Attention-deficit/hyperactivity disorder; sex differences in psychiatric comorbidity and transgenerational recurrence risks

A population-based study using Norwegian registry data

Berit Skretting Solberg

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

The work included in this thesis were conducted at the K.G. Jebsen Centre for Neuropsychiatric Disorders/Department of Biomedicine as well as at the Department of Global Public Health and Primary Care, both at the University of Bergen, Norway. During the PhD period, I have been an affiliate member of the National Research School in Population-Based Epidemiology (EPINOR), and the Research School in Public Health and Primary Care.

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Berit Skretting Solberg Bergen, October 2019

"After all, as psychiatrists, we have chosen to study the most complex functions of the human being's most intricate organ. The human brain/mind not only self-wires—a system far more intricate than the genome can specify in any one-to-one relationship—but also is the great organizer and compiler of our own existence. It remembers and changes in ways that the liver, kidney, or heart can never do. It interfaces between our organism and the psychological, social, and cultural world around us to provide the structure and meaning of our existence. We have chosen to study and treat the most complex of human disorders, the causes of which span the many levels of our biology, our psychology, and our social existence. If the common, morbid dysfunctions of the human cardiovascular, immune, hormonal, musculoskeletal, and gastrointestinal systems, which cause most of the morbidity in our country, are highly multifactorial, could we realistically expect anything else from the parallel dysfunctions of our mind/brain system?"

K.S. Kendler, JAMA Psychiatry, 2019

Contents

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
AFE	Attributable fraction among the exposed
ALSPAC	Avon Longitudinal Study of Parents and Children
ANX	Anxiety disorder
ASD	Autism Spectrum Disorder
ATC	Anatomical Therapeutic Chemical Classification System
BD	Bipolar Disorder
DAG	Directed acyclic graph
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorder
e.g.	Exempli gratia – for example
GWAS	Genome Wide Association Study
HKD	Hyperkinetic disorder
HUNT	An acronym for the Norwegian name: Helseundersøkelsen i Nord-Trøndelag
HUSK	Hordaland Health Studies
ICD	International Classification of Diseases
i.e.	id est – that is
INFO	IMPUTE-Info metric ≥ 0.40 “good-quality” and ≥ 0.80 “high-quality
LD Score	Linkage Disequlibirum Score regression
MBRN	Medical Birth Registry of Norway
MDD	Major Depressive Disorder
METAL	Tool for meta-analysis of genomewide association studies
MICE	Multiple Imputation with Chain Equations
NED	National Education Database

NEO-5	Personality traits, neuroticism, extraversion, openness to experience, agreeableness, conscientiousness
NIMH	National Institute of Mental Health
NOMESCO	NCSP (surgical), NCMP (medical), NCRP (radiological)
NorPD	Norwegian Prescription Database
NPR	Norwegian Patient Registry
PAF	Population Attributable Fraction
PD	Personality Disorder
PDs	Prevalence Difference
POE	Parent-of-origin effect
PRs	Prevalence ratio
RDoC	Research Domain Criteria
RERI	Relative excess risk due to interation
r_g	Denotion of genetic correlation
RR	Relative risk
SCZ	Schizophrenia spectrum disorder
SES	Socio-economic status
SNP	Single nucleotide polymorphism
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUD	Substance use disorder

Thesis at a glance

	PAPER I	*PAPER II*	*PAPER III*
SOURCE	MBRN, NorPD, NPR, NED /+GWAS (*paper II*)		
DESIGN	CROSS-SECTIONAL/+ GENERATIONAL (*paper III*)		
EXPOSURE	ADULT ADHD	ADULT ADHD/ASD	PARENTAL ADHD
OUTCOME	ANX, MDD, BD, PD, SCZ, SUD		ADHD OFFSPRING
STATISTICS	POISSON REGRESSION/+LD SCORE REGRESSION (*paper II*)		
MEASURES	PREVALENCE RATIO, PREVALENCE DIFFERENCE, RELATIVE RISK Statistical significance p<0.05, 95% confidence interval		

Figure. *Brief overview of the methods and measures in paper I-III. MBRN=Medical Birth Registry of Norway, NorPD= Norwegian Prescription Database, NPR=Norwegian Patient Registry, NED= Norwegian Education Database, GWAS= genome wide association study, ADHD=attention-deficit/hyperactivity disorder, ASD=autism spectrum disorder, ANX=anxiety, MDD=major depressive disorder, BD=bipolar disorder, PD=personality disorder, SCZ=schizophrenia spectrum disorder, SUD= substance use disorder, LD= linkage disequlibirum,*

Abstract

Background Attention-deficit/hyperactivity disorder (ADHD) is a heterogeneous, multifactorial and life-spanning neurodevelopmental disorder for which the underlying mechanisms and causes are not fully understood. Psychiatric comorbidity is common, but there is limited knowledge about sex differences and patterns of comorbidity in adults with ADHD. Likewise, ADHD is known to be highly heritable, but little is known about sex patterns in the transgenerational recurrence risks of ADHD, both for parents and offspring. Gaining more knowledge about these topics will increase the understanding of ADHD both from clinical and neurobiological perspectives.

Aims This thesis is based on three scientific papers with the following main aims; 1) investigate potential sex differences in the risk of comorbid psychiatric disorders in adults with ADHD compared with adults without; 2) investigate patterns of psychiatric comorbidities between adults with ADHD, ASD, both ADHD and ASD, and adults without these disorders, and evaluate these patterns in light of available genetic data, and 3) investigate the parent-offspring recurrence risk of ADHD by parental and offspring sex.

Material and methods Data from four nation-wide registries were linked and were the main basis for all the papers: The Medical Birth Registry of Norway (MBRN), the Norwegian Patient Registry (NPR), the Norwegian Prescription Database (NorPD), and the National Educational Database (NED). The NPR (2008-2015) and NorPD (2004-2015) provided ADHD information. *Papers I* and *II* included only adults, born 1967-1997, and the outcomes were psychiatric disorders (anxiety, depression, bipolar, personality, substance use, and schizophrenia spectrum disorder). Effect measures were determined by Poisson regression and evaluated both on the absolute and the relative scales in all three papers. For *paper II,* genetic correlations were also calculated by linkage disequilibrium score regression, exploiting summary statistics from relevant genome-wide association studies. In *paper III*, all individuals born 1967-2011 and their parents were identified using the MBRN, and transgenerational recurrence risks for mothers and fathers to offspring were calculated. Additionally, individuals born 1967-1968 were followed to 2011 and linked to any own children to evaluate the cumulative

reproduction and the age at first childbirth in men and women with and without ADHD. Age at first childbirth was then taken into account when re-calculating recurrence risks in men born 1967-69 and women born 1970-73.

Results Adults with ADHD had a 4-9 times higher prevalence of other psychiatric disorders than adults without ADHD. Compared to men and women without ADHD, the differences in prevalence of anxiety, depression, bipolar and personality disorders were significantly larger in women than in men, whereas the prevalence difference of schizophrenia and substance use disorder were significantly larger in men than in women. When using prevalence ratios, the sex patterns were opposite. Risks differed between ADHD and ASD for all psychiatric comorbidities. Risks were highest in individuals with ADHD and ADHD+ASD for most comorbidities, both in men and women. Genetic correlations supported these patterns. Regarding transgenerational recurrence risk of ADHD, mothers with ADHD showed stronger associations with offspring ADHD than fathers, and recurrence risks were higher in female offspring than in male offspring from either parent. Prevalence of offspring ADHD when both parents had ADHD was 41.5% in sons and 25.1% in daughters. Men diagnosed with ADHD had lower cumulative reproduction than women with ADHD (75.2% versus 90.4%, respectively) and were generally older at childbirth.

Conclusions Psychiatric comorbidities are frequent in adults with ADHD but differ significantly between men and women. Adults with ADHD, ASD or the combination, have specific patterns of psychiatric comorbidities, and differed by sex. Stronger ADHD recurrence risk from mothers than fathers could be due to stronger maternal genetic effects, a stronger effect of maternal non-transmitted alleles, maternal health-seeking behavior, or a combination.

List of publications

The thesis is based on the following three original papers:

I. Solberg BS, Halmøy A, Engeland A, Igland J, Haavik J, Klungsøyr K. Gender differences in psychiatric comorbidity: a population-based study of 40 000 adults with attention deficit hyperactivity disorder. *Acta Psychiatr Scand 2018: 137: 176–186*

II. Solberg BS, Zayats T, Posserud MB, Halmøy A, Engeland A, Haavik J, Klungsøyr K. Patterns of psychiatric comorbidity and genetic correlations provide new insights into differences between attention-deficit/hyperactivity disorder and autism spectrum disorder. *Biol Psych 2019: 86 (8): 587-598*

III. Solberg BS, Hegvik TA, Halmøy A, Engeland A, Haavik J, Klungsøyr K. Parent-offspring recurrence of attention-deficit/hyperactivity disorder. *(submitted)*

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a worldwide[1], frequent neurodevelopmental disorder with childhood-onset, characterized by a persistent, trans-situational pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development[2-5]. ADHD affects millions of both children and adults across the world and is of major public health concern[6,7]. The estimated worldwide prevalence of ADHD is 5-7 % in children and adolescents[8-10], and ~2.5% among adults [1,11].

ADHD is a condition with large consequences for the affected individual; increased risk of lower education[12], occupational disability[13], somatic[14-16] and psychiatric disorders[17], and premature death[18,19]. Thus, ADHD seriously affects the productivity, life expectancy, and quality of life throughout the lifespan of affected individuals[20].

ADHD symptoms persist into adulthood in about 2/3 of the individuals[6,21,22]. Further, in the last two decades, ADHD has been extensively documented as a condition also in adults[6,23,24]. The question of an idiopathic adult-onset ADHD has been raised after three population-based studies reported prevalences from 2.7-10.3%[25-27]. However, all studies had major limitations further described by Franke and colleagues[6]. Inattentiveness is the most persistent symptom into adulthood, whereas hyperactivity tend to decline with age[28,29]. Persistence of subthreshold symptoms can still cause significant impairment[6,30]. ADHD is now accepted as representing an extreme tail of a continuous distribution of ADHD symptoms in the population[31,32], and a diagnosis of ADHD is defined by high levels of core symptoms interfering with and reducing quality of life, academic, or occupational functioning[3,4,33]. It has also been shown that fewer ADHD symptoms are associated with a lower degree of impairment and less problems for the individual[34]. Some theoretical developmental trajectories of ADHD across the lifespan have been suggested, describing different levels of ADHD symptoms reaching the diagnostic threshold at different ages, depending on the increasing demands towards adulthood or accidents like brain injury ("acquired" ADHD), Figure 1[6].

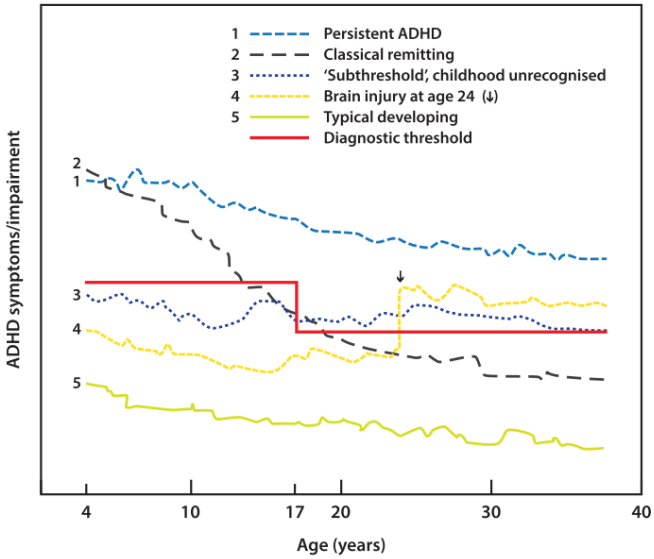

Figure 1. *Theoretical developmental trajectories of ADHD across the lifespan. Reprinted from Eur Neuropsychopharmacol, Vol 28/10, Franke et al. Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. 2018; 28(10):1059-1088. Copyright with permission from Elsevier*[6].

The developmental ADHD trajectories across the lifespan is supported by a recent population-based study showing that persistence of ADHD symptoms in childhood and adolescence in the general population is associated with higher polygenic risk scores for ADHD[35].

The ADHD diagnosis is still made based on clinical evaluation, and no tests are available for diagnosing ADHD in a more objective way. Several treatment approaches are available; non-pharmacological (educational, dietary or behavioural interventions), and pharmacological options (stimulants and non-stimulants), with pharmacological options as the first-line treatment for individuals with moderate to severe ADHD[33,36-38].

1.1 Diagnostic classification of attention-deficit/hyperactivity disorder

For ADHD, two diagnostic classifications systems are currently used, the International Classification of Diseases, version 10 (1998) by the World Health Organization (ICD-

10)[4,39,40] and Diagnostic and Statistical Manual of Mental disorders, 5th revision (DSM-5), by American Psychiatric Association from 2013[3]. ICD-10 is the formal diagnostic system used in European countries (including Norway), using the term Hyperkinetic disorders, while DSM-5 was developed in the USA, with the term Attention-deficit/hyperactivity disorder (ADHD). The DSM-system is widely used in research also outside the US, and the term ADHD has also gradually replaced the term hyperkinetic disorder in every-day language and is thus used in this thesis.

