22.7 (3.4) | Total group: 47.3 % |
| Kooij et al., 2001 (Kooij, Middelkoop, van Gils, & Buitelaar, 2001) | The Netherlands | Open-label case-control study. Adult ADHD patients from an outpatient clinic and healthy matched controls. No information on from where the controls were selected, or participation rate. | 16 | **Sleep disorders (G47):**<br><br>Sleep log and actimeter six consecutive nights. | 8 | Semi-structured interview using *DSM-IV* criteria. Presence of ADHD symptoms in childhood confirmed by family report. | ADHD: 29.4 (8.2) Controls: 33.1 (7.2) | ADHD: 62.5% Controls: 50% |
| Langberg et al., 2014 (Langberg, Dvorsky, Becker, & Molitor, 2014) | USA | Prospective, longitudinal study including undergraduate students with ADHD. Flyers, poster and e-mails offering a free diagnostic evaluation of students with previous ADHD diagnosis or difficulties with concentration and attention. Responders: 139, after telephone screening 94 eligible, 62 taking at least three courses at university. | 62 | **Sleep disorders (G47):**<br><br>The Pediatric Daytime Sleepiness Scale.<br><br>The Barkley Functional Impairment Scale. The Behaviour Assessment System for Children 2nd ed., Self-Report of Personality - College Version. | Total: 62 Inattentive: 35<br><br>Combined: 27<br><br>ADHD medicine: 36 | *DSM-IV* criteria. BAARS-IV*, CAADID* to both student and parent/guardian. | ADHD: 19.50 (2.46) | ADHD: 56.5 % |
| Mahajan ., 2010 (Mahajan, Hong, Wigal, & Gehricke, 2010) | USA | Case study including unmedicated ADHD patients without any major health problems, recruited from local colleges and clinical referrals. Participation rate not given. | 22 | **Sleep disorders (G47):**<br><br>PSQI (self-report questionnaire). | 22 Inattentive: 10 Combined: 9 Hyper-active/ impulsive subtype: 3 | Semi structured interview by expert clinicians: QUEST*; SCID*. | 29 (8.2) | 81.8 % |
| Middelkoop et al., 1997 (Middelkoop, Van Gils, & Kooij, 1997) | The Netherlands | Case-control comparison of sleep characteristics between unmedicated ADHD patients and controls reporting to be physically and mentally in good health without sleep complaints. | 22 | **Sleep disorders (G47):**<br><br>Actimetry and sleep logs during six consecutive nights. Subjective sleep | 11 | Diagnostic interview according to the *DSM-IV* criteria including childhood history of ADHD confirmed by family members. | ADHD: 32 (8).<br><br>Controls: 34 (11) | ADHD: 63.6%<br><br>Controls: 63.6% |

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| | | No information on recruitment or participation rate. | | quality assessed by using a five-point scale. | | | | |
| Naseem et al., 2001 (Naseem, Chaudhary, & Collop, 2001) | USA | Case report describing 3 ADHD cases referred to a sleep center. | 3 | **Sleep disorders (G47):**<br>Sleep apnea diagnosed at a sleep clinic. Polysomnography, clinical examination. | 3 | Clinically diagnosed.<br><br>No further information. | 19, 23 and 44 years old. | 100% |
| Oguzturk et al., 2013 (Oguzturk, Ekici, Cimen, Ekici, & Senturk, 2013) | Turkey | Clinically based survey of 113 patients referred to a hospital for assessment of sleep apnea after clinical referral. Cases: diagnosed with sleep apnea. Controls without sleep apnea. No further information on how controls were selected. Participation rates not given. | 113 | **Sleep disorders (G47):**<br><br>Obstructive sleep apnea: nocturnal polysomnography and ESS. | 81 | ADHD scale based on *DSM-IV* criteria. | Sleep apnea: 48.1 (8.9)<br><br>Controls: 44.1 (13.2) | Sleep apnea: 81.5 %<br><br>Controls: 62.5 %. |
| Oosterloo et al., 2006 (Oosterloo, Lammers, Overeem, de Noord, & Kooij, 2006) | The Nether-lands | Self-report questionnaire based study.<br><br>The ADHDRS* and the ESS* were sent to 140 patients previously diagnosed with primary hypersomnia at a narcolepsy clinic (returned with both questionnaires completed from 52.9%) and given to 61 ADHD patients from outpatient clinic specialized in adult ADHD (completed by 100%). | 135 | **Sleep disorders (G47):**<br><br>ESS* | 61 | ADHD patients: ASRS*, SGIK*<br><br>Diagnosed by experienced clinicians according to *DSM-IV* criteria.<br><br>Investigator-based ADHD Rating Scale. | Hypersomnia: 48.5 (6.2)<br><br>ADHD: 35.0 (10.3). | Hypersomnias: 40.5%.<br><br>ADHD: 57.4% |
| Philipsen et al., 2005 (Philipsen et al., 2005) | Germany | Case control study including aADHD patients from an outpatient ADHD clinic and sex- and age matched healthy controls.<br><br>Controls assessed by psychiatrists to rule out psychopathology, and healthy on the basis of physical examination and routine blood counting. Participation rate not given. | 40 | **Sleep disorders (G47):** Subjective: PSQI*, the Schlaffragebogen A.<br><br>Objective: polysomnography: 2 nights in a sleep laboratory. First night adaption and exclusion of sleep apnea syndrome. | 20 | Fulfilling *DSM-IV* or *ICD-10* criteria.<br>WURS*.<br>Severity of symptoms in adulthood self-rated on a 3-point Likert scale corresponding to *DSM-IV*.<br>Psychiatric comorbidity assessed by structural clinical interview by experienced clinicians. | ADHD: 33.5 (8.9)<br><br>Controls: 33.3 (8.8) | 55% both ADHD and controls. |
| Sangal & Sangal, 2004 (Sangal & Sangal, 2004) | USA | Retrospective analysis of medical records in a neurophysiology practice investigating consecutive patients presenting with symptoms of sleep disorders or ADHD. Consecutive patients presenting with snoring and sleepiness and consecutive patients presenting with childhood inattention to evaluate the relationship between sleepiness and inattention. | 56 | **Sleep disorders (G47):** ESS*<br><br>Sleepy snorers (n=38):<br>Polysomnography and multiple sleep latency test. | 18 | ADHDRS* in patients who presented inattention in childhood. They met *DSM-IV* criteria for ADHD or ADHD in partial remission. Number of partial remission: N/A. | ADHD: 31.9 (12.2)<br><br>Snoring and sleepiness: 48.7 (15.5) | ADHD:83.3%<br><br>Snoring and sleepiness: 76.3% |
| Schredl et al., 2007 (Schredl et al., 2007) | Germany | Case- control study with ADHD cases from an out-patient clinic. See above | 564 | Sleep disorders (G47):<br>Sleep questionnaires:<br>The Schlaffragebogen A<br>The Schlaffragebogen B<br>LISST* | 120<br><br>See above. | All cases met *DSM-IV* diagnoses of ADHD. See above. | See above. | See above. |