DSM-5 (American Psychiatry Association, 2013)	**Symptoms**
A. Persistence 6 months and interferes with function/development and negatively impacts directly on social and academic/occupational activities	1. Inattention >=6 of 9 (5 of 9 for adults) AND/OR 2. Hyperactivity>=6 of 9 (5 of 9 for adults)
B. Several symptoms present prior to age 12 years	
C. Several symptoms present in two or more settings	
D. Clear evidence of symptoms interferes with/reduce quality of social, academic/occupational functioning	
E. Symptoms occur not exclusively during psychosis/schizophrenia and not better explained by emotional, dissociative, personality disorders or substance intoxication/withdrawal	
ICD-10 (World Health Organization, 1998)	
A. Persistence 6 months	1. Inattention >=6 of 9 AND 2. Hyperactivity>=3 of 5 AND 3. Impulsivity>=1 of 4
B. Abnormal symptoms onset before the age of 7	
C. Abnormal symptoms in at least two settings	
D. Excessive abonormality of symptoms for the childs age/ developmental level	
E. Does not meet criteria for autism, mania, depressive or anxiety	
F. IQ>50	

***Table 1**. Simplified overview of DSM-5 and ICD-10 criteria for the diagnosis of attention-deficit/hyperactivity disorder (ADHD) and hyperkinetic disorder (HKD), respectively.*

The symptom description is similar in both systems but differ in their categorization and cut-off for diagnostic thresholds. ICD-10 is more restrictive for the ADHD diagnosis to be fulfilled, demanding both criteria for inattentiveness (6 of 9 symptoms), and impulsivity (1 of 4 symptoms) and hyperactivity (3 of 5 symptoms)[4], while DSM-5 allows three ADHD clinical presentations: mainly inattentive type (6 of 9 symptoms), or mainly hyperactivity type (6 of 9 symptoms) or the combined type; with both

inattentiveness and hyperactivity symptoms[3] (see Table 1). The hyperkinetic disorder in ICD-10 thus corresponds to the combined phenotype in DSM-5 (which also is the most common of the three[6,22]). In DSM-5, compared to DSM-IV and ICD-10, there is an adjustment for adult ADHD (individuals aged 17 or older), allowing the diagnosis to be given if only 5 of 6 criteria are met in each sub-phenotype of ADHD. The age of onset criteria also differs, in which symptoms must appear before the age of 7 years in ICD-10 and DSM-IV, and before 12 years of age in DSM-5[3,4,41]. The requirement of symptom persistence and functional impairment is similar in both ICD-10 and DSM-5, i.e. the symptoms should be present/impairing in two or more settings in social, academic or occupational situations[3,4].

In current clinical practice in Norway, the criteria of ADHD and the different clinical presentations from DSM-5 are widely used, although the formal diagnostic coding is according to the ICD-10, meaning that the code F90.0 in patient registries may include any of the ADHD clinical presentations described in DSM-5. Further, ICD-10 code F90.1 is used for ADHD with additional conduct disorder, and more rarely F90.8 and F90.9 for unspecified hyperkinetic deficits[33,42]. The dimensional perspective in ADHD is not taken into account by these categorical diagnostic criteria. However, this is the purpose of a third classification system, the Research Domain Criteria (RDoC), developed by National Institute of Mental Health (NIMH). RDoC was mainly developed for research perspective, based on dimensions of observable behaviour and neurobiological measures across single disorders[43,44]. However, even if several studies using the RDoC template are underway, few of them have been succesful in describing clinical presentations useful for prediction of outcome across traditional boundaries between single disorders[45].

1.2 Sex differences of ADHD across a lifespan

"Sex is a fundamental biological characteristic that influences nearly all human traits" [46]. Thus, sex is among the most important characteristics both in somatic and mental health, however, the role of sex is still not fully understood. Knowledge about the effects of sex on risk, prevalence, prognosis, and treatment of diseases is important to

increase the possibility of giving the best treatment in both males and females for health conditions with sex differences[47].

In *paper I*, the term "gender" is used instead of "sex" because the study concerns adults, and "gender" is shaped by environment and life-experience in addition to the biological characteristics determined by sex[48]. Further, in *papers II & III*, focusing more on genetic/biological mechanisms, we use the term "sex". In the thesis the term "sex" is used.

ADHD was primarily described in young boys[49,50], and later, similar diagnostic symptoms were recognized in girls[51]. The diagnostic criteria are mainly based on observations of school-boys, and it has been suggested that the criteria do not fit very well for females with ADHD[51,52]. However, ADHD is believed to be the same disorder from childhood to adulthood and for males and females, despite phenotypic differences expressed by sex[23,53,54].

In ADHD, there is a strong male predominance among children, with a male-female ratio of 9:1 decreasing to almost 1:1 in adulthood in clinical samples[23,55,56]. However, the male-female ratio is reported to be more stable between childhood and adulthood in community samples[55,57]. In the UK, two population-based studies found prevalences of around 3 % in boys and 0.3 % in girls[32,58]. The larger prevalence of ADHD for boys in clinical childhood samples, is suggested to be due to the more externalized behaviour in boys than girls[51,59], leading to easier identification and referral[6,51]. In population-based studies of adults with ADHD, the prevalence of ADHD in men ranged between 2.1-5.4%, and in women between 1.1-3.2%[55,57]. Thus, the difference in male-female ratio in childhood and adulthood may be influenced by the difference in referral source, from teacher/parent referral in childhood to self-referral in adulthood[51,52].

The inattentive subtype is more frequently diagnosed in women with ADHD[3,23]. This may reflect a relative absence of hyperactive/impulsive symptoms more than excessive inattentive symptoms in women compared to men[52]. In line with this, both the hyperactivity and the combined subtypes are less likely to be diagnosed in women[60].

Women with ADHD reported a greater subjectively experienced impact of negative life events compared to men with ADHD[61], while another study assessing objective life events, like repeated grades, showed no sex differences[62]. Further, in a study based on self-reports among adults, women with ADHD reported a history of treatment for other psychiatric disorders more often than men[13]. Women with ADHD also reported more impairment compared to males[23,63-65], and more comorbid internalizing symptom disorder like anxiety and depression[51,52,66]. Men were more frequently diagnosed with the combined subtype with more externalizing symptoms[29], and SUD and anti-social personality disorder were more often diagnosed[23,52]. The observation that females appeared to be more severely affected and impaired by ADHD compared with males despite a lower prevalence, is called the "gender paradox"[52]. Twin- and adoption studies of children with ADHD have estimated the heritability of ADHD to be 76%[67]. Later studies in adults found a heritability of ~35% in studies when using self-reported ADHD symptoms[68,69]. When using cross-informant data, with either combined parent reports and self-ratings or clinical diagnoses information, the heritability estimate was found to be the same in adults as for children, ~80%[70]. The genetic heritability may be different in males and females, as a putative "female protective effect" in ADHD is discussed[71,72]. In epidemiological studies, the "female protective effect" implies that females require greater exposure to genetic and environmental factors associated with ADHD in order to develop the condition[54,72,73]. A higher genetic load in females is suggested to explain the increased risk of ADHD (and other psychiatric disorders) in siblings of female probands with ADHD compared to siblings of male probands[72,74]. Interestingly, this "protective effect" occurs in either sex with the lower prevalence, and was originally developed by Cedric Carter in the 1960s, therefore, also called the "Carter-effect" or the sex- dependent liability threshold[46]. However, in a recent study of molecular genetic analyses, the autosomal common genetic variants could not explain the sex bias in ADHD prevalence[74].

Nevertheless, sex-specific heritability has been estimated in 551 traits from the UK Biobank, and significantly different heritability in males and females were found for only 2.5% of these traits[75]. This means that heritability estimates for males and females

are similar for most traits. Further, in all phenotypes with sex differences in the heritability estimates, females tend to show higher heritability than males[75].

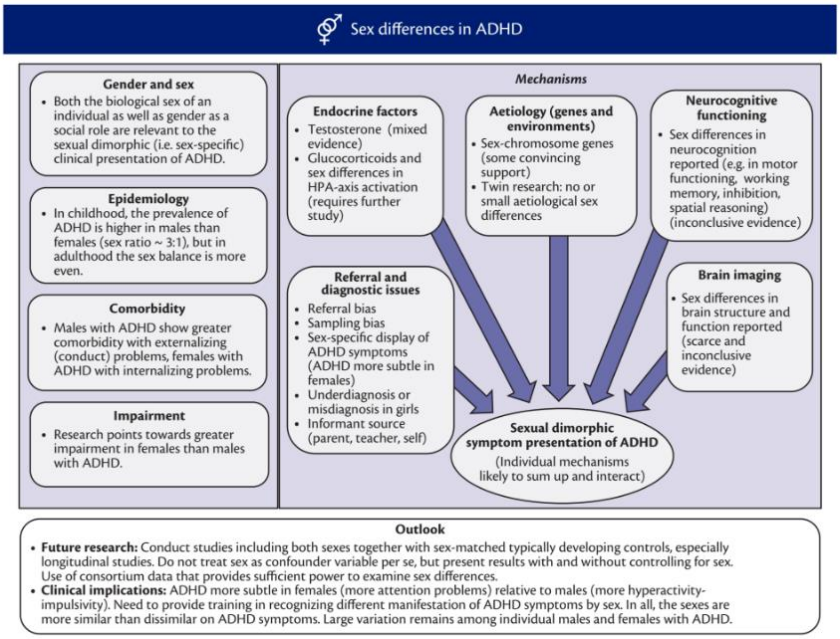

Figure 2. *Clinical presentation of sex/gender-differences in ADHD, underlying mechanisms and future outlook. Oxford Textbook of Attention Deficit Hyperactivity Disorder, edited by T Banaschewski. D Coghill, A Zuddas © Reproduced with the permission of the Licensor through PLSclear*[76].

In spite of the differences between men and women with ADHD regarding prevalence, symptom presentation, psychiatric comorbidity and heritability (see Figure 2), only a minority of studies of ADHD have acknowledged the possibility of an effect of sex[52]. Therefore, these questions remain to be fully explored in large representative population-based samples. Few previous studies have evaluated sex differences in comorbidity among adults with ADHD, and the results are conflicting. Most of the previous studies have been small and under-powered[23]; the male-female ratio has been high[23,77,78]; most study populations have been young[78,79]; self-report or screening questionnaires were used more than clinical diagnoses[80], or without appropriate comparison group[52]. Some studies did not find any sex difference[62,80]. Few studies were population-based and large enough to study smaller groups of different psychiatric disorders[52]. A better understanding of sex differences is critical for developing

informed diagnostic assessment and tailored treatment strategies for both men and women with ADHD and gaining more knowledge about development of ADHD.

1.3 Psychiatric comorbidities in ADHD

Comorbidity refers to any additional co-existing disorder in a patient with a defined index disease[81]. In the study of psychiatric comorbidity in this thesis, I have chosen to differ between neurodevelopmental disorders and other psychiatric "symptom disorders". Neurodevelopmental disorders are a group of conditions described by childhood-onset and impairment or developmental delay[2]. The neurodevelopmental disorders are assumed to be childhood-onset even if individuals are first diagnosed as adults[6]. Neurodevelopmental disorders comprise, e.g. learning disorders, speaking difficulties, intellectual disabilities, autism spectrum disorder (ASD), and ADHD, and do not have overlapping diagnostic criteria[2]. Psychiatric "symptom disorders" typically have a later onset in childhood, adolescence and adulthood[82], like the six studied disorders in *papers I & II*, e.g. anxiety, major depressive disorder (depression), bipolar disorder (BD), personality disorders (PD), schizophrenia spectrum disorder (schizophrenia), and substance use disorder (SUD). In these disorders, the diagnostic criteria are sometimes overlapping, both with each other and also with some symptoms of the neurodevelopmental disorders, like inattention. Inattention is a criterion both for depression and ADHD. Both neurodevelopmental disorders and psychiatric "symptom disorders" can co-occur with each other and are then defined as psychiatric comorbidities. Recent genome-wide association (GWA) studies have shown that genetics are shared to some extent between both neurodevelopmental and psychiatric "symptom disorders"[83]. To sum up, the extensive comorbidity among neurodevelopmental and other psychiatric disorders seem to be caused both by overlapping diagnostic criteria, shared genetic factors, and probably to some degree other similar causal factors[2].

The index disorders discussed in this thesis are the neurodevelopmental disorders ADHD (*papers I-III*) and ASD (*paper II*), in which whenever diagnosed, are considered to have an onset in childhood. Therefore, we assume that ADHD or ASD

was present before the psychiatric comorbid disorders, which all are typically diagnosed in late adolescence and adulthood[82]. Comorbid disorders in an individual can alter the clinical course by affecting the time of detection, prognostic issues, the choice of therapy, and the therapeutic outcome of the index disorder[81]. Therefore, it is important to gain knowledge on the comorbidity pattern of individuals with ADHD both to tailor the best treatment for the individual patient and to inform further research of biological/etiological mechanisms.

Adults with ADHD have a life-time risk of comorbid psychiatric disorders of ~80% [17,84,85]. Several studies have focused on psychiatric comorbid disorder in adults with ADHD, e.g. anxiety and depression[23,57,85], BD [17,23,85-87], PD [88,89], schizophrenia [78,87,90], and SUD[23,80,85]. Recently, a large GWA study demonstrated that common genetic factors are shared between several different psychiatric disorders, including ADHD[83]. However, the risk for other psychiatric comorbidities in individuals with ADHD may also be mediated through other behavioural symptoms developing as a consequence of ADHD, e.g. SUD may be mediated by conduct disorder in childhood, and antisocial behaviour in adulthood[91-94].

Increased knowledge about psychiatric comorbidity in adults with ADHD, including sex differences, is of importance for clinicians trying to find the best treatment for the individual patient. In addition, information about sex-specific patterns of psychiatric comorbidities can inform further research investigating biological mechanisms in ADHD. In *papers I-II*, we focus on the six above-mentioned psychiatric disorders, typically diagnosed in the adolescence/young adulthood[82], and in *paper II*, we compare the risk of these six psychiatric disorders among adults with the neurodevelopmental disorders ADHD and ASD.

1.4 Psychiatric comorbidity in adults with autism spectrum disorder

Autism spectrum disorder (ASD in this thesis) is an umbrella term of highly heritable pervasive neurodevelopmental disorders with childhood-onset[3,95,96]. ASD has a

considerable impact on the individual, family, social life, and educational and occupational attainment[95].

In DSM-IV, ASD was defined by a triad of characteristics: impairments both in social interaction, communication, and restrictive, repetitive, and stereotyped behaviour, interests, and activities[41]. DSM-IV further described four separate categories of autistic disorder: Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorder-not otherwise specified. In DSM-5, these subcategories are now put into one umbrella term "autism spectrum disorder"[3]. The new criteria better emphasize the dimensional nature of autism.

ICD-10 precludes a diagnosis of ADHD if the criteria of ASD is met[4]. However, since the publication of ICD-10, extensive research has shown that ADHD and ASD often co-occur[97-100]. Further, genetic, epidemiological and twin studies[97,99-103] have demonstrated common underlying genetic factors between the two disorders, with an estimated genetic correlation of 0.36[104]. The structure and function of molecular networks in the brain are possibly influenced by the shared genetic factors in the etiology of ADHD and ASD[37,104]. The DSM-5 thus now allows the combination of ADHD and ASD to be diagnosed as comorbid disorders, and this has also been implemented into clinical Norwegian guidelines[42]. However, even if significant genetic correlations between different phenotype-specific traits of ADHD and ASD have been demonstrated[98,104-106], the core phenotypic characteristics of these two neurodevelopmental disorders remain quite different[3,4,98].

In addition, studies have reported more impairment in children with both ADHD and ASD than in children with only one of the disorders[102,107].

Reported prevalences of ASD have increased from 4.5 in 10,000 individuals to 62-70 in 10,000 worldwide[108,109]. However, estimates of 1-2% have been shown in recent surveys[95,110]. This increase is explained by improved awareness and recognition, as well as changes in diagnostic criteria[95,108]. There is a considerable sex difference in the prevalence of ASD, with early studies showing a male-female ratio of 4:1, while later large population-based studies have shown that 2-3 times more males are affected.

Under-recognition of females with ASD might be an explanation[111,112]. Like in ADHD it seems like affected females "need" more cognitive or behavioural impairments than males to be diagnosed. This may be explained by females having better compensation abilities or by the "female protective effect" previously described for ADHD, where females are suggested to need a higher genetic load to develop the symptoms needed to fulfill the criteria for the diagnosis[110,111].

As in individuals with ADHD, adults with ASD also have a high risk (~65-90%) of developing comorbid psychiatric disorders[113,114], but with seemingly different patterns of comorbidity. Anxiety and depression frequently co-occur in adults with ASD[114], and the same is true for BD and schizophrenia[115-117]. Studies of sex differences in psychiatric comorbidities in adults with ASD are almost absent, mainly because of the late acknowledgment and practice of diagnosing ASD in adults[102,107]. As demonstrated in studies of individuals with ADHD, ASD also share genetic factors with the above-mentioned psychiatric disorders[83]. Both overlapping diagnostic criteria, shared symptoms and pathophysiology or secondary effects of living with ASD, could explain the high prevalence of comorbidities[95]. A recent study from Bai and colleagues, shows that the risk of ASD is primarily genetic with little or no effect of shared environment[118]. The genetic factors are complex and polygenic, including both rare genetic variants with large effect sizes and common variants with smaller effect sizes[104,119,120].

Patterns of psychiatric comorbidities have not been systematically studied and compared between adults with ADHD or ASD, except for a couple of small clinical studies[121,122], and no large study has taken sex differences into account. Further, comparable studies in adults with both ADHD and ASD are lacking[102,107]. To our knowledge, only a single population-based study on psychiatric comorbidity has compared individuals with ADHD alone, ASD alone or both ADHD and ASD, with individuals without ADHD and ASD. This study was, however, carried out in a population too young to be diagnosed with the psychiatric disorders of interest, which are all usually diagnosed in early adulthood[123]. Further, the contradictory findings of both shared genetics and different phenotypic characteristics in ADHD and ASD

remain unanswered. No previous study has compared the epidemiological patterns of psychiatric comorbidity with patterns of genetic correlation between the corresponding traits in individuals with ADHD or ASD. Such comparison could be informative regarding possible underlying factors.

1.5 Risk factors for ADHD

ADHD is an etiologically multifactorial disorder involving genetic, environmental, and gene-environment interaction risk factors[5], with strong evidence of familial origin based on family, twin and adoption studies and large-scale genome-wide association studies[5,36,70], see Figure 3.

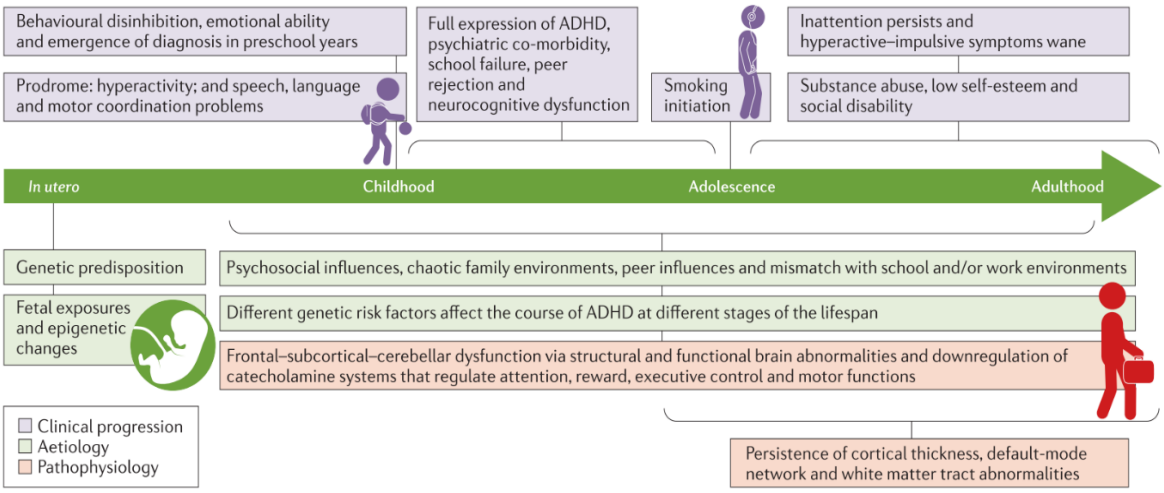

Figure 3. *Developmental course of adult ADHD. Describes possible risk factors that influence the development. Reprinted by permission from Macmillian Publishers Ltd: Nature Reviews Disease Primers © 2015*[37].

Genetic factors

Heritability is defined as the proportion of the variance of a phenotype that is explained by genetic factors[124]. In adults with ADHD, the heritability is ~80%, mainly shown in genetic epidemiology using cross-informant approaches via either parent and self-ratings or clinical diagnoses[70].

Genetic factors thus play a vital role in the etiology of ADHD[5], and ADHD also shares genetic factors with other psychiatric disorders[83,125]. ADHD is now recognized as a

polygenic disorder, which means that many common genetic variants contribute to the risk, each having very small effects. Common genetic variants are usually defined as having a frequency greater than 1% in the population and rare genetic variants smaller than 1%[5]. However, it has been difficult to establish the exact genetic mechanisms explaining ADHD. Research on single candidate genes of ADHD important in pathways of drugs that successfully treat ADHD has shown contradictory results and has not succeeded in explaining the etiology of ADHD[5,24,126]. Some rare genetic variants have also been found to play a role in rare syndromes often diagnosed with ADHD, like di George syndrome/velocardiofacial syndrome[5].

Different genetic variants contribute to the risk of ADHD through rare and common variants, by gene×environment interaction as well as by parent-of-origin effects (POE), as demonstrated by GWA studies[5,127]. POE refer to the different contribution from mothers and fathers' genotype to the development of a phenotype in their offspring, and this can influence the heritability/recurrence of ADHD[128]. Genomic imprinting, effects of the maternal genome on the intrauterine environment (i.e pre- and perinatal factors like premature birth[129], intra-uterine growth restriction[130]), mitochondrial genome and sex chromosomes, are examples of genetic mechanisms that could account for such differential parental effects[46,127]. Genomic imprinting results in the expression of only one of the parents' chromosomes[131]. Methylation of the DNA is one of the mechanisms that can lead to alterations of gene expression, defined as epigenetics. Some of the studied examples of genomic imprinting, indicate a paternal effect in schizophrenia[132,133], and maternal[134] or paternal transmission in BD[135]. However, in the field of ADHD research, studies on DNA methylation are still scarce[127,136].

The primary task of the sex chromosomes is to determine the sexual differentiation of ovaries in females and testes in males and production of sex steroid hormones[46]. Males are more vulnerable to some recessive disorders because they only have one X-chromosome (e.g. Duchenne syndrome, Rett syndrome, fragile x syndrome), thus if a recessive X-linked gene causes disease, this will be expressed. Females with a mutation on one of the X-chromosomes are more protected if there is a functional allele on the

other X-chromosome. However, more subtle gene expression in the X-chromosome in females may contribute to polygenic complex disease (like ADHD), but the contribution of sex chromosomes to non-syndromic traits is less characterized[46].

"Genetic nurturing effect" is the term of an alternative causal pathway for maternal and paternal effects on the child after birth, i.e. an environmental effect with a genetic component[137]. An example of "genetic nurturing effect" is educational attainment where the attained educational level of parents influences the environmental effect for the child, but with a genetic component[137]. The effect size can differ between fathers and mothers even if both parents contribute to genetic nurture[137]. Kong and colleagues found that both parents have similar effects on educational attainment, and mothers had a stronger nurturing effect on health aspects of the child than fathers[137]. The genetic nurture effects are likely to be bi-directional between the parent and the child, however, might dominate from the parents to the child[137].

Previous studies have shown conflicting results regarding maternal and paternal effects in ADHD. Several genetic studies found that transmitted ADHD risk alleles from mothers and fathers were equally related to ADHD in the offspring[138-141]. Two studies found a larger effect from maternal ADHD on risk in offspring[142,143]. Regarding the parental effect by offspring sex, one study found that ADHD risk allele transmission from either parent was strongest to daughters[144]. However, most of these studies were small and originate from a time when being diagnosed with ADHD as adults were less likely. Further, no population-based epidemiological study has yet been large enough to examine parent-offspring recurrence of ADHD by both parental and offspring sex. The evaluation of POE on ADHD recurrence risk in epidemiological data can add new information about the heritability and transmission of this trait. This will also increase knowledge that may prove to be important for earlier diagnosis and treatment for offspring of parents with ADHD.

Environmental factors

A heritability of ~80% in ADHD means that ~20% of the etiology is explained by environmental factors. Several environmental risk factors have been associated with

ADHD, from maternal smoking during pregnancy[145] to postnatal factors like negative life events[61,146], parenting style[147], and parental mental health[148]. However, most of the environmental risk factors for mental disorders are non-specific in that they are associated with a range of different disorders[149,150], e.g. reduced fetal growth and neurodevelopmental disorders[130].

Socioeconomic factors (SES) or social determinants are documented to affect a variety of disorders and aspects of health and are important to assess[151], and may also contribute to the high prevalence of psychiatric comorbid disorders in individuals with ADHD. Individuals with ADHD have lower education and occupational disability compared to individuals without this condition[12,13]. Further, the causality for some of these risk factors has been difficult to prove, as unmeasured familial confounding may explain the associations [152]. Such unmeasured familial confounding may, however, be assessed by study designs examining whether the associations with (shared or non-shared) environmental factors persist within sibling pairs or twin pairs, since they will be partly matched with the cases regarding for example, socioeconomic status and genetics[69]. A couple of recent studies controlling for this confounding have confirmed that fetal growth was associated with several mental health conditions like ADHD[130], and that maternal infection during pregnancy did not show an association with ADHD when controlling for unmeasured familial confounding[153].

Reproduction patterns in men and women with psychiatric disorders

Parent-offspring and transgenerational recurrence risk of psychiatric disorders may also be influenced by specific reproduction patterns for individuals with the actual disorder. Reproduction is here evaluated at the age of 45 when close to 100% of mothers and 98% of fathers had finished their reproduction in the Norwegian population. A recent report on reproduction in Norway showed that 10% of women and 25% of men have not had any child by the age of 45 years[154]. In individuals with psychiatric disorders, the reproduction is generally lower compared to their unaffected siblings, especially in men[155]. Further, lower reproduction rates in both men and women with versus without ADHD were found in a Danish study focusing on teenage parenthood[156]. They also reported that among those who had children, the proportion

starting their reproduction at a young age was higher among individuals with ADHD[156]. Large-scale epidemiological studies with the possibility of including such information show that women with ADHD become mothers at a younger age compared with women without ADHD[157]. This is further confirmed in a study by Demontis and colleagues where they evaluated the genetic correlation between ADHD and various reproductive factors. They found a negative correlation with age of first birth (r_g= -0.61) and a positive correlation with the number of children ever born (r_g=0.42)[158]. There is also an increased risk of ADHD in offspring of young parents[159,160]. Reproduction patterns are therefore important to consider when studying transgenerational recurrence risks, especially when evaluating sex-specific recurrence risks.