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| Sobanski et al., 2008(Sobanski, Schredl, Kettler, & Alm, 2008) | Germany | Matched case-control study including consecutive non-medicatied aADHD patients referred to adult ADHD clinic and healthy controls.<br><br>Controls: participated in different sleep studies (referenced in article). | 68 | Sleep disorders (G47):<br><br>The Schlaffragebogen A The Schlaffragebogen B. Polysomnography.. Psychiatric comorbidity: | 34 | Clinical interview: Consensus on diagnosis between senior psychiatrist and senior child-and adolescent psychiatrist.<br><br>ADHD during childhood and present according to *DSM-IV* criteria. WURS*. BADDS*.<br><br>Psychiatric comorbidity: A semi-structured clinical interview, not named. | ADHD whole sample: 36.1 (9.3)<br><br>Controls: age/sex matched. | ADHD whole sample: 61.8%<br><br>Controls: age/sex matched. |
| Surman et al., 2006 (Surman, Thomas, Aleardi, Pagano, & Biederman, 2006) | USA | Case study of ADHD patients consecutively referred to an adult ADHD program at a major academic center. | 6 | **Sleep disorders (G47):**<br><br>MEQ*, PSQI*, ESS*, polysomnography. | 6<br><br>Inattentive: 2<br><br>Combined:4 | *DSM-IV* criteria. SCID* and modules from Kiddie-SADS*. | Range ADHD: 40-54 | ADHD: 66.7 % |
| Surman et al., 2009 (Surman et al., 2009) | USA | Case-control study of adults with and without ADHD. Participants recruited via advertisements in the greater Boston area. ADHD subjects also from referrals to a psychiatric hospital clinic.<br>Response rate not given. | 299 | Sleep disorders (G47):<br><br>Self-report survey including "own made" questions about sleeping habits, and the Children´s sleep behaviour scale. | 182 | Lay interviewers: SCID-*I, modules from Kiddie-SADS*. Committee of clinicians: reviewed the data from the interviews and agreed on diagnosis. | ADHD: 36.3 (10.8)<br><br>Controls 29.4 (8). | ADHD: 52%<br>Controls: 47% |
| Van Veen et al., 2010 (Van Veen, Kooij, Boonstra, Gordijn, & Van Someren, 2010) | The Nether-lands | Matched case- control study. Cases with aADHD consecutively recruited from an out-patient clinic, grouped in those with and without sleep-onset insomnia.<br>Controls: physically healthy with no history or symptoms of mental or sleeping disorders. No information on recruitment.<br>Total number of controls not specified: 38 controls with data on dim light melatonin onset, 24 with actigraphy data.<br>Participation rates not specified. | Not specified. | Sleep disorders (G47):<br><br>SDQ* (Dutch).<br><br>Actigraphy measured 7 consecutive days/nights. Salivary melationin samples (one night). | 40 | Lifetime ADHD with childhood onset according to the *DSM-IV* criteria, diagnosed by experienced clinicians. Semi structured interview for ADHD and comorbidity. | Range ADHD 18-55 years,<br><br>Controls: dim light melatonin onset: 28.9 (9.9)<br><br>Controls: actigraphy 29.1 (7.9). | ADHD: 52.5%<br><br>Controls: dim light melatonin onset: 53%<br><br>Controls: actigraphy: 50%. |
| Vogel et al., 2015 (Vogel et al., 2015) | The Nether-lands | Case control study,<br><br>see above | 470,<br><br>see above | Sleep disorders (G47):<br>Circadian rhythm disturbance and obesity.<br>Chronotype and sleep characteristics assessed with the "Vragenlijst Ochtend/Avondmens" (Questionnaire Morning /Evening type) and the Munich Chronotype Questionnaire | 202 | Not described in detail, but they were included "after extensive diagnostic assessment at the PsyQ outpatient clinic", see above. | See above | See above |
| Voinescu et al., 2012 (Voinescu, Szentagotai, & David, 2012) | Romania | Study based on self-report questionnaires from two samples, one consisting of students (sample 1) and one from the general population from all over Romania (sample 2). Participation by self-selection. Individuals with likely ADHD, based on | 551<br><br>Sample 1: 301 Sample 2: 250 | **Sleep disorders (G47):**<br><br>Self-report: The Sleep Condition Indicator, The Sleep Timing Questionnaire, SDQ*, CMQ*. | 46 | ASRS*, BAARS-IV* | Sample 1: 21.8 (2.5)<br>Sample 2: 38.6 (12.4) | Sample 1: 15.3%<br><br>Sample 2: 29.6%<br><br>ADHD: 30.4% |

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| | | questionnaire scores, matched with controls with low scores. | | | | | Likely ADHD: 26.9 (10.1)<br>Controls: 27 (10.3) | Controls: 30.4% |
| Douniol et al., 2009 (Douniol et al., 2009) | France | Case study of individuals diagnosed with myotonic dystrophy type 1 at a specialized institute on muscle diseases and assessed for psychiatric comorbidity.<br>47 invited, participation rate 59.6%. | 28 | **Myotonic dystrophy (G71.1):**<br><br>Confirmed by molecular diagnosis and onset between 1-10 years. | 8, all inattentive | MINI*, ASRS* | Overall:<br><br>17.3 (4.6) | Overall: 46.4%. |
| Echenne et al., 2008 (Echenne et al., 2008) | France and Canada | Retrospective follow-up study with chart review of patients with myotonic dystrophy, including congenital and infantile/juvenile forms, followed by the same neurologists over 7-28 years (median 17 years). | 32 | **Myotonic dystrophy (G71.1):**<br><br>Diagnosed by molecular biology analysis in the patients themselves or in their family | 11<br>Myotonic dystrophy type 1: N=7<br>Post-natal myotonic dystrophy: N= 4 | No information on how ADHD was diagnosed or if the subjects were tested for ADHD as adults. | N/A | Total: 71.9% |
| Saez-Francas et al., 2012 (Saez-Francas et al., 2012) | Spain | Clinical sample of consecutive adults referred to an outpatient program at a university hospital due to symptoms of chronic fatigue.<br><br>Original sample 169, after exclusions: 93.5%. | 158 | **Chronic Fatigue Syndrome (G93.3):**<br>Diagnosed according to the Centers for Disease Control and Prevention criteria, a complete clinical assessment.<br><br>The Fatigue Severity Scale and Fatigue Impact Scale. | 33 | WURS*, CAADID*, ADHD-RS*, BIS*. | Total CSF: 48.6 (8.9)<br><br>Adult ADHD: 47.6 (8.0) | Total CSF: 6.4%<br><br>Adult ADHD: 3%. |
| Young, 2013 (Young, 2013) | USA | Case study.<br><br>Three cases with chronic fatigue syndrome (CSF) responding poorly to treatment and referred for psychiatric consultation. | 3 | **Chronic Fatigue Syndrome (G93.3):**<br>No information on how CSF was diagnosed.<br>ESS* and the Fatigue Severity scale to measure sleep and the severity of fatigue. | 3 | Comprehensive psychiatric interview. BADDS*, A-ADDES*. | 38, 48 and 58 years old. | 0 |
| Kooij & Bijlenga, 2014 (Kooij & Bijlenga, 2014) | The Netherlands | Online survey with self-selected participants who reported photophobia. Participants invited through ADHD patient organizations, authors' Facebook and Twitter accounts, and therapists from outpatient Adult ADHD clinic. | 494 | **Photophobia (H53.14)**<br>Online survey:<br>Question on having photophobia apart from any migraine episodes ("My eyes are sensitive to light," yes or no), and more detailed questions if positive answer. | Total ADHD group: 231<br><br>ADHD diagnosis: 149<br><br>ADHD symptoms: 82 | Online survey:<br><br>A multiple choice question on having diagnosed ADHD (I have a diagnosis of ADHD; I do not have a diagnosis but I do have ADHD symptoms; I do not have ADHD). | Self-reported ADHD diagnosis yes: 37.0 (9.4)<br>Self-reported ADHD symptoms yes: 36.3 (10.2)<br>Control group: 38.4 (11.7) | Self-reported ADHD diagnosis yes: 23%<br>Self-reported ADHD symptoms yes: 33%<br>Control group: 19% |
| Olson et al., 2012 (Olson, Louwagie, Diehl, & Mohney, 2012) | USA | Retrospective case-control study, using review of medical records for cases with congenital esotropia (CES), and matched controls. Selection of cases through the resources of Rochester Epidemiology Project (REP), a medical records database where all medical records from all health care delivered in the region are linked. | 254 | **Congenital esotropia (H50.00):**<br><br>Recorded with diagnosis code in the REP. | 14<br><br>CES cases: 8<br><br>Controls: 6 | Medical records reviewed for diagnoses of mental illness as defined by *DSM-IV,* diagnosed by psychiatrist, family physician or emergency physician. Age at ADHD diagnosis not specified. | Mean age at psychiatric diagnosis:<br>CES cases: 16.0 (3.1-37.7)<br>Controls: 14.4 (3.2-32.0) | CES cases: 52%<br>Controls: 52% |