Literature review completed September 2019.

2. Aims of the thesis

The overall objective of this thesis was to gain more knowledge about psychiatric comorbidity and heritability patterns in adults with ADHD using nation-wide population-based registries that are large enough to study subgroups of ADHD. The work has a particular focus on sex differences in psychiatric comorbidity and transgenerational recurrence risks.

Specific research aims were:

I. To investigate sex differences in psychiatric comorbidities in adults with ADHD (*paper I*).

II. To investigate patterns in psychiatric comorbidities in adults with ADHD only, ASD only or both compared to unaffected adults, and evaluate these patterns with genetic correlations from summary statistics (*paper II*).

III. To examine the recurrence risk of ADHD across generations by parent and offspring sex, while taking account of reproduction patterns in men and women with ADHD (*paper III*).

3. Material and Methods

Table 2. *An overview of material and methods used in papers I-III.*

	Paper I	***Paper II***	***Paper III***
Aims	To investigate the risk of psychiatric comorbidity in adults with ADHD by sex	To investigate the risk of psychiatric comorbidity in adults with ADHD only, ASD only, or both ADHD and ASD, and evaluate the risk patterns in light of genetic correlation	To investigate the recurrence of ADHD from parents to child, by parent and offspring sex
Data source	*Papers I-III*: Medical Birth Registry of Norway (MBRN), Norwegian Prescription Database, Norwegian Patient Registry, National Education Database *Paper II*: In addition, summary statistics from relevant large GWAS		
Design	Nation-wide, population-based registry study Cross-sectional		Nation-wide, population-based registry study Cross-sectional Generation data
Population	Adults born 1967-1997 n=1.7 million		All born 1967-2011 n= 2.5 mill Reproduction cohort born 1967-1968
Exposure	Adults with ADHD (n= 40,103)	Adults with ADHD/no ASD (n=38,636) ASD/no ADHD (n=7,528) ADHD+ASD (n=1,467)	I. Mothers and fathers with ADHD and offspring in MBRN M+/F- (n=20,032) M-/F+ (n=16,952) M+/F+ (n=1,545) II. Mothers and fathers with ADHD registered as born in MBRN, linked to own children in MBRN
Outcome	Adults diagnosed with anxiety, depression, bipolar disorder, personality disorder, schizophrenia and substance use disorder		Male and female offspring with ADHD identified in MBRN
Covariates	Year of birth, maternal marital status, maternal and paternal age at delivery, parental attained education, gestational age, gestational age- and sex specific birthweight z-scores, parental psychiatric diagnoses		Year of birth
Statistical methods	Poisson regression	Poisson regression LD Score regression	Poisson regression
Measure of association	Prevalence difference Prevalence ratios Population attributable fraction 95% CI	Prevalence ratio Prevalence difference 95% CI	Relative risk Prevalence differences Absolute prevalences 95% CI

3.1 Data sources

The national central health registries are used for health analysis, health statistics, improving the quality of healthcare, research, administration, and emergency preparedness to maintain national functions of health services. Clinicians are obliged by law to send data to the registries electronically. All registries are regulated by The Personal Health Data Filing System Act which is further specified in registry-specific regulations and provide the legal basis for these registries[161,162]. Information about the registries is similar to the information in Supplementary of *papers I- III*.

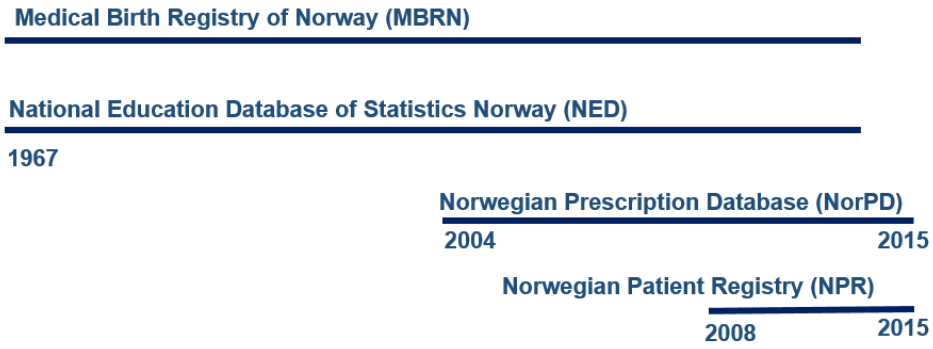

Figure 4*. Overview of periods covered by the different registries for this PhD-project.*

The Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) is a nation-wide, population-based medical health database. The MBRN, the oldest national birth registry in the world[163] was established in 1967 after the Thalidomide disaster and contains information about all births in Norway, including spontaneous abortions and stillbirths from 16 weeks of gestation[164]. The aim of the registry is to clarify the causes and consequences of health problems related to pregnancy and birth and monitor the incidence of adverse outcomes. The registry is based on compulsory notification and includes demographic information on both the mother and father, data on maternal health before and during pregnancy, e.g. chronic diseases like diabetes and hypertension, pregnancy complications, complications and interventions during delivery, and birth outcomes.

Information on the infant, such as vital status, anthropometric measurements, and neonatal diagnoses including congenital anomalies, are also notified. The unique national identification numbers, given to all live born infants and all parents residing in the country, are included in the registry, and makes linkage with other databases possible. The MBRN is routinely linked with the National Registry to ensure complete notification and this linkage provides dates of death and emigration.

The Norwegian Prescription Database

The Norwegian Prescription Database (NorPD) is also a nation-wide health-registry and contains data about all drugs prescribed and dispensed in Norway since 2004[165]. The aim of the NorPD is to collect and process data on drug consumption, based on electronically notified data every month from all pharmacies in Norway. It is therefore the most complete data source with regards to information about dispensed prescriptions at the individual level in the Norwegian population. Drugs purchased without a prescription are not included, and medication given to an individual during a hospital stay is also not available at the individual level. For reimbursed medications, information about the indication is included; however, for psychiatric disorders, this information is only specific from 2008. The medications are classified by the Anatomical Therapeutic Chemical (ATC) classification system. The register provides the basis for research, health analyzes and overall supervision and management of drug use and treatment in Norway.

The Norwegian Patient Registry

The Norwegian Patient Registry (NPR) is an administrative nation-wide health-registry containing information about diagnoses and procedures given to individuals treated in secondary health care, both in hospitals and out-patient clinics. The main aim of the registry was primarily to be a basis for financial allocations/prioritizing within secondary health care. Diagnoses are registered by the International Classification of Diseases (ICD) codes (at present version 10), and interventions by the NOMESCO Classifications of Surgical, Medical and Radiological Procedures (NCSP, NCMP, NCRP) codes. The NPR was established in 1997 but has only had data available for linkage on an individual level from 2008.

The National Education Database

The National Education Database (NED), established in 1970, contains information about the level of education of every Norwegian inhabitant who has received education in Norway from the age of 16 years. It includes data from completed lower secondary education to tertiary education including PhD level, and is updated every year[166].

Genome-wide association studies

The aim of GWAS is to investigate the entire genome to detect DNA variants associated with a trait of interest. GWAS are well suited to study psychiatric disorders with complex and polygenic traits, and results have been reported for several common diseases, for quantitative traits that are risk factors for disorders (e.g. educational attainment and body mass index), and also for behavioural and social traits like social well-being[175]. GWAS identify single nucleotide polymorphism (SNPs, common/rare variants defined by a frequency of >/< 1% in the general population, respectively) that are associated with a disease or phenotype by comparing the DNA of participants having varying phenotypes for a particular trait or disease. Each common DNA variant has very small effects. Due to the large number of multiple comparisons performed when studying the whole genome at a time, the observed association must have p-values less than 10^{-8} to achieve statistical significance. Large samples are thus needed to uncover the genetic variance in the population[175]. Therefore, only lately a consortium of ADHD succeded in finding twelve loci achieving genome-wide significance in a meta-analysis of several previous GWAS[158].

Trait	Sample size (cases and controls)		Reference (PubMed ID)
ADHD	20,183	35,191	Demontis, 2019[158]
ASD	18,381	27,969	Grove, 2019[104]
Schizophrenia Spectrum Disorder	36,989	113,075	Schizophrenia Working Group of the Psychiatric Genomics C, 2014[167]
Alcohol Dependence*	14,904	37,944	Walters, 2018[168]
Ever_vs_never smoked*	41,969	32,066	Tobacco Genetics C, 2010[169]
Bipolar Disorder	7,481	9,250	Psychiatric GCBDWG, 2011[170]
Major Depressive Disorder	135,458	344,901	Wray, 2018[171]
Anxiety Disorders	7,016	14,745	Otowa, 2016[172]
Anti-social behaviour**	Total sample=16,400		Tielbeek, 2017[173]
NEO-5-personality traits***	Total sample=17,375		de Moor, 2012[174]

Table 3. *Overview of the genome-wide association studies used for genetic correlation analyses in paper II.* **Abbreviations**: * proxy for substance use disorder (SUD); **proxy for anti-social personality disorder; ***NEO-5-personality traits; Neuroticism, Extraversion, Openness to experience, Agreeableness and Conscientiousness

In *paper II*, we used summary statistics from large-scale GWAS for the psychiatric disorders examined[104,158,167-174], downloaded from the Linkage Disequilibirum (LD) Hub GWAS share centre (http://ldsc.broadinstitute.org/gwashare/)[176], see Table 2. The data were derived from individuals of European descent only. LD Hub is a centralized database of summary-level GWAS results for SNP heritability and genetic correlations analyses from different publicly available resources, and with a web interface for LD score regression analysis[176]. LD score regression is further described in chapter 3.4.3.

3.2 Study-populations and design

All three papers have a cross-sectional, population-based study design, utilizing the above-mentioned four nation-wide registries; the Medical Birth Registry of Norway, the Norwegian Prescription Database, the Norwegian Patient Registry and the National Educational Database of Statistics Norway. In addition, we use a generational design in *paper III*. To guide the reporting of these studies, we used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[177]. STROBE has been developed to improve the quality of reporting observational studies[177]. In *paper II*, we also used data from large summary statistics from GWAS described in section 3.1.4.

3.3 Exposure variables, outcomes and covariates

Exposure variables

The primary exposure variable in *papers I-III* was "having an ADHD diagnosis in adulthood", and in addition, in *paper II*, a diagnosis of ASD in adulthood.

In *paper I*, we defined the exposure variable "'having an ADHD diagnosis in adulthood" as being either dispensed ADHD medication during 2004 to 2015 registered in the NorPD, or having an ADHD-diagnosis (ICD-10 code F90), registered in the NPR during 2008 to 2015, both at the age of 18 years or more. The ADHD medications were methylphenidate, racemic amphetamine, and dexamphetamine as well as atomoxetine. Individuals prescribed central stimulants exclusively for narcolepsy were excluded.

In *paper II*, the ADHD-definition in adults (ADHD) was as described above, with the additional criterion of not having an ASD-diagnosis registered. Adults with ASD only (ASD) were defined as individuals with an ASD diagnosis (ICD-10 codes: F84.0-1+F84.5+F84.8-9)[157,178] who were 18 years of age or older, were registered in the NPR during 2008 to 2015, and having no ADHD diagnosis registered. Adults (18 years of age or older) with both ADHD and ASD as defined above comprised the combined group (ADHD+ASD). The remaining population included all adults who neither had been dispensed ADHD medication registered in the NorPD nor had an ADHD or ASD diagnosis registered in the NPR. Since both ADHD and ASD are neurodevelopmental disorders, we assume that they were present before the psychiatric comorbid disorders, which all are typically diagnosed in late adolescence and adulthood[82].

In *paper III*, we used the linked data-file for our main analyses with the individual as the observation unit, registered born 1967 to 2011 in the MBRN, and alive at record linkage in 2015. We had data available on both mothers and fathers for each child, either through record linkage or as information in the MBRN. Further, individuals (both children and parents) with ADHD were defined as in *paper I*. We defined three exposure groups based on parents' ADHD: children where only the mother, only the father or both parents had ADHD. All remaining children served as the reference group. We excluded individuals where information on fathers was missing in the MBRN (n=19,264, 0.8%); including 455 (2.1%) offspring with maternal ADHD and 18 809 offspring (0.8%) without maternal ADHD.

To evaluate reproduction patterns (*paper III*) in men and women with and without ADHD, we identified, unique men (n=63,040) and women (n=60,935) born in 1967-1968 (from the MBRN), and linked them to any own offspring born in Norway by 2011, when potential parents were 43-44 years old. ADHD was defined as in *paper I*.

Outcomes

An outcome variable is the dependent variable observed and measured by changing the exposure or independent variable.

In *papers I & II,* the outcomes were the following six major comorbid psychiatric disorders typically diagnosed in late adolescence and adulthood[82], all registered in the NPR, at 18 years of age or older: anxiety disorders (ICD-10 codes F40-F42); depression (F32-F33); BD (F30-F31); PD (F60-F61), with a separate analysis on anti-social personality disorder (F602) (only included in the main analyses because of a small number of cases); schizophrenia (F20-F29); and SUD (F10-F19). For BD in *paper I*, we also included individuals who were prescribed and dispensed either lithium during 2004-2015 or antiepileptic drugs with mood disorders as the indication, obtained from the NorPD during 2008-2015 (indications for psychotropic medications are only available in the NorPD since 2008). However, for BD in *paper II*, we included only those who were dispensed lithium during 2004-2015 according to NorPD. The reason for this difference was that antiepileptic drugs with mood disorders as the indication, may be used also for behaviour problems and not necessarily for BD in individuals with ASD.

In *paper II*, when analyzing genetic correlations for traits between individuals with ADHD and ASD, the exact corresponding outcome variables for all the six psychiatric comorbidities were not readily available in the current published GWAS. Genetic correlations for anxiety, depression, BD, and schizophrenia were available[167,170-172], but not for SUD and PD. To compensate for the lack of these specific disorders, we chose to analyze the traits "ever versus never smoked"[169] and "alcohol dependence"[168] as proxy traits for substance use disorder, since they are documented to be highly associated risk of SUD. For PD, only a small GWAS on anti-social personality behaviour has been published[173]. Therefore, and in addition to anti-social behaviour, we combined data from GWAS on the five NEO-Personality Inventory (NEO) traits[174]. The five NEO-traits are neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness[179]. Personality traits are not the same as a PD, however, we decided to use these traits and anti-social behavior and compare the genetic correlations of these traits between ADHD and ASD, as the best option we had.

The outcome in *paper III* was offspring ADHD by maternal ADHD only, paternal ADHD only or ADHD in both parents relative unaffected parents. Results were

stratified by offspring sex. ADHD was defined as described in section 3.3.1, but without an age restriction. Additional outcomes in *paper III* were reproduction patterns, evaluated as proportion of men and women born in 1967-68, with and without ADHD as adults, who had reproduced by 2011, and the mean and median age at their first childbirth (overview of the different parent-offspring recurrence analyses in *Appendix I*).

Covariates

Covariates are characteristics describing the participants in a study. A covariate could also be called explanatory variable, independent variable, or predictor. If these characteristics are known and registered, they can be used to control for the influence of each covariate and this can increase the accuracy of the results, controlling for bias. The covariates included in the analyses should be based on expert knowledge of clinical importance about the exposures, outcomes, and potential confounders[180]. A confounder is defined as a variable associated with the exposure which is an independent risk factor for the outcome (a common cause), and not in the causal pathway[180].

To evaluate how risk factors for both ADHD (and ASD in *paper II*) and other psychiatric disorders influenced the relative risk we ran two regression models, including covariates obtained from the MBRN. We adjusted for the same covariates when calculating the risks on the relative scale in *papers I & II*. All covariates have been documented as risk factors for ADHD and for psychiatric disorders[129,146,181-186]: Model I: year of birth (5-year groups from 1967 to1997, with 1967-1973 as the reference), maternal marital status (single, married/cohabiting (reference category), other) , maternal age (<20, 20-24, 25-29 (reference value), 30-34, 35-39, 40+) and paternal age (<20, 20-24, 25-29, 30-34 (reference value), 35-39, 40-44, 45-49, 50+) at delivery, parent's highest attained educational level at record linkage (low (<10 years of education), middle (10-12 years of education) and high level (>12 years of education (reference category)), the individual's gestational age in weeks (<27, 28-31, 32 to 34, 35 to 36, 37 to 41 (reference value), 42+) and gestational age- and sex specific birthweight z-scores (<-2.0; -2.0 to -0.51; -0.5 to 0.5 (reference value); 0.51 to 2.0; 2.01+). Model II: the same covariates as in model I, and additionally mothers' and

fathers' psychiatric diagnoses (yes/no), including ADHD or any other psychiatric diagnosis from the NPR, from 2008 to 2015.

In *papers I* and *II*, when calculating the prevalence differences on the absolute scale, we adjusted for year of birth of the included individuals.

In *paper III*, as our main aim was to evaluate the risk of offspring ADHD from mothers and fathers with and without ADHD, no confounding variables were relevant, as illustrated by the directed acyclic graph (DAG) in Figure 5. Thus, we only adjusted for offspring year of birth, to control for the acknowledged time trends in diagnosing ADHD.

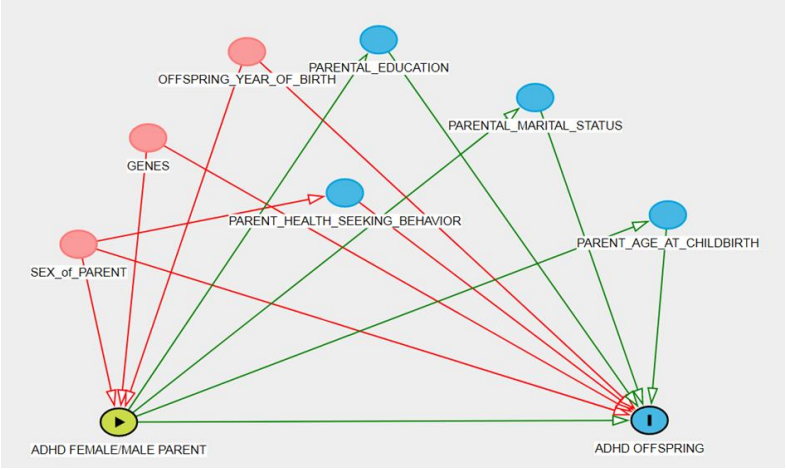

Figure 5. *Proposed Directed Acyclic Graph (DAG) exploring the causal pathway in the study relevant for paper III. (DAGitty.net)*

3.4 Statistical analyses

The main aim with statistical analyses is to explore the association between variables of interest, e.g. between ADHD and psychiatric comorbidities. When relations are complex and many variables must be considered, a method of choice is to model associations using an appropriate multivariable regression model. In a regression model used for evaluating mechanisms and causal factors (a causal model), we include explanatory variables that are potential confounders, i.e. independent risk factors for the outcome, associated with the exposure in the source population and not affected by

neither the exposure nor the outcome. We need to use our expert knowledge to choose explanatory variables of clinical and biological/physiological importance[180], and a graphical method like a DAG may be helpful when evaluating what variables to include in the final statistical model. An example is shown in Figure 5 for the analyses in *paper III*. Finally, it is important to evaluate whether the data fulfill the conditions of the statistical model.

Two-sided tests with a significance level of $p<0.05$ were chosen for statistical significance in all analyses, and the prevalence differences (PDs), prevalence ratios (PRs), and relative risks (RR) were expressed with their corresponding 95% confidence intervals (CI).

Analyses for all three studies were carried out with SPSS version 22.0/23.0 (IBM Corp., Armonk, NY) and STATA Intercooled version 14 (StataCorp, College Station, TX).

Regression

In all three papers, the associations between the exposure of interest, and the outcomes were estimated by using predicted prevalence from a Poisson regression model with robust standard errors[187]. Poisson regression models are generalized linear models, a form of regression analysis used to model count data. Robust error variance procedure was used to rectify the overestimation of the error for the estimated relative risk[187]. An important assumption of regression analysis is that all observations are assumed to be independent. To "cluster" means to take into account the fact that one individual might contribute to several observations or that one observation is being dependent on another observation. The mother's identification number was used as a cluster variable in the analyses to account for correlations (or dependency) between siblings in *paper I* & *II*[188].

Absolute measures versus relative measures

Absolute effect measures are differences in occurrence, while relative effect measures are ratios of occurrence measures[189]. While it has been suggested that effect measures and interactions on the relative scale are better suited to "assess causality", risk

differences and interactions on the absolute scale are the most important to assess public health relevance, indicating which group may benefit the most from treatment or preventive measures[190]. Nevertheless, it is recommended to report the results on both the relative and the absolute scales, and if not, it is important to clarify on which scale the effect measures are analysed.

On the absolute scale, we estimated prevalence differences (PDs) (*papers I-II*) of psychiatric disorders in men and women with and without ADHD, and in *paper III,* PDs of ADHD in children in the three different exposure groups of parents with and without ADHD. We also estimated adjusted prevalence rates in all three papers. On the relative scale, we estimated prevalence ratios (PRs) (*papers I-II*) and relative risks (*paper III*) comparing the same groups, i.e. we reported measures on both the absolute and relative scales in all three papers. In line with this, we evaluated effect modification/interaction on both the additive and multiplicative scales (see 3.4.4).

Linkage disequilibrium score regression

Linkage disequilibrium (LD) quantifies the similarities in genetic architecture between two traits by evaluating the relationship between SNP association strengths and genetic LD[125]. SNPs are the most common type of genetic variation among people. Each SNP represents a difference in a single DNA building block, called a nucleotide. LD is the non-random association of alleles at different loci in a given population. Loci are said to be in LD when the frequency of association of their different alleles is higher or lower than what would be expected if the loci were independent and associated randomly[191].

Linkage disequilibrium score regression (LDSC) was used to examine the association between LD scores and the test statistics of the SNPs from the GWAS which were downloaded from the Linkage Disequilibirum (LD) Hub GWAS share centre (http://ldsc.broadinstitute.org/gwashare/)[176]. Due to sample overlap between the examined datasets, the correlations were calculated without constraining the intercept. In all analyses, the examined data were restricted to SNPs of good imputation quality (IMPUTE Info metric ≥ 0.8 (high-quality)), and common genetic variation (≥ 1%). To

account for multiple testing, Bonferroni correction was applied to a significance threshold of 0.05, bringing the adjusted significance threshold to 0.00625.

Genetic correlations (*paper II*) were calculated using LDSC from relevant GWAS. Genetic correlations denoted r_g, is defined as the proportion of variance shared between two traits explained by genetic factors. A genetic correlation of 0 implies that the genetic effects on one trait are independent of genetic effects on the other, while a correlation of 1 implies that all the genetic influences on the two traits are identical. Different traits are analyzed in *paper II*, from disorders like ADHD to traits like "ever_vs_never_smoked" and "neuroticism". To analyze the five GWAS on NEO-traits for personality in *paper II*, the METAL software was used. METAL is a tool developed to do metanalysis of GWAS[192].

Interaction – on the additive and multiplicative scales

Possible effect measure modification (interaction) by sex was evaluated in both *paper I* and *paper II*. An interaction occurs when the effect of one causal variable on an outcome depends on the state of a third variable. It is important to explore the effect of exposure in different levels of the third variable (stratify on the potential effect modifier), e.g. if the association of ADHD on the risk of SUD is the same in men and women. On the multiplicative scale, one method to test this potential difference in effect (interaction) is to do regression analyses with an interaction term. This interaction term is handled as a new variable, a product of the two relevant variables[190]. The model gives a p-value and a confidence interval for the interaction term and statistical significance can be evaluated, e.g. if the effect of exposure on outcome differs significantly among men and women.

Statistical interaction is dependent on the scale used as described in section 3.4.2. In a recent guide on interaction analysis, it is recommended to estimate interaction both on the relative and absolute scales[190].

In *papers I & II*, significance of interaction by sex on the multiplicative scale was evaluated by comparing Poisson regression models with and without the interaction term (sex x ADHD) included, as tested by likelihood ratio tests. Further, the

significance of interaction by sex on the additive scale was evaluated using relative excess risk due to interaction (RERI)[190].

Population Attributable Fraction

Population attributable fraction (PAF) is a way of quantifying the contribution of a risk factor to the burden of a disease or death in the population. PAF is a measure used to assess the public health impact of exposures in populations, and in a population, the fraction of all cases with a particular disease or adverse condition that is attributed to a specific exposure is defined as the PAF[193]. The term "attributable" has a causal interpretation: PAF is the estimated fraction of all cases that would not have occurred if there had been no exposure[193,194]. In *paper I*, we estimated the proportion of the studied psychiatric disorders in the adult population that could be attributed to a comorbid ADHD among men and women with ADHD (Attributable fractions in the exposed - AFE) and in the population (PAF).

Missing information – using multiple imputation

In research, missing data are a common problem. Missing data need to be handled in a correct way to avoid bias of the results. If the information is missing at random, the best way of handling this is to use multiple imputations, where missing data for a subject are imputed/replaced by a value that is predicted using the subject's other, known characteristics[195].

In *papers I & II* we used multiple imputations with chained equations (MICE)[196] in sensitivity analyses to evaluate possible biases due to missing information in gestational age when adjusting for gestational age and birthweight by gestational age z-scores. In the main analyses, missing values in covariates (6% for gestational age and birthweight z-scores, other variables < 1%) were handled by listwise deletion. We ran sensitivity analyses using MICE to impute the missing values in gestational age and z-scores. Variables used in the MICE analyses were the outcome variables, all specified covariates and also birthweight, maternal preeclampsia and mother's chronic diseases (yes/no), all known to be associated with gestational age and birthweight.

3.5 Ethical approval

All three studies were approved by the Regional Research Ethical Committee of Norway, (2011/2272). No informed consent was required for the analyses as the records were anonymized.