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| Bijlenga et al., 2013 (Bijlenga, van der Heijden, et al., 2013) | The Nether-lands | Cross sectional analysis; see above. | 391 | **Diseases of the Circulatory System (Chapter IX):**<br><br>Self- report questionnaires; see above. | 202 | Diagnosed by trained psychologist/ psychiatrist at outpatient clinic for adult ADHD; see above | See above | See above |
| Hodgkins et al., 2011 (Hodgkins et al., 2011) | USA | Retrospective analysis of health care claims and employer-rated health and productivity management database in 2006; see above. | 156,973 | **Diseases of the Circulatory System (Chapter IX):**<br>Information from databases, see above. | 31,752 | Diagnosis based on *ICD-9-CM*. See above. | See above. | See above. |
| Semeijn et al., 2013 (Semeijn et al., 2013) | The Netherlands | Case control study; see above. | 231 | **Diseases of the Circulatory System (Chapter IX):**<br>Respondents asked about cardiac diseases and hypertension. Information from general practitioners. See above. | 23 | Screening list and DIVA*; see above | See above | See above |
| Spencer et al., 2014 (Spencer et al., 2014) | USA | Case control study; see above | 198 | **Diseases of the Circulatory System (Chapter IX):**<br>Self-reported history and measurements; see above. | 98 | Structured clinical interview for *DSM-IV*, and ASRS*; see above | See above. | See above. |
| Bijlenga et al., 2013 (Bijlenga, van der Heijden, et al., 2013) | The Nether-lands | Cross sectional analysis; see above. | 391 | **Allergic diseases in general (Chapter X):**<br><br>Self-report questionnaires; see above. | 202 | Diagnosed by trained psychologist/ psychiatrist at outpatient clinic for adult ADHD; see above | See above. | See above. |
| Chen et al., 2013 (Chen et al., 2013) | Taiwan | Registry based cross- sectional comparison of cases with ADHD, cases with TIC disorder, cases with both ADHD and TIC and a matched, randomly chosen control group using data from the Taiwan National Health Insurance Research Database (NHIRD). | Total<br><br>39,880<br>Cases: 7976<br>Controls: 31,904 | **Allergic diseases in general (Chapter X):**<br>Asthma, allergic rhinitis, atopic dermatitis, allergic conjunctivitis, based on *ICD-9-CM* codes registered in Taiwan NHIRD. Diagnoses given at least twice. | ADHD alone: 5811<br>ADHD and Tic disorder: 34 | Based on *ICD-9-CM* diagnosis codes registered in NHIRD, Diagnoses given at least twice | ADHD alone: 15.81 (7.33)<br>Tic alone: 21.85 (16.7)<br>ADHD + Tic: 15.22 (4.14)<br>Controls: 17.17(10.49) | ADHD alone: 76.6%<br>Tic alone: 68.6%<br>ADHD + Tic: 90.5%<br>Controls: 77.4% |
| Schmitt et al., 2016 (Schmitt, Stadler, Kuster, & Wustenberg, 2016) | Germany | Cohort study with German National Health Insurance beneficiaries registered in a population-based administrative healthcare database covering 55% of the population in Saxony; age and gender representative for the region and for Germany. | Total cohort: 1,811,094 | **Allergic Rhinitis (J30):**<br><br>Based on the *ICD-10* code registered in the healthcare database at least twice between 2005 and 2011 | Numbers not given, only % and only for those <18 years | Based on the ICD-10 code (F90) registered at least twice in the healthcare database between 2005 and 2011 | Overall cohort:<br><br>45.3 (23.5)<br>ADHD not described in adults | Overall cohort: 45.9%.<br>ADHD not described in adults |
| Bijlenga et al., 2013 (Bijlenga, van der Heijden, et al., 2013) | The Nether-lands | Cross sectional analysis; see above. | 391 | **Respiratory Disorders in general (Chapter X):**<br><br>Self-report questionnaires; see above. | 202 | Diagnosed by trained psychologist/ psychiatrist at outpatient clinic for adult ADHD; see above | See above. | See above. |

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| Semeijn et al., 2013 (Semeijn et al., 2013) | The Netherlands | Case control study; see above. | 231 | **Respiratory Disorders in general (Chapter X):** Respondents asked about having chronic nonspecific lung disease (asthma, chronic bronchitis, pulmonary emphysema) Information from general practitioners. See above. | 23 | Screening list and DIVA*; see above. | See above. | See above. |
| Fasmer et al., 2011 (Fasmer, Halmoy, Eagan, Oedegaard, & Haavik, 2011) | Norway | Cross sectional study based on self-report questionnaires comparing an ADHD case group with a control group | 1313 | **Asthma (J46):** Based on positive response to the question: Have you ever had asthma? | 594 | 340 patients recruited from a national registry of adult ADHD patients, all diagnoses verified by 1 of 3 national expert committees. Remaining 254 recruited through psychiatrists / psychologists nation-wide. Diagnosis according to *ICD-10-R* criteria with modifications allowing the inattentive subtype to be sufficient for diagnosis. | ADHD: 34.0 (10.3) Controls: 29.6 (6.5) | ADHD: 51.7% Controls: 40.6% |
| Chen et al., 2013 (Chen et al., 2013) | Taiwan | Registry based cross- sectional comparison between cases with ADHD, cases with TIC disorder, and with both and a matched, randomly chosen control group, see above | See above | **Asthma (J46):** Based on *ICD-9-CM* codes registered in Taiwan NHIRD. See above | See above. | Based on *ICD-9-CM* codes registered in Taiwan NHIRD. See above | See above. | See above. |
| Fasmer et al., 2011 (Fasmer, Riise, et al., 2011) | Norway | Regsitry based cross sectional study using data from the Norwegian Prescription Database | Source popu-lation: 4,640,219 | **Asthma (J46):** Defined as individuals being dispensed anti-asthma drugs at least once in 2006 | 18,481 | Defined as individuals being dispensed ADHD drugs at least once in 2006 | ADHD: 29% were 20 years or more | ADHD: 66% in age 20-29; decreasing till 45% in age 70-79 |
| Hodgkins et al., 2011 (Hodgkins et al., 2011) | USA | Retrospective analysis of health care claims and employer-rated health and productivity management database in 2006; see above. | 156,973 | **Asthma (J46):** Information from databases, see above. | 31,752 | Diagnosis based on *ICD-9-CM*. See above. | See above. | See above. |
| Karlstad et al., 2012 (Karlstad, Nafstad, Tverdal, Skurtveit, & Furu, 2012) | Norway | Registry based cross sectional study based on linked data from Norwegian census data, the Central Population Registry of Norway and the Norwegian Prescription Database | Standard pop.: 1,239,533 Study pop.: (asthma cases): 37,060 | **Asthma (J46):** Defined as individuals being dispensed reimbursed drugs for asthma, reimbursement diagnosis based on *ICD-10* or *ICPC-2* codes. | ADHD 20-29 years: Males: 89 (1.6%) Females: 108 (1.6%) | Individuals being dispensed reimbursed drugs for ADHD, with reimbursement codes based on *ICD-10* or *ICPC-2*. | Age 20-29 years in standard population: Males: 27.2% Females: 39.6% | In standard population age 20-29: 45.2% |
| Secnik et al., 2005 (Secnik et al., 2005) | USA | Registry based matched case control study; see above. | See above | **Asthma (J46):** Registered *ICD-9* diagnoses; see above | See above | Registered *ICD-9* code; see above | See above | See above |
| Spencer et al., 2014 (Spencer et al., 2014) | USA | Case control study; see above. | 198 | **Asthma (J46):** Self-reported history of asthma; see above. | 98 | Structured clinical interview for *DSM-IV* and ASRS*; see above. | See above. | See above. |
| Bijlenga et al., 2013 (Bijlenga, van der | The Nether-lands | Cross sectional analysis; see above. | 391 | **Diseases of the Digestive System in general (Chapter K):** Self-report questionnaires; see above. | 202 | Diagnosed by trained psychologist/ psychiatrist at outpatient clinic for adult ADHD; see above | See above | See above |