4. Summary of main results

4.1 Paper I

Paper I is a population-based study of associations between ADHD and psychiatric comorbidities in adults, and how these differ by sex. By linking Norwegian national registries, we identified 40,103 adults with ADHD (44% women) and compared them with 1,661,103 adults (49% women) in the remaining population, all born from 1967 to 1997. ADHD and BD were registered in the NorPD from 2004 to 2015, and BD and other psychiatric disorders in the NPR from 2008 to 2015. Prevalence differences (PDs) and prevalence ratios (PRs) of psychiatric disorders in adults with and without ADHD were determined by Poisson regression. Interaction by sex was evaluated on the additive (for PDs) and multiplicative (for PRs) scales. Proportions of psychiatric disorders attributable to ADHD were calculated.

PDs associated with ADHD were significantly larger in women than in men for anxiety, depression, BD and PD, e.g. depression women: 24.4 (95% CI, 23.8-24.9) versus men: 13.1 (95% CI, 12.8-13.4), see Figure 6. PDs were significantly larger in men for schizophrenia and SUD, e.g. SUD men: 23.0 (95% CI, 22.5-23.5) versus women: 13.7 (95% CI, 13.3-14.0). On the relative scale, the sex relations were opposite: Stronger associations in men than women for anxiety, depression, and PD, with PRs ranging from 3.7 (95% CI, 3.6-3.8) for anxiety and depression in women to 8.9 (95% CI, 8.5-9.3) for BD and PD in men. Between 5.6% and 16.5% of psychiatric disorders in the population were attributable to ADHD.

In summary, we found that the association between ADHD and psychiatric comorbidities differed significantly among men and women. Clinicians treating adults with ADHD should be aware of these frequent and sex-specific comorbidities, such that early identification and treatment can be offered.

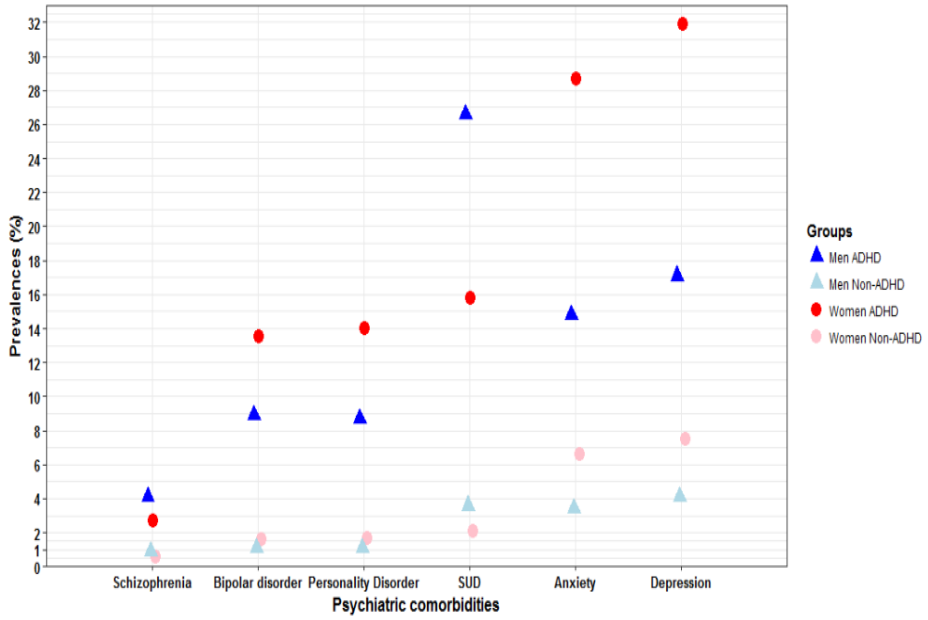

Figure 6. *Adjusted prevalences of psychiatric disorders in men and women with and without ADHD. Prevalence were adjusted for year of birth, 5-year periods, from 1967 to 1997, with 1967-1073 as the reference period. SUD= substance use disorder.*

4.2 Paper II

In *paper II*, we used data from Norwegian population-based registries to assess patterns of psychiatric disorders (e.g. BD, schizophrenia, SUD) in adults with ADHD only (n=38,636; 2.3%), ASD only (n=7,528; 0.4%) and ADHD combined with ASD (n=1,467; 0.1%) compared to adults in the remaining population without ADHD or ASD (n=1,653,575). PRs determined by Poisson regression were evaluated in light of genetic correlations (r_g) calculated by linkage disequilibrium score regression based on summary data from relevant genome-wide association studies.

For all psychiatric comorbidities, PRs differed between ADHD and ASD, see Figure 7, left panel. PRs were largest for individuals with ADHD and ADHD+ASD for most of the psychiatric comorbidities. However, the PR of schizophrenia was three times larger in ASD than in ADHD (PR_{ASD}=13.9, 95% CI, 12.7-15.2, PR_{ADHD}=4.4; 95% CI, 4.1-4.7, p<.001), while the PR of SUD was three times larger in ADHD than in ASD

(PR_{ADHD} 6.2; 95% CI, 6.1-6.4, PR_{ASD} 1.9; 95% CI, 1.7-2.2, p<.001). For the genetic correlation analyses, the patterns were similar, although differences between ADHD and ASD were significant for only two comorbidities: the proxy of SUD (alcohol dependence and smoking) and for the proxy of personality traits (NEO-5), see Figure 7, right panel.

Specific and similar patterns of psychiatric comorbidities based on both epidemiological data and genetic correlations, contribute to our understanding of ADHD and ASD as being neurodevelopmental disorders with common factors, however, with different levels of risk for different psychiatric comorbidities.

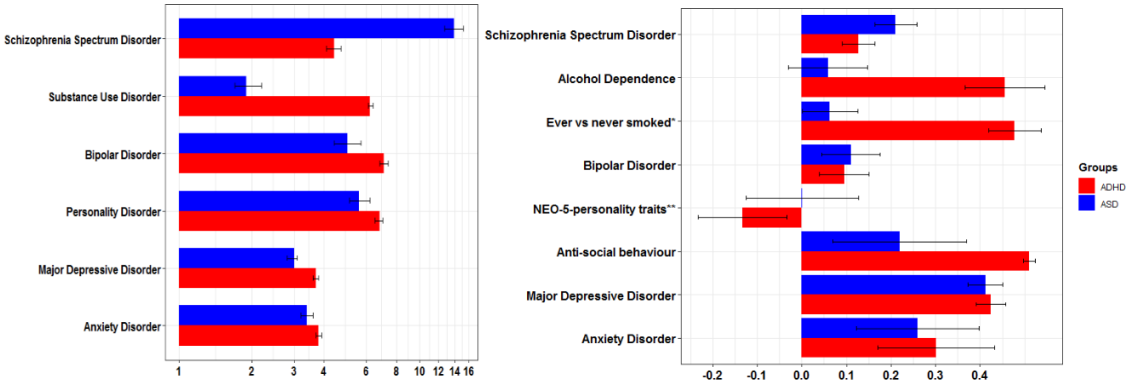

Figure 7. *The pattern of prevalence ratios of psychiatric comorbidity in adults with ADHD and ASD observed in this study (ADHD; n=38,636, ASD; n=7,528) (left panel) and genetic correlations (rg) calculated from genome wide association studies (right panel)*

Left panel: Prevalence ratio, model II, log-scale, 95% CI error bars. Adjusted for year of birth (5-year groups, from 1967 to 1997, with 1967-1973 as the reference), maternal marital status (single, married/cohabiting (reference), other), maternal and paternal education (low (<10 years of education), middle (10-12 years of education and high level (>12 years of education (reference)), maternal age (<20, 20-24, 25-29(reference), 30-34, 35-39, 40+) and paternal age (<20, 20-24, 25-29, 30-34(reference), 35-39, 40-44, 45-49, 50+) at delivery, gestational age (<28, 28-31, 32 to 34, 35 to 36, 37 to 41 (reference), 42+), gestational age and sex specific birth weight z-scores (<-2.0; -2.0 to -0.51; -0.5 to 0.5 (reference); 0.51 to 2.0; 2.01+), maternal and paternal psychiatric disorders (yes/no).
Right panel: Genetic correlations, r_g, linear scale, SE error bars.
** "ever_vs_never_smoked" and "alcohol dependence" as proxies for SUD, ** 'NEO-5-personality traits' as proxy for personality disorder.*

4.3 Paper III

In *paper III,* we aimed at evaluating whether the transgenerational recurrence of ADHD differed by parental and offspring sex and whether reproduction rates and proxies for ADHD-severity influenced this recurrence risk. The nationwide MBRN was used to identify individuals born from 1967 to 2011 with their parents, and those born from 1967 to 1968 were followed to 2011 for their own reproduction. We used Poisson regression to calculate the adjusted prevalence and relative risk (RR) for ADHD in offspring of mothers with ADHD (n=20,032; 0.8%), fathers with ADHD (n=16,952; 0.7%) or both parents with ADHD (n=1,545; 0.06%). The remaining children (of parents without ADHD) served as reference (n=2,447,559; 98.5%). The reproduction (the cumulative proportion of individuals born from 1967 to 1968 with any offspring by 2011 in the MBRN) was calculated for men and women with and without ADHD.

Parental ADHD was a strong risk factor for childhood ADHD. Maternal ADHD had a stronger association with offspring ADHD than paternal ADHD ($RR_{maternal}$ 8.4; 95% CI, 8.2-8.6 versus $RR_{paternal}$=6.2; 95% CI, 6.0-6.4). We found the highest recurrence risk when both parents were diagnosed with ADHD (RR_{both}11.7; 95% CI, 11.0-12.5). Using absolute measures, mother-son associations were the strongest, and the risk of offspring ADHD when both parents had ADHD was 41.5% in sons and 25.1% in daughters. Using relative measures, recurrence risks from maternal and paternal ADHD were higher in daughters than in sons, however, even higher from mothers than fathers ($RR_{mother\text{-}daughters}$ 10.4; 95% CI, 10.0-10.8; $RR_{mother\text{-}sons}$ 7.4; 95% CI, 7.2-7.6; $RR_{father\text{-}daughters}$ =6.7; 95% CI, 6.4-7.1; $RR_{father\text{-}sons}$: 5.8; 95% CI, 5.7-6.1). Men diagnosed with ADHD had lower cumulative reproduction compared to women with ADHD (75.2% versus 90.4%, respectively), and were older at childbirth, compared to women with ADHD, see Figure 8. However, the main results were not influenced by the differences in reproduction patterns, see Figure 9.

We found that transgenerational ADHD recurrence risk is high and was higher for maternal than paternal ADHD regardless of offspring sex and use of relative or absolute effect measures. This difference in recurrence risk could be due to stronger genetic effects from mothers, a stronger effect of non-transmitted alleles from mothers,

maternal health-seeking behavior, or a combination. Our results may prove helpful for health-care professionals when it comes to the identification of children at high risk of ADHD.

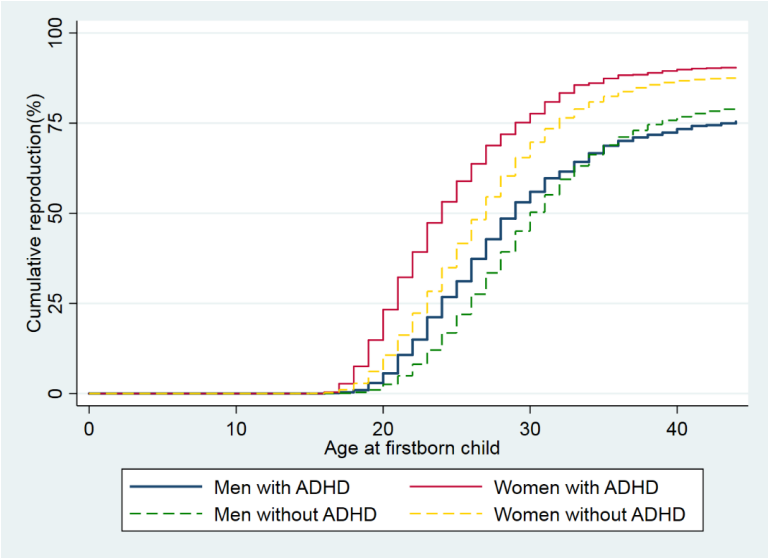

Figure 8. *The reproduction of men and women in Norway (men and women (with and without ADHD) registered born in the MBRN during 1968-1969; percentage with first offspring and age at first offspring).*

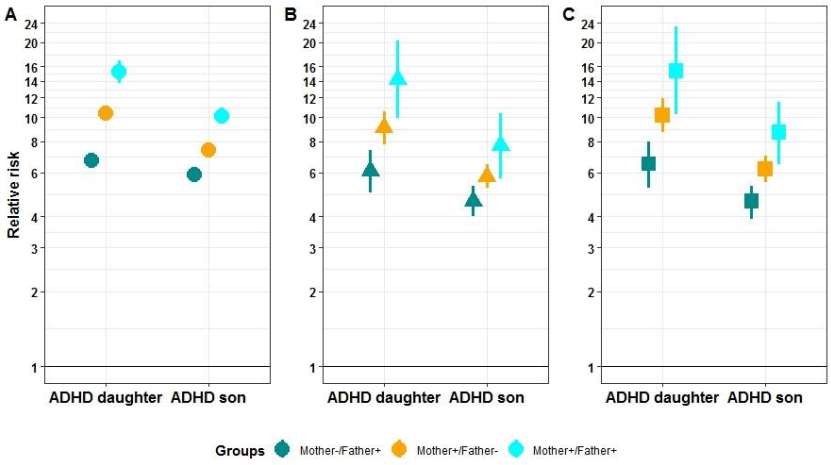

Figure 9. *Parent-offspring recurrence of ADHD.* ***A****. Mothers and fathers to offspring registered born 1967-2011, Medical Birth Registry of Norway (MBRN).* ***B.*** *Mothers (born 1970-1973) and fathers (born 1967-1970), offspring born 1981-2011, MBRN.* ***C****. Mothers (born 1970-1973) giving birth at 20 years or more, fathers (born 1967-1970), offspring born 1981-2011, MBRN*

5. Discussion

5.1 Methodological considerations

The overall aim of this thesis was to gain more knowledge about psychiatric comorbidity and heritability patterns in adults with ADHD using nation-wide population-based registries large enough to study subgroups of ADHD. The work has a particular focus on sex differences in psychiatric comorbidity and transgenerational recurrence risks.