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| Heijden, et al., 2013) | | | | | | | | |
| Hodgkins et al., 2011 (Hodgkins et al., 2011) | USA | Retrospective analysis of health care claims and employer-rated health and productivity management databases in 2006; see above. | 156,973 | **Irritabel bowel syndrome (K58):** Information from databases, see above. | 31,752 | Diagnosis based on *ICD-9-CM*. See above. | See above. | See above. |
| Secnik et al., 200 (Secnik et al., 2005) | USA | Registry based matched case control study; see above. | See above | **Irritabel bowel syndrome (K58):** Registered *ICD-9* diagnosis; see above. | See above | Registered *ICD*-9 code; see above. | See above. | See above. |
| Nieder-hofer & Pittschieler 2006 (Niederhofer & Pittschieler, 2006) | Italy | Case report of ADHD symptoms in 78 patients (60% of invited) with celiac disease before and after starting gluten-free diet. | 78 | **Celiac disease (K90.9):** Diagnosis based on positive blood serum levels (endomysium antibodies and other biomarkers) and histological examination of jejunal or duodenal mucosa. | Only given ADHD–like symptoms assessed by Conner Scale Hype-scheme | ADHD symptoms were assessed by Conner Scale Hypescheme (based on *DSM-IV* criteria) before and 6 months after starting gluten-free diet. | Invited population 19.3 (3-57) | Included population: 46.2% |
| Niederhofer, 2011 (Niederhofer, 2011) | Italy | Case report of 67 ADHD patients (87% of invited) where 10 were diagnosed with celiac disease. ADHD symptoms in these 10 were evaluated before and 6 months after starting gluten-free diet. | 67 | **Celiac disease (K90.9):** Blood serum levels of all included patients checked for endomysium antibodies and other biomarkers | 67 | All included patients had a diagnosis of ADHD, but unknown from where or based on what criteria. ADHD symptoms were assessed by Conner Scale Hypescheme (based on *DSM-IV* criteria) before and 6 months after starting gluten-free diet. | Total group: 11.4 (7-42) years | Total group: 77.6% |
| Zelnik et al., 2004 (Zelnik, Pacht, Obeid, & Lerner, 2004) | Israel | Matched case control study. Celiac disease (CD) cases recruited from pediatric gastroenterology clinic, non-CD control group recruited from same clinic. Participation rates not given. | 322 | **Celiac disease (K90.9):** Diagnosis based on postivie blood serum levels (endomysium antibodies and other biomarkers) and intestinal biopsies | Only given combined with learning disabilities: CD cases: Females: 13 (20.3%); Males: 10 (21.2%) Controls: Females: 11 (8.7%); Males: 11 (12.9%) | Initially based on self-report questionnaires (no details given), followed by full neurological examination for those who reported neurological symptoms. ADHD diagnosis and learning disabilities based on the diagnostic criteria of *DSM-IV* | CD-patients: 20.1 (8.9); Controls: 20.1 (9.0) | CD-patients: 42.3%; Controls: 40.3% |
| Bijlenga et al., 2013 (Bijlenga, van der Heijden, et al., 2013) | The Nether-lands | Cross sectional analysis; see above. | 391 | **Skin disorders in general (Chapter XII):** Self-report questionnaires; see above. | 202 | Diagnosed by trained psychologist/ psychiatrist at outpatient clinic for adult ADHD; see above. | See above. | See above. |
| Cicek et al., 2009 (Cicek et al., 2009) | Turkey | Case control study from a dermatology clinic. | 110 | **Atopic dermatitis (L20):** Diagnosed in accordance with Hanifin Rajka classification. | Inattention criterion: 19 AD cases, 3 controls. | Clinical interview using *DSM-IV* criteria. | AD cases: 27.96 (6.3)<br><br>Controls: 27.82 (7.9) | AD cases: 20%<br><br>Controls: 24% |

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| | | Cases: atopic dermatitis (AD) patients. Controls: non-atopic patients from same clinic.<br><br>Participation rates not given. | | | Hyper-activity / impulsivity<br>20 AD cases, no controls<br><br>Both criteria:<br>12 AD cases, no controls | Self-report by Adult ADD/ADHD DSM-IV-Based Diagnostic Screening and Rating Scale. | | |
| Chu et al., 2012 (Chu et al., 2012) | Taiwan | Registry based matched case control study using data from the Taiwan National Health Insurance Research Database (NHIRD) from 2000 to 2009 | 25,585 | **Alopecia areata (L63):**<br><br>Alopecia areata (AA) based on registered *ICD-9* code in the NHIRD, and diagnosed by a dermatologist. | Total: 93;<br>AA patients: 19 (0.4%);<br><br>Controls: 74 (0.4%) | Based on registered *ICD-9* codes in the NHIRD, and diagnosed by a psychiatrist | AA cases:<br>Median age at diagnosis:<br>31 years (IQR 22-42)<br>Controls matched on age and sex | AA cases: 49.2%<br><br>Controls:<br><br>49.2% |
| Gupta et al., 2014 (Gupta, Gupta, & Vujcic, 2014) | Canada | Registry-based retrospective cross sectional study comparing acne patients with all other dermatology patients in national databases (National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey) | 55,825 | **Acne (ICD-10: L70).**<br><br>Based on registered *ICD9-CM* codes. | 110 (total group), the majority < 18 years | Based on registered *ICD9-CM* codes | 14.27 (1.16) | 64.7% |
| Bijlenga et al., 2013 (Bijlenga, van der Heijden, et al., 2013) | The Nether-lands | Cross sectional analysis; see above. | 391 | **Musculoskeletal disorders in general (Chapter XIII):**<br><br>Self-report questionnaires; see above. | 202 | Diagnosed by trained psychologist/ psychiatrist at outpatient clinic for adult ADHD; see above | See above | See above |
| Spencer et al., 2014 (Spencer et al., 2014) | USA | Case control study; see above. | 198 | **Musculoskeletal disorders in general (Chapter XIII):**<br>Self-reported history; see above | 98 | Structured clinical interview for *DSM-IV* and ASRS*; see above | See above | See above |
| Stray et al., 2013 (Stray et al., 2013) | Norway | Case control study. Cases: ADHD patients from outpatient clinic. Participation rate not given.<br><br>Controls: self-selection through word-of-mouth and flyers on bulletin boards to students and health care workers. | 48 | **Musculoskeletal disorders in general (Chapter XIII):**<br><br>Motor regulation problems assessed by the Motor Function Neurological Assessment battery (MFNU).<br>Pain assessed by the Pain Drawing and the Numerical Pain Rating Scale | 25 | All were outpatients at an addiction unit and had been diagnosed with ADHD, no information given on how diagnosed. All were responders to methylphenidate, none had Substance use disorder. | ADHD group: 33 (8.9)<br>Controls: 41 (14.1) | ADHD group: 56%<br>Controls: 34.8% |
| Semeijn et al.,<br><br>2013 (Semeijn et al., 2013) | The Netherlands | Case control study; see above. | 231 | **Rheumatoid arthritis (M05-M06):**<br>Respondents asked about having rheumatoid arthritis. Information from general practitioners.<br>See above. | 23 | Screening list and DIVA*; see above. | See above. | See above. |

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| Gao et al., 2015 (Gao, Lo, & Mok, 2015) | China | Matched case control study. Cases: consecutive adult patients at university-affiliated lupus clinic (participation rate not given). Participating cases were asked to invite one friend or peer of same age and sex who had good past health as healthy control. | 181<br><br>117 SLE cases; 64 healthy controls | Systemic lupus erythematosus (M32):<br><br>Patients recruited from lupus clinic. No current or recently active disease. Disease activity assessed by SLE Disease Activity Index, clinical manifestations and autoantibody profile from medical records. | SLE patients: Possible ADHD: 9 (7.7%) Controls: Possible ADHD: 4 (6.3%) | Possible ADHD based on self-report questionnaire: Chinese version of the ASRS*; Part A (Inattention) and Part B (Hyperactivity/ Impulsivity) | SLE cases: 40.9 (8.9) Control group: 38.8 (9.4) | SLE cases: 6.8% Control group: 6.2% |
| Garcia et al., 2013 (Garcia et al., 2013) | USA | 1) Matched case control study. Cases: Systemic lupus erythematosus (SLE) patients, no info on how recruited or participation rate;<br>Controls: "healthy subjects" recruited when donating blood for immune-biologic studies, no info on participation rate.<br><br>2) Placebo controlled trial with N-acetylcysteine to evaluate effect on ASRS* scores in SLE patients | 1) Total: 95 SLE cases: 49; Controls: 46<br>2) Clinical trial:<br>24 SLE patients | **Systemic lupus erythematosus (M32):**<br>Disease activity assessed by British Isles Lupus Assessment Group Index, and SLE Disease Activity Index. Fatigue assessed by the Fatigue Assessment Scale | N/A | Assessed by ASRS* self-report questionnaire. Scores compared. | SLE cases: 45.9 (1.8) Control group: 48.0 (1.5) | SLE cases: 6.1% Control group: 4.3% |
| Derksen et al., 2015 (Derksen, Vreeling, & Tchetverikov, 2015) | The Netherlands | Case report.<br>89 consecutive fibromyalgia patients from an outpatient rheumatology clinic were invited.<br>50 patients included, 44 patients completed a psychiatry interview (49.4%) | 44 | **Fibromyalgia (M79.7):**<br>Diagnosis met the 1990 American College of Rheumatology criteria. | 11 | Interview by trained psychiatrist or assistant psychiatrist; not further specified. | Not specified more than "adult" | No information |
| Krause et al., 1998 (Krause, Krause, Magyarosy, Ernst, & Pongratz, 1998) | Germany | Pilot study evaluating effect of ADHD-drug (moclobemide) on subjective and objective findings in fibromyalgia (FM) patients | 24 | **Fibromyalgia (M79.7):**<br>No information given, patients had «proven fibromyalgia» | FM patients: 7 “probable ADHD” and 5 “highly probable”.<br><br>Controls: 2 “probable ADHD”, none “highly probable” | Scores on Brown ADD* and WURS* compared between FM patients and controls | FM patients: 46.7 (9.4)<br><br>Controls: 47.1 (10.5) | FM patients:<br><br>8.3%<br><br>Controls:<br><br>8.3% |
| Hailer et al., 2014 (Hailer, Haag, & Nilsson, 2014) | Sweden | Case study (patients with Legg-Calve-Perthes disease (LCPD)) comparing results with published data from the Swedish general population. Participation rate 80% | 116 | **Calvé-Legg-Perthes (M91.1):**<br>Patients diagnosed or treated at Uppsala University Hospital between 1978-1995. | 29 likely ADHD based on ASRS* scores, 4 were previously diagnosed with ADHD and used medication | ASRS* symptoms checklist by interview | 27.6 (7.1) | 84% |
| Berry et al., 2005(Berry, Leitner, Clarke, | Australia | Review of clinical records for cases of genetically confirmed Angelman syndrome (AS) and presumed AS from clinical features, from an AS clinic. Compared with matched individuals with | 431 | **Congenital syndromes and anomalies (Chapter XVII):**<br>Angelman syndrome, gentically confirmed (N=62) and presumed based on clinifical features (N=29). Behavior | N/A | Behavior patterns from the DBC were grouped in "ADHD type" and "Food-related" behaviors | Genetically tested AS: 13.6 (1.3-40.7), Phenotypic AS: 11.8 (1.7-31.5) | Genetically tested AS: 56.5% Phenotypic AS: |