To our knowledge, all three papers were the first and largest population-based studies on their topics; *paper I* in investigating sex differences in psychiatric comorbidity in adults with ADHD, *paper II* in comparing psychiatric comorbidity in adults with ADHD, ASD or both ADHD and ASD, overall and by sex, and comparing the pattern with genetic correlations from summary statistics (GWAS), and *paper III* in studying parent-offspring recurrence risk of ADHD by parent and offspring sex using generational data.

In this final part of the thesis, the findings are discussed in light of the current literature. First, some major methodological aspects of our studies are considered. Second, the major contribution of our findings to the existing literature on ADHD, psychiatric comorbidities, and parent-of-origin effects are discussed, emphasizing sex differences.

5.1.1 Strengths and limitations of registry-based studies

Our main data source for defining participants in the study was the MBRN, the oldest birth registry in the world with information about all births in the country from 1967[163]. The MBRN is routinely linked with the National Registry, and this linkage ensures complete notification of births for the entire population. The unique national identification number given to every resident in Norway is included in all the central health registries and allows information from the registries used in the present study (NPR, NorPD, NED) to be linked. We could define our exposures and outcomes with information from the NPR and NorPD.

Internal validity and bias of data

Bias in observational studies is any systematic factor other than the exposure of interest that can influence the observed result in the outcome. In observational studies, three sources of bias can influence the internal validity (bias or systematic error) of the study: selection bias, information bias and confounding[197].

Selection bias

Selection bias is a type of systematic error caused by factors that influence the selection of study participants or factors influencing study participation. Selection bias exists if the association between exposure and outcome differs between those who participate and those who do not participate in the study[198].

The main strength in *papers I-III* is the unique data sources we used, utilizing large, nation-wide population-based registries with compulsory notification allowing the inclusion of the total population. The potential for selection bias is therefore much less in the present studies than in the majority of previous studies in the field, especially clinical studies. Our study population was based on the MBRN, covering all births in the country. However, since we conditioned on everyone to be alive at record linkage, individuals who died or emigrated before record linkage were not included. We know that premature mortality is higher in individuals with ADHD[18], and conditioning on everyone to be alive at record linkage may have caused a selection bias since we may have lost more exposed individals (adults with ADHD) than unexposed individuals (the remaining population). However, mortality is very low in the age group we studied, also in ADHD individuals, and the number of losses is probably too low to cause a noticable problem. Mortality in the ADHD group could be associated with psychiatric comorbid disorders, e.g. suicide or accidents. Therefore, it is possible that psychiatric comorbidity among the ADHD individuals who died is even higher than what we find in the included population. Thus, if this selection bias should have influenced the results, it has most likely led to an underestimation of the associations.

Information bias

Information bias or misclassification can induce error in the results if the participants in the study have measurement errors in the information about the individual

themselves, of the exposure, or of the outcome. In epidemiological studies, information bias can occur even if the sample sizes are large[198].

The NPR was our main source both for the studied outcomes (i.e. psychiatric disorders in *papers I & II*, ADHD diagnosis in the offspring in *paper III*), and exposures (ADHD diagnosis in *papers I-III,* and ASD in *paper II*). Therefore, a main concern in studying comorbidities in this study is the diagnostic validity of the diagnoses registered in the NPR. Validity of a diagnosis is the degree to which this diagnosis represents a distinct entity across different cultures/clinicians, and is associated with explanatory variables like causal factors, pathogenetic mechanisms and treatment response[199]. In psychiatric disorders, this has been difficult to establish properly.

Diagnostic validation is done for one of the exposures in *paper II* (ASD)[200,201], and for two of the outcomes in *papers I & II*; BD and schizophrenia[202], but is lacking for the ADHD diagnosis. However, validation of ADHD in corresponding patient registries in Sweden and Denmark has been done with good results[87,203]. This is also expected to be the case in Norway, as the diagnoses are always based on a clinical evaluation by specialists. Therefore, the validation studies from the Scandinavian patient registries may be comparable to the NPR.

The prevalence of disorders in the NPR are based on the registered diagnoses in clinical practice and is not necessarily reflecting the real prevalence in the population. The information from NPR has some important limitations. We will probably underestimate the real prevalence of ADHD and the other psychiatric disorders for two reasons: First, the individual has to visit special health care service to be registered; and second, this must have happened after 2008 (when the NPR was available for linkage). Therefore, it is not possible to estimate lifetime prevalence using data from the NPR. However, by using information also from the NorPD, we were able to get information also from individuals being dispensed medication from 2004. This was possible for ADHD and BD for which specific medications were available for detection. We believe that this strengthens our study by increasing the years available and number of cases. Further, the specific medications we used to define ADHD and BD are only prescribed after a

thorough evaluation by a specialist in psychiatry/child- and adolesecent psychiatry, and only if diagnostic criteria are met. The prevalence of ADHD among adults (>18 years) in our study population was 2.4%, which is comparable with previous studies[1,11]. Therefore, we believe that our definition of ADHD has acceptable validity for this diagnosis in adulthood.

Since diagnoses registered in the NPR are from specialist health care, patients who are treated in primary care only, will be missed. While patients with most of the severe psychiatric diagnoses in our studies will be in touch with specialist care, there may be patients with milder forms of anxiety and depression that are lost in our study.

As mentioned, we chose to identify ADHD cases not only from the NPR, but also by having been dispensed ADHD medication, registered in the NorPD. This allowed us to increase the sample size and representation of cases, and further to compare data to other Scandinavian studies using the same method[87,204-206]. The NorPD contains data about all drugs prescribed and dispensed in Norway since 2004. Therefore, we have no information about prescriptions before 2004, and adult individuals who got an ADHD diagnosis before 2004, and who were not prescribed any ADHD medication after 2004, or who have ”outgrown” their ADHD (ADHD in remission) are missed in our study. This could lead to a selection of more severe adult ADHD disorder in those adults we capture in our studies. Further, we also know less about the most affected individuals with severe problems, possibly also persons with undiagnosed ADHD, who do not seek help/health service, i.e. individuals struggling with substance use disorders, criminality, without a home, or with a criminal record, as these may seek health service to a lesser degree. Finally, adult ADHD is a relatively new concept, and some affected adult individuals may not have been diagnosed because of lower awareness of adult ADHD, even if the prevalence of ADHD increases in adults during our study period.

In Norway, formal diagnoses of ASD and ADHD, and decisions about pharmacological treatment of ADHD are always based on a clinical evaluation by specialists. Thus, identification of ADHD and ASD cases was not based only on symptom scores or self-reports. Further, adults with ADHD were diagnosed by clinicians from all over the

country, and as the health care service in Norway is expected to be available for everyone, this reduces the influence of selection bias and represents a naturalistic clinical setting.

Some further limitations regarding the diagnoses should be discussed. In *paper I-II*, it may be argued that adults with ADHD or ASD could more easily get other psychiatric diagnoses, because they are already in touch with the health care system[207]. However, all adults with severe psychiatric disorders are likely to be in touch with secondary health care throughout life, independent of underlying neurodevelopmental disorders[208]. In *paper III* it may be argued that offspring with ADHD could more easily get this diagnosis if parents have the same diagnosis, or vice versa. This type of bias could influence on the prevalence ratios and recurrence risk estimates, because of the health-seeking behaviour in parents, and especially if the health-seeking behaviour is different between mothers and fathers (*paper III*). Health-seeking behaviour is discussed more in details in chapter 5.2.1.

Misclassification can also be a problem in psychiatric diagnostic practice, due to similar symptoms for several psychiatric disorders, like inattention symptoms both in ADHD, depression and anxiety disorders. However, this type of misclassification is likely non-differential between the different psychiatric disorders, expected to be similar among individuals with ADHD and the remaining population. We are comparing adults with ADHD and an additional psychiatric disorder with the population without ADHD (*paper I & II*). In a sensitivity analysis, we repeated analyses including only individuals with one psychiatric (comorbid) disorder, and the pattern and estimates were similar.

Relevant for *paper II*, up to 2013 (time of introduction of DSM-5) an ASD diagnosis would preclude a diagnosis of ADHD according to DSM-IV and ICD-10[4,41]. This may have affected the diagnostic procedures and hindered clinicians to diagnose both disorders if the criteria for ASD were fulfilled. However, clinical practice has not adhered strictly to these criteria in the nearest years before 2013, as growing evidence supported the importance of diagnosing both conditions when present to provide the

best treatment[102,107]. Diagnosing psychiatric comorbidities in adults with ASD is difficult, as most standard diagnostic tools are not customized for these individuals[102,209] Therefore, we cannot exclude possible misdiagnosis of schizophrenia and ASD. To assess a schizophrenia diagnosis in a person with established ASD is challenging, and vice versa. However, the developmental history in ASD vs schizophrenia is quite distinctly different and a minimal requirement to establish the ASD diagnosis. Both diagnoses have a severe impact and are thus not lightly administered and usually applied only after lengthy observation and detailed assessment.

The possibility of misclassification/overlapping, and the validity of psychiatric diagnoses, may also affect the results of the genetic correlation analyses in *paper II*, as they are a mix of different samples of clinically diagnosed cases and self-report cases from large health surveys. However, the largest GWAS of ADHD to date, showed that regardless of using cohorts of individuals with clinically diagnosed ADHD, a sample with self-reported ADHD symptoms, or a meta-analysis of quantitative measures of ADHD symptoms in the population, results that supported the validity of clinical diagnoses of ADHD to ADHD-related behaviour in the general population[158].

Confounding

A confounder is a variable that influences both the exposure and the outcome causing a false association because of the presence of shared common causes, and by that, introduces bias[198]. Confounders may be known and measured (for example educational level or perinatal factors in the present studies) and can then be handled in the analysis phase, but for most studied relations, there will also be unknown and/or unmeasured confounders, resulting in residual confounding. Such residual confounding must be evaluated for each specific situation.

From the MBRN we had information about the perinatal variables. Several of the perinatal factors are associated with both ADHD (exposure) and psychiatric comorbidities (outcome)[129,146,181-186]. The perinatal factors were prospectively registered (birth weight and gestational age) for the whole study population, and any

potential misclassification of these variables would be similar for individuals who later do or do not develop ADHD. Adjusting for the potential confounding perinatal factors in *paper I & II* had little impact on the estimates.

Inequality in socioeconomic level is known to influence the risk of both somatic and psychiatric health. Therefore, we also adjusted for socioeconomic factors in *papers I&II*, like highest attained parental education (from NED), maternal marital status (MBRN), and age when becoming a parent (MBRN). These adjustments also had very little impact on the estimates. Selection bias of participants due to socioeconomic factors is minimal (or practically non-existent), since the entire population is included. Adjustments for SES are controversial in highly heritable disorders like ADHD, as it is not well known where on the causal pathway the SES are located, either as a common cause (confounder) or as a common effect (collider). Finally, we also adjusted for parental psychiatric disorders (from NPR/NorPD), including ADHD (model II, *papers I&II*). This could represent common genetic factors for ADHD and other psychiatric disorders in the offspring, however, this adjustment reduced the estimates only slightly. There is a possibility for unmeasured confounding related to familial factors, which could have been evaluated better in other designs, such as sibling designs[130,210].

Sample size

Another main strength in *papers I-III* is the large sample size, including the entire population in Norway. This also ensures a "real life" sex distribution, thus a large proportion of women with ADHD (44%), which allowed us to compare psychiatric comorbidity by sex with representative numbers in both groups. Further, in *paper II*, our patient groups were large enough to study subgroups of individuals with either ADHD only, ASD only or both conditions (ADHD+ASD).

In our main analyses, the confidence intervals were narrow, meaning that the association measures were rather precise. However, in *paper II*, analyzing the risk of psychiatric comorbid disorder in adults with both ADHD and ASD, with a smaller number in the exposure group, the confidence intervals were broader, indicating less precise measures. This was also the case in some of the sensitivity analyses with fewer individuals in the sub-groups. However, the point estimates were high for all analyzes, indicating strong associations, and associations were significant also in the

ADHD+ASD. In very large datasets, it is a problem that associations may be statistically significant between prevalent exposures and almost every outcome studied. Therefore, triangulation (doing different models of analyses or different study design) can help researchers to be more confident about identifying which risks are genuinely causal[211].

Study design

We used a cross-sectional design in all three papers, since both our exposures (ADHD, and ASD in *paper II*) and our outcomes were based on data registered during 2008 to 2015 (NPR) and during 2004 to 2015 (NorPD). The differences in time-periods covered by the registries (MBRN, NorPD, NPR) were a major limitation (see Figure 4), and made it impossible to study temporal relations between ADHD (ASD) diagnosis and the comorbid psychiatric disorders in *papers I-II.* It also precluded the examination of whether parents received their diagnosis before or after their child (*paper III)*. However, as our exposures ADHD *(papers I-III)* and ASD *(paper II)* are defined as neurodevelopmental disorders with onset in childhood, we assume that they were present before the comorbid psychiatric disorders studied (*papers I-II*), or in parents before their child (*paper III*).