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| & Einfeld, 2005) | | intellectual disability (ID) from an epidemiological register. | | tested by questionnaires including questions from the Developmental Behavior Checklist (DBC) | | | Controls: Not given | 37.9%<br>Controls: Not given |
| Cornish et al., 2008 (Cornish et al., 2008) | United Kingdom | Matched case control study<br>Cases recruited through the UK Clinical Genetics Service and the UK Fragile X Society<br>No information on participation rate or control selection | 107 | **Congenital syndromes and anomalies (Chapter XVII):** Fragile X Syndrome premutation (carriers) (FXSp), genetically tested.<br>IQ and neuropsychological tests.<br>Neurology questionnaire on tremor symptoms and problems with gait and lower extremities | N/A | Increasing problems with response inhibition with age, and decreased selective attention in all ages in FXSp | FXSp group: 46.88 (14.50)<br>Controls: 45.33 (14.87) | FXSp group: 100%<br>Controls: 100% |
| Dorn et al., 1994 (Dorn, Mazzocco, & Hagerman, 1994) | USA | Family informant study, where 24 daughters of Fragile X syndrome (FXS) carrier fathers and 32 daughters of control fathers were interviewed of their fathers' behaviors retrospectively. Recruitment from a regional developmental assessment clinic at hospital serving FXS families nationwide. Participation rate not given. | 56 | **Congenital syndromes and anomalies (Chapter XVII):**<br>FXS carrier status.<br>24 fathers with FXS carrier status determined by pedigree analysis and DNA analysis. Outcome variables assessed by the Family Informant Schedule Criteria, an abuse questionnaire, the Parental Bonding Instrument and the Adult Attention-Deficit Hyperactivity (A-ADHD) checklist | N/A | FXS carrier and control fathers were interviewed by the Adult Attention-Deficit Hyperactivity (A-ADHD) checklist (*DSM-III-R* criteria). | Only information about the informants:<br>Daughters of FXS carriers: 37.5 (8.3)<br>Daughters of controls: 33.3 (7.8) | 100% in both FXS carriers and controls |
| Edvardson et al., 2014 (Edvardson et al., 2014) | Israel | Case study. Participants recruited from a Center for Down syndrome at a University Medical Center, Jerusalem. Participation rate 97.6%. | 83 | **Congenital syndromes and anomalies (Chapter XVII):**<br>Down syndrome recruited from a Center for Down syndrome | Overall: 26 (31.3%)<br>Mostly inattentive; 17 (65.4%)<br>Mostly impulsive-hyper-activity; 4 (15.4%)<br>Combined: 5 (19.2%) | Telephone interview of parents and guardians using the ADHD module of the Autism-Tics, Attention-Deficit/Hyperactivity Disorder, and other Comorbidities (A-TAC) Questionnaire | 16.2 (5-38) | 56.6% |
| Gothelf et al., 2004 (Gothelf et al., 2004) | Israel | Case study.<br><br>51 consecutive patients with Velocardiofacial syndrome (VCFS), age 6-30 years, recruited from the clinical genetic departments of two major hospitals, 2001-2003. Participation rate not given | 51 | **Congenital syndromes and anomalies (Chapter XVII):**<br>Velodcardiofacial syndrome, all genetically diagnosed, and all sporadic de novo cases. | Overall: 21 (41.2%)<br>Mostly inattentive:7 (33.3%)<br>Combined type:14 (66.7%) | Child psychiatrist blinded to the psychiatric status of the individual, interviewed parents using Schedule for Affective Disorders and Schizophrenia for School-Age children (K-SADS). If screen positive on ADHD, the full-module section of the K-SADS was used | Overall: 12.6 (6.9)<br><br>VCFS + ADHD: 11.1 (5.9)<br><br>VCFS - ADHD: 13.6 (7.4) | Overall: 64.7%<br><br>VCFS + ADHD: 85.7%<br>VCFS - ADHD: 50% |
| Halmoy et al., 2012 (Halmoy, Klungsoyr, Skjaerven, & Haavik, 2012) | Norway | Registry based nested case-control study. Cases were adult ADHD patients who were found eligible for stimulant treatment after a systematic diagnostic evaluation by one of three regional Expert committees on ADHD. Included cases were born from | 1,172,396 | **Congenital syndromes and anomalies (Chapter XVII):**<br>Congenital oral clefts as registered in the MBRN at birth or the following stay at the Neonatal intensive care unit. | 2323 | Adult patients with suspected ADHD, were referred to one of three regional Expert Committees of ADHD for assessment of central stimulant treatment in a national trial period 1997-2005. Based on a | ADHD patients: 27.2 (18-38)<br>Remaining birth cohort: 35.6 (25-45) | ADHD patients: 70.9%<br>Remaining birth cohort: 51.2% |

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| | | 1967 and registered in the Medical Birth Registry of Norway (MBRN). Controls were the remaining population, born in the same years, registered in the MBRN and surviving to adulthood. | | | | systematic diagnostic evaluation, 70% were found eligible for stimulant treatment (diagnosis confirmed and no contra-indications). | | |
| Muzykewicz et al., 2007 (Muzykewicz, Newberry, Danforth, Halpern, & Thiele, 2007) | USA | Retrospective chart review of 241 patients meeting clinical criteria for tuberous sclerosis (TSC). Charts were first screened, then reviewed by a psychiatrist, and 43 of 241 patients were referred to and seen by at least one of two psychiatrists affiliated with the TSC clinic. | 241 | **Congenital syndromes and anomalies (Chapter XVII):**<br>Details on diagnosis of **Tuberous sclerosis (TSC)** not given other than "meeting clinical criteria for tuberous sclerosis (TSC) and seen by a single neurologist". | 73 | From chart review: "73 (30%) patients had a history of ADHD type behaviors".<br><br>9 (21%) of the 43 patients seen by psychiatrist had ADHD, 8 combined type and 1 predominantly inattentive type. | Total group: Mean: 20 (8 months – 63.4 years)<br>ADHD group: Mean; 13 (3.2-46.2 years) | Total group: 49%<br><br>ADHD group:58% |
| Niklasson et al., 2009 (Niklasson, Rasmussen, Oskarsdottir, & Gillberg, 2009) | Sweden | Case study.<br>In-depth neuro-psychiatric assessment of 100 consecutive patients with 22q11.2 deletion syndrome (VCFS), all genetically confirmed, referred to a child neuro-psychiatric clinic. | 100 | **Congenital syndromes and anomalies (Chapter XVII):**<br>22q11.2 deletion syndrome, all genetically confirmed. | 30 | Neuropsychiatric evaluation by experienced psychiatrist, using extensive structured and semi-structured interviews, in accordance with *DSM-IV* criteria.<br>Neurocpsychological test battery and questionnaires. | 16 individuals > 16 years | Total group: 42%<br>In the > 16 years group: 38% |
| Piran et al., 2011 (Piran et al., 2011) | Canada | Matched case control study, comparing three groups of Tetralogy of Fallot (TOF) patients: those with 22q11.2 deletion syndrome, those with syndromic features and those without syndromic features. Adult patients prospectively included from a cardiac center, for screening and chart review. Initially 447 patients with TOF, 207 (51%) included in study | 207 | **Congenital syndromes and anomalies (Chapter XVII):**<br>Tetralogy of Fallot: three groups (syndromic, non-syndromic and with 22q11 deletion syndrome.<br>Extracardiac anomalies.<br>Endocrine disorders, other somatic disorders | Total: 8<br>6 in the syndromic group,<br>2 in the 22q11DS group,<br>none in the non-syndromic group | No information on how the ADHD diagnosis was set, but there was "extensive chart reviews" | Total group: 36 (10) | Total group: 51% |
| Schneider et al., 2014 (Schneider et al., 2014) | Inter-national con-sortium | Collaborative case study of 22q11.2 deletion syndrome cases, age span 6-68 years. Cohorts from 15 sites in North America, Europe, Australia, Middle East. Participation rates from the various sites not given. | 1402 | **Congenital syndromes and anomalies (Chapter XVII):**<br><br>22q11.2 deletion syndrome, all genetically confirmed. | Overall 253.<br>Prevalence among adults = 15.6%<br>Inattentive type: 63 %<br>Hyper-active-impulsive type: 6.5%<br>Combined type: 30.5% | Assessments by well-validated instruments, for adults, including SCID*, Schedules for Clinical Assessment in Neuropsychiatry (SCAN), MINI* and more.<br>Psychiatric diagnosis in accordance with *DSM-IV-TR* criteria. | Total population: 18.8 (10.7)<br>Emerging adults (18-25 years): N=323<br>Young adults (26-35 years): N=150<br>Mature adults (>35 years): N=127 | Total population: 47%<br>Adults: 44% |
| Tang et al., 2014 (Tang et al., 2014) | USA | Case study. Participants recruited from a children's hospital and from social networks. Participation rate not given. | 112 | **Congenital syndromes and anomalies (Chapter XVII):**<br><br>22q11.2 deletion syndrome, all genetically confirmed. | Overall:<br>35 (31%)<br>Adults (18-23 years):<br>6 (27%)<br>Adults (>23 | Assessments by validated instruments, e.g. Structured Interview for Prodromal Syndromes (SIPS), and SCID*. Interviews of probands and informants by experienced interviewers.<br>Narratives of each case discussed | Total population: 18.1 (8.1)<br>Adults, 18-23 years, N=22: 20.8 (1.9)<br>Adults, >23 | Total population: 53%<br>Adults, 18-23 years: 50%<br>Adults, >23 years: 26% |

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| | | | | | years):<br>4 (21%) | on case conference attended by doctoral-level clinicians. | years, N=19:<br>32.9 (6.3) | |
| Bijlenga et al., 2013 (Bijlenga, van der Heijden, et al., 2013) | The Netherlands | Cross sectional analysis; see above. | 391 | **Symptoms/signs involving the urinary system, in general:**<br>Self-report questionnaires; see above. | 202 | Diagnosed by trained psychologist/ psychiatrist at outpatient clinic for adult ADHD; see above | See above | See above |
| Caci et al., 2014 (Caci et al., 2014) | France | Questionnaires from parents of youths participating in a large study on ADHD symptoms in the community; see above.. | 1171 | **Enuresis (R32):**<br><br>Based on answering yes to a question about having enuresis. | ADHD defined by 2-phase method:<br>2.99% | ASRS* filled in and scored in three ways; see above. | See above | See above |
| Hodgkins et al., 2011 (Hodgkins et al., 2011) | USA | Retrospective analysis of health care claims and employer-rated health and productivity management database in 2006; see above. | 156,973 | **Enuresis (R32):**<br>Information from databases, see above. | 31,752 | Diagnosis based on *ICD-9-CM*. See above. | See above. | See above. |
| Secnik et al., 200 (Secnik et al., 2005) | USA | Registry based matched case control study; see above. | See above | **Enuresis (R32):**<br>Registered *ICD-9* diagnosis; see above. | See above. | Registered *ICD-9* code; see above. | See above. | See above. |
| Bijlenga et al., 2013 (Bijlenga, van der Heijden, et al., 2013) | The Netherlands | Cross sectional analysis; see above. | 391 | **Cancer, unspecified:**<br>Self-report questionnaires; see above. | 202 | Diagnosed by trained psychologist/ psychiatrist at outpatient clinic for adult ADHD; see above | See above. | See above. |
| Semeijn et al., 2013 (Semeijn et al., 2013) | The Nether-lands | Case control study, see above. | 231 | **Cancer, unspecified:** Respondents asked about having cancer. Information from general practitioners. See above. | 23 | Screening list and DIVA*, see above. | See above. | See above. |

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Supplementary 3.

**Different diagnostic tools used to evaluate ADHD, other psychiatric disorders, and tools used to assess specific somatic disorder described in several articles in this review. Due to the large number of comorbid somatic disorders, only the most frequently used evaluating tools are described. We refer to each specific article for more information.**

| Type | Name | Abbreviation | Use |
|---|---|---|---|
| **ADHD** | | | |
| Self-report questionnaire | | | |
| | Adult ADHD clinical diagnostic scale | ACDS | Clinician-based, semi-structured interview consisting of 18 items investigating current adult symptoms of ADHD. Version 1.2 includes a retrospective assessment of all symptoms of childhood ADHD and assessment of recent (past 6 months) symptoms of adult ADHD (aADHD) covering both *DSM-IV* symptoms and 14 non- *DSM* symptoms believed to be relevant to aADHD such as mood lability (Adler & Cohen, 2004). |
| | ADHD self-rating behaviour questionnaire | ADHD-SR | German self-rating behavior questionnaire covering aADHD symptoms according to *DSM-IV* and *ICD-10* research criteria (Rosler et al., 2004). |
| | Adult Behavior Checklist | ABC | An 18-item checklist divided in two subscales, Attention and Hyperactivity, assessing ADHD symptoms according to *DSM-IV* criteria based on self-report data (Kass, Wallace, & Vodanovich, 2003). |
| | ADHD Rating Scale | ADHDRS–IV | Check list for parents and teachers covering ADHD symptoms to closely approximate the *DSM-IV* diagnostic criteria in children and adolescence from 4-20 years. The purpose is to provide clinicians information on ADHD (DuPaul, 1998). |
| | Adult ADHD Self-Report Scale / Adult ADHD Self-Report Scale Screener | ASRS<br>ASRS-S | Developed in conjunction with the World Health Organization and is designed to measure current ADHD symptoms. Consists of 18 items covering the *DSM-IV-TR* criteria for ADHD and the core symptoms of ADHD: inattention, impulsivity and hyperactivity. A high symptom score on ASRS is not sufficient to clinically diagnose ADHD in adults, but is frequently used both clinically and in research to define study populations with possible ADHD (Kessler et al., 2005). |
| | The Assessment of Adult Attention Deficit Hyperactivity Disorder | | In longitudinal studies, a questionnaire designed to follow-up ADHD symptoms in adults diagnosed with childhood ADHD (Mannuzza et al., 2011) |
| | Barkley Adult ADHD Rating Scale-IV | BAARS-IV | Based on the *DSM* diagnostic ADHD criteria, it covers both childhood and adult ADHD symptoms (Barkley, 2011) |
| | Barrat Impulsivity Scale | BIS | Self-report measure designed to evaluate impulsivity at the time of assessment (Patton, Stanford, & Barratt, 1995). |

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|---|---|---|---|
| | Brown Attention Deficit Disorder Scale | BADDS | Covers a wide range of symptoms focusing on inattention (Thomas E Brown, 1996). Hyperactivity and impulsivity are not sufficiently addressed (Kooij et al., 2008). |
| | Conners' Adult ADHD Rating Scale | CAARS | Covers inattention, hyperactivity, impulsivity, as well as emotional lability (Conners, Erhardt, & Sparrow, 1999). |
| | Wender Utah Rating Scale | WURS | Retrospectively assesses symptoms of ADHD in childhood (Ward, Wender, & Reimherr, 1993). |
| Interviews | | | |
| | Adult Attention Deficit Disorders Evaluation Scale | A-ADDES | Provides clinicians information on aADHD symptoms. It is available in three versions, one self-report, one reporting from close relation/friend, and one from co-workers (McCarney S., 1996). |
| | Hyperactivity disorder (ADHD) Screening List | | A short questionnaire developed to distinguish adults with ADHD from community controls and people with clinical disorders other than ADHD. It has shown good validity when used in older individuals > 60 years (Semeijn et al., 2013). |
| | The Diagnostic Interview for ADHD in adults | DIVA | A semi-structured interviewed shown to be reliable in diagnosing ADHD in adults (Ramos-Quiroga et al., 2016). |
| | Structured interview Conners' adult ADHD diagnostic interview for the DSM-IV | CAADID | Assesses current and childhood symptoms, impairment and pervasiveness of symptoms over time (Conners, Epstein, & Johnson, 2001). |
| | The QUEST method | QUEST | A semi structured clinical interview assessing adult ADHD symptoms according to *DSM-IV,* providing age-appropriate probes. Queries about current problems, symptoms and comorbidities are included (Wigal et al., 2007). |
| | The Schedule for Affective Disorders and Schizophrenia for School-Age Children | Kiddie-SADS | A semi structured diagnostic interview used to assess current and lifetime psychiatric history, and can be adapted to be used in adults. One module assesses ADHD symptoms (Kaufman et al., 1997). |
| | | SGIK | Dutch semi structured diagnostic interview assessing current and childhood ADHD symptoms (Bekker et al., 2005) |
| **Psychiatric comorbidity** | | | |
| | Beck Depression Inventory | BDI | Measuring severity of depressive symptoms, consisting of 21 questions assessing depressive symptoms the last two weeks. It is not intended to serve as a sole diagnostic instrument for depression. (Beck & Beamesderfer, 1974). |

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|---|---|---|---|
| Self-report questionnaire | The Hospital Anxiety and Depression scale. | HAD | The Hospital Anxiety- Depression Scale (HAD) is designed to recognize symptoms of anxiety and depression in patients with physical illness. It also measures the severity of emotional disorder (Zigmond & Snaith, 1983). |
| | Hamilton Anxiety Rating Scale | HAM-A | Rating scale used by clinicians to rate the severity of anxiety symptoms (Hamilton, 1959) |
| | Hamilton Depression Rating Scale | HAM-D | Rating scale used by clinicians to rate the severity of depression symptoms (Hamilton, 1980) |
| | Mood Disorder Questionnaire | MDQ | Short screening questionnaire for bipolar spectrum disorders validated for use in the general population and in psychiatric patient populations (Hirschfeld et al., 2003; Hirschfeld et al., 2000). |
| | The Symptom Checklist-90 (-R) | (SCL-90-R) | A multidimensional inventory assessing psychiatric symptoms and psychological distress the preceding seven days. It can be used in both clinical and community samples and gives a severity index of general mental distress as well as assessing nine psychiatric symptoms dimensions (Derogatis, 1996). |
| Interview. | | | |
| | The World Health Organization World Mental Health Composite International Diagnostic Interview | CIDI | A comprehensive, fully-structured standardized interview designed to be used by trained lay interviewers for the assessment of mental disorders consistent with *DSM-IV* and *ICD-10* (Robins et al., 1988). |
| | Diagnostic Interview Schedule for DSM-IV | DIS-IV | A fully-structured interview designed to diagnose major psychiatric disorders according to *DSM-IV* that can be used by non-clinican interviewers (Segal, 2010). |
| | The Mini-International Neuropsychiatric Interview | M.I.N.I | A short structured diagnostic interview developed to investigate major psychiatric disorders as described in *DSM-IV* (Axis 1) and *ICD-10*. It was designed to capture routine and repetitive information to be used in clinical trials and epidemiology studies, and as a first step in a clinical evaluation of a patient (Sheehan et al., 1998). |
| | Mini International Neuropsychiatric Interview Plus | M.I.N.I. Plus | Similar to M.I.N.I., but with a more extensive interview, also including a module for ADHD (Sheehan et al., 1998). |
| | Psychiatric Research Interview for Substance and Mental Disorders | PRISM | A diagnostic interview to assess affective disorders, anxiety disorders, psychotic symptoms, eating disorders and personality disorders in individuals who drink heavily or use drugs. (Hasin et al., 1996) |
| | The Structured Clinical Interview for the Diagnostic and Statistical | SCID I | A diagnostic semi-structured interview assessing major *DSM-IV* Axis I (clinical) diagnoses (First, Spitzer, Gibbon, & Williams, 1997) |

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|---|---|---|---|
| | Manual of Mental Disorders-IV (DSM-IV) Axis I disorders | | |
| **Somatic comorbidity** | | | |
| Nutritional disorder, Obesity | | | |
| Can be both self-reported and objectively measured. | Body mass index | BMI | Used to identify overweight and obesity, and is defined as weight in kilograms divided by height in meters squared. In adults, < 18.5 kg/$m^2$ is defined as underweight, 18.5 to <25 kg/$m^2$ defined as normal, 25.0 to <30 kg/$m^2$ is defined as overweight and a BMI of ≥30 kg/$m^2$ is defined as obese (World Health Organization, 1992). BMI is a simple and easy way to evaluate obesity and is useful to evaluate obesity trends in the general population. However, BMI does not provide an accurate measurement of body fat on the individual level, nor does it take sex, age and ethnicity into account (Bhurosy & Jeewon, 2013). |
| Self-reported questionnaire | | | |
| | The Dutch Eating Behaviour Questionnaire | DEBQ | Self-reported questionnaire measuring emotional, external and restrained eating, eating styles likely to be associated with the development of overweight (van Strien, Frijters, Bergers, & Defares, 1986). |
| **Sleep disorders** | | | |
| Self-report questionnaire | | | |
| | The Composite Scale of Morningness | CMQ | Determines circardian typology (morning activities, morning affect, and eveningness) (Smith, Reilly, & Midkiff, 1989). It is developed from a combination of some items from the MEQ (Horne & Ostberg, 1976) and a diurnal scale by Torsvall and Akerstedt (Torsvall & Akerstedt, 1980). |
| | Epworth Sleepiness Scale | ESS | Measures daytime sleepiness and can be used to differentiate between different sleep disorders, such as central hypersomnias and sleep-disordered breathing from insomnia (Johns, 1991) |
| | Horne-Ostberg Morningness and Eveningness Scale/Morningness–Eveningness Questionnaire | MEQ | Suited to measure circadian sleep-phase, and is an indicator of natural sleep cycle (Horne & Ostberg, 1976) |
| | The Landecker Inventar sur Erfassung von Schlafstörungen | LISST | A screening instrument to detect different sleep disorders, like insomnia, nocturnal breathing disorders, restless legs, parasomnias and sleep/wake rhythm disorders (Weeß, Schürmann, & Steinberg, 2002). |

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|---|---|---|---|
| | Pittsburgh sleep quality index | PSQI | Subjectively measures sleep quality and disturbances over a 1-month time. It is a screening tool identifying patients that may require further sleep testing and is accurate in distinguishing good versus bad sleep patterns (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). It is not designed to define the presence of insomnia, but has been useful to differentiate people with and without insomnia (Backhaus, Junghanns, Broocks, Riemann, & Hohagen, 2002). |
| | The Schlaffragebogen A | | German sleep questionnaire measuring sleep quality the preceding night (Görtelmeyer, 1985, 2011). |
| | The Schlaffragebogen B | | German sleep questionnaire measuring sleep quality and the feeling of being refreshed in the morning the previous 2 weeks (Görtelmeyer, 2011). |
| | The Sleep Disorders Questionnaire | SDQ | Self-report questionnaire evaluating the presence of insomnia according to the *DSM-IV* and International Classification of Sleep Disorders-Revised (Violani, Devoto, Lucidi, Lombardo, & Russo, 2004). |
| | The Dutch Sleep Disorder Questionnaire | SDQ (Dutch) | (SDQ) is a questionnaire used to evaluate symptoms of common sleep disorders including insomnia, sleep apnea and restless legs syndrome (Sweere et al., 1998). |
| | Sleep log/sleep diary | | A simple and convenient way to self- report sleep patterns at a daily basis, and is used to diagnose sleep disorders such as insomnia, delayed sleep phase syndrome and narcolepsy (Ramar & Olson, 2013). The information provided can also be used to assess the effect of the treatment of sleep disorder. |
| Objective measurement | | | |
| | Actigraphy | | Used to assess sleep patterns and circadian rhytms. Actigraphy is a non-invasive objective method performed by an actigraph, traditionally records motor activity and sleep parameters. It as an electronic device worn on the body, often like a small watch-like device. Later year actigraphs have developed and can include features such as light- and temperature measurement and pulse recording. The sleep patterns are derived from nightly activity scores (De Crescenzo et al., 2016). Compared to PSG, actigraphy can assess sleep in a natural environment and can easily record sleep patterns over week's duration. Compared to sleep logs, it is more reliable as it does not depend on the patient´s recall. On the other hand, polysomnography collects more comprehensive information from different data sources (Ancoli-Israel et al., 2003). |
| | Polysomnography (PSG). | | Used to record several physiologic parameters relevant to sleep, such as electroencephalography (EEG), electrooculography (EOG), electrocardiography (ECG), chin- and anterio tibilais electromyography (EMG), respiratory effort, airflow and oximetry (Chesson et al., 1997). Polysomnography is used assessing a number of different sleep related disorders, such as restless legs syndrome, periodic limb movements during sleep, central hypersomnias, circadian rhythm sleep disorder and sleep-disordered breathing (Kushida et al., 2005). |

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