For *papers I* and *II*, we designed the studies specifically to examine an adult population, allowing all participants to reach the typical age of diagnosis of the outcome conditions investigated[82]. In addition, in *paper II* we had the possibility of studying the first birth cohort for which ASD became prevalent enough in adulthood. In *paper III*, since the MBRN has information about the mother and father of the child since 1967, we had a unique possibility to study the parent-offspring recurrence risk of ADHD by parental and offspring sex. Further, because of the size of our population-based data set we could study the recurrence risk in families where only the mother, only the father or both parents had ADHD. Finally, since the first cohorts of the MBRN had reached the end of their reproductive ages (~45 years) by 2011, we could study reproduction rates in males and females with and without ADHD.

In all three papers we used logistic regression, with clustered standard error in *papers I & II*. In *paper III*, due to the generational design, additional analyses without clustering was done to allow each offspring to be its own outcome and not being clustered together with siblings, making an average of the ADHD risk. However, doing both kinds of analyses did not change the point estimates, clustered analyses only produced slightly wider confidence intervals.

Genetic data

Patients' comorbidities are not always taken into account in genetic studies, due to strict exclusion criteria (DSM-IV) at least in the early GWAS (e.g. in ADHD GWAS, individuals were excluded if comorbid ASD)[158,212]. Therefore, our ability to examine the genetic variability that may be responsible for the different psychiatric symptoms and phenotypes are limited in the current GWAS. At the time of our study, large-scale GWASs with available summary statistics was lacking for SUD and PD, as defined in our data. We therefore chose to examine the 'best proxy' of available GWAS' phenotypes for these disorders, i.e. smoking habits and alcohol dependence as proxies for SUD, and the five NEO-Personality Inventory traits in addition to anti-social behavior for PD (see chapter 3.3.2). It would have been better for the comparison between epidemiological associations and genetic correlations if we had had available GWAS with information about exactly the same phenotypes, i.e. in this case the whole group of SUD and PD. However, as genetic vulnerability for complex disorders (like psychiatric disorders) is probably more correlated to underlying traits than the defined disorders, it may be argued that using personality traits as proxies for disorders may be a good approach[213]. Further, individuals with known combined ADHD and ASD were excluded from some GWAS and thus we could not study the genetic correlation of this combined case group. The estimations were highly dependent on the sample size of the utilized GWAS with regard to the genetic correlations. Large samples are needed to uncover the genetic variance in the population[175]. Further, the GWAS were of European descent only, making the generalizability of the results limited to a similar population.

5.1.2 Strengths and limitations of the psychiatric diagnoses

Mental illnesses are complex, diverse, dynamic and heterogeneous conditions, and their nosology, i.e. categorizing them into discrete entities by diagnostic manuals like the DSM and ICD classification system, is challenging. DSM-5 and ICD-10 are useful tools in the communication between clinicians and play an important role in research and clinical management, even if they are only explanatory constructs and not "systematic classifications" in the sense in which that term is applied in biology ; distinct natural entities and mutually exclusive diagnostic categories[199].

Further, the overlapping phenotypic characteristics between the different diagnoses often leads to several psychiatric diagnoses for each patient, included in the concept of psychiatric comorbidity. The increased overall number of diagnoses in DSM, from 106 diagnoses listed in DSM-I in 1952, to 297 diagnoses in DSM-IV, and similar numbers in DSM-5, (however, with a change in the criteria (or tresholds) of diagnoses), contribute to an increased psychiatric comorbidity, as the criteria do not sufficiently differentiate between disorders[214]. Comorbidity seems to be more prevalent in the field of psychiatry and mental health compared to other medical fields[215]. This is also supported by the recent GWAS study from The Brainstorm Consortium, where all psychiatric disorders studied had some shared genetic factors, as opposed to the studied neurological disorders[83].

However, although not perfect, the usefulness, and utility of clinical diagnoses to the clinician are invaluable, and still the best tool to provide information about prognosis, future function and impairment, guide treatment decisions, and guide research[214,216]. Therefore, although the study of psychiatric comorbidity is challenging for these reasons, such studies are needed both for clinical work and to inform future research into possible underlying causes and mechanisms.

5.2 The contribution of the findings

5.2.1 Sex differences in risk of psychiatric comorbidities in adults with ADHD

Using population-based, nationwide registries, the results from our studies establish sufficient evidence of significant sex-specific psychiatric comorbidities in adults with ADHD, and sex-specific generational recurrence risks of ADHD. Sex is severely understudied in psychiatric research, despite being a major predictor of individual differences in the prevalence of psychiatric disorders[45,217]. As previously described in chapter 1.2, only a minority of studies on adults with ADHD have acknowledged the possibility of an effect of sex, and the few exisiting studies have shown conflicting results[52] (for further details see chapter 1.2). Varying outcome measures, sample characteristics, and methodologies can be possible explaining factors for this[62,157]. A better understanding of sex differences is important in order for clinicians to be in a position to provide personalized prevention and treatment strategies for both men and women with ADHD[51,52], e.g. the importance of sex-specific psychiatric comorbidities, but also a scientific relevance by providing a better understanding of causation.

Two studies on sex differences in psychiatric comorbidities have been published after *paper I* was published; another cross-sectional study by Chen and colleagues in 2018, and a follow-up/longitudinal study by Ottosen and colleagues, in 2019[218,219]. Chen and colleagues studied adult ADHD and comorbid SUD, BD, depression and anxiety, and report somewhat higher prevalence estimates than ours, probably because their sample included older individuals (a larger age range of 18-64 compared to our sample of 18-45), with an increased possibility to be diagnosed with a psychiatric disorder within a longer period of time. Therefore, absolute prevalence rates are not directly comparable with those in our studies. However, the strongly increased risk of psychiatric comorbidity among individuals diagnosed with ADHD was confirmed. The sex differences from their study regarding anxiety, depression, BD and SUD were however possible to compare, as the male-female ratio of both the cases and non-cases were similar to ours, and their results showed the same pattern of sex-specific psychiatric comorbidity as in our *paper I.*

Ottosen and colleagues also confirm the higher risk of individuals with ADHD to receive a comorbid psychiatric disorder, even if their estimates are not directly comparable with our study, as their study has a longitudinal follow-up design. However, with a younger population (born 1981-2013 with an age range of 4-32 years), many of the individuals with ADHD may not have reached the typical age of onset for most psychiatric disorders investigated in *paper I*. Further, the low female representation of 28.2% gives a high male-female ratio of 2.54 (compared to the male-female ratio of 1.4 in *paper I)*, which obviously influences the relative measures.

In addition, Ottosen and colleagues' follow-up design did not include individuals receiving a diagnosis of ADHD after one of the comorbid disorders. This is potentially a large limitation of the results, as many adults with ADHD in today's clinical practice actually get their ADHD diagnosis after first being diagnosed with another psychiatric disorder. However, due to the younger age span of individuals diagnosed with ADHD in their study, this may not be such a severe bias.

Even though Ottosen and colleagues reported that the prevalence of other psychiatric disorders was higher in male than in female individuals with ADHD, the associations with ADHD were stronger in females than in males on the relative scale, as opposed to our findings. This is probably due to the high male-female ratio in their sample and that the reference prevalence in females was very low (e.g. 0.5% for ASD and 0.2% for ODD/CD).

In *paper I*, the sex-specific pattern of psychiatric disorders that we find among adults with ADHD is similar to the pattern found in the general population, see Figure 6[82,217,220]. Further, the absolute prevalence rates are much higher for both men and women with ADHD. Although the presence of ADHD enhances the trend between men and women in the general population, it is evident that the magnitude of this enhancement differs between men and women, and is also dependent on the specific disorder. The male-female ratio in our adult ADHD sample is low (*papers I & II*) compared to what is usually reported in studies of ADHD in childhood[23], and almost the same as in the remaining population (44% females among adults with ADHD and

49% females among those without). The finding could rather be interpreted as an increased risk of psychiatric disorders in adults with ADHD in general, either mediated by common genetic factors between ADHD and the other six psychiatric disorders[83], by other behavioural traits as a consequence of ADHD (e.g. inattention or hyperactivity/impulsivity), or by misclassification/overlapping diagnostic criteria[2].

Risk of psychiatric comorbidity in adults with ADHD or ASD

In *paper II*, the sex differences in risk of psychiatric comorbidities were different between adults with ADHD or ASD, on both the relative and absolute scales. There were no previous population-based studies regarding sex differences in adults with ASD or ADHD+ASD to compare our results with. When stratifying on sex, patterns of psychiatric comorbidity corresponded with those in the total sample: For both men and women, prevalence ratio (PR) estimates for SCZ were significantly larger in ASD than in ADHD, while for SUD, estimates were significantly larger for ADHD than for ASD. The male-female ratio in adults with ASD was higher than in adults with ADHD (*paper II*), and the sex differences in psychiatric comorbidity were not as evident as among adults with ADHD. Further, on the relative scale, the prevalence of all (ADHD) and three (ASD) psychiatric disorders (anxiety, depression, schizophrenia) increased more in men than in women in both exposure groups. When evaluating associations and interactions on the additive scale, sex differences were more pronounced, and the prevalence difference estimates were significantly different for all disorders in women and men with ADHD but for only three disorders (BD, depression, PD) in men and women with ASD (*Appendix 2 and 3*). We suggest that the smaller sex differences observed in adults with ASD than ADHD may partly be explained by the larger male-female ratio in adults with ASD and partly by women with ASD struggling more to communicate internalizing symptoms than women with ADHD[221].

Parent-of-origin effects in the recurrence risk of ADHD

In *paper III*, we found sex differences in the parent-of-origin effect on recurrence of ADHD. The recurrence risk from mother to offspring was stronger than the father-offspring risk regardless of offspring sex, and regardless of using absolute or relative effect measures. A couple of studies support the stronger recurrence of ADHD from

mother to offspring than from father to offspring[142,143]. However, in a large multi-center study, Anney and colleagues found that ADHD risk alleles from mothers and fathers were equally positively related to ADHD in offspring[140]. However, none of these studies were population-based. In *paper III,* using the relative scale, recurrence risks from mothers and fathers with ADHD were higher in female than in male offspring, although the associations from the father were lower than associations from the mother. On the absolute scale, the prevalence differences were larger for sons than for daughters in all three exposure groups (i.e. father, mother or both parents with ADHD). Further, although the prevalence of offspring ADHD was around 1.6 times higher in boys than girls regardless of parental ADHD, the difference in prevalence between boys and girls was larger in all exposure groups than in offspring to unaffected parents, and largest if both parents had ADHD. This may be a true sex difference, or an indication of a diagnostic bias towards male offspring due to ADHD symptoms being more descriptive for male behaviour[51,52].

Regarding reproduction patterns (for the cohort in MBRN born 1967-1968) in *paper III*, we also found sex differences. Men and women with ADHD were younger when they had their first child compared to men and women without ADHD. This finding is supported by Ostergaard and colleagues[156]. Further, the cumulative proportion who had at least one child by 2011 in our sample (when the cohort was 43-44 years of age) was significantly different between women with and without ADHD (90.4% versus 87.5%, p=.017), and between men with and without ADHD (75.2% versus 79.1, p=.007), see Figure 8 in chapter 4.3. In other word, and in line with Ostergaards findings, a lower proportion of men with than without ADHD ever reproduced. An interesting finding in Figure 8 is the crossing of the lines of men with and without ADHD at the age of ~35 years. Here it seems like men with ADHD reproduce at a younger age, but those who have not reproduced by the age of ~35 are less likely than men witout ADHD to reproduce at all. We found the opposite for women: a larger proportion of women with ADHD reproduced compared to women without. This was contradictory to the study by Ostergaard and colleagues, reporting that fewer women with ADHD ever became mothers compared to women without[156]. Our findings may be related how we could

define our ADHD cases: individuals being dispensed ADHD medication from 2004 and/or being registererd with an ADHD diagnosis in the NPR from 2008. The cohort of women in the calculation of cumulative reproduction was born 1967-1968, and could thus only be included as ADHD cases at the earliest age of 36-37 years. However, a replication of this analysis would be of interest.

We hypothesized that men with ADHD who did not reproduce likely were men with more severe ADHD symptoms, while more severe ADHD in women could relatively frequently be related to teenage pregnancies. We therefore repeated the analyses, taking account of the difference in age at first childbirth between men and women, and then also after excluding teenage mothers. These results were in line with the overall results, see Figure 9 in chapter 4.3. As an additional sensitivity analysis, we excluded mothers with low education (<11 years) instead of teenage mothers as a proxy for severe ADHD in women, and the results remained similar (not shown). These sensitivity analyses strengthened the conclusions based on our main results.

Sex differences in psychiatric comorbidities in adults with ADHD and in parent-offspring recurrence risk: possible mechanisms

The sex differences we found in *papers I-III* are interesting. In all three papers adult females with ADHD either had the highest risk of being diagnosed with four of the six psychiatric disorders studied (*papers I & II*), or showed the highest parent-offspring recurrence risk of ADHD (*paper III*). There may be several possible explanations for these findings. First, there may be a true difference between males and females caused by neurobiological/genetic factors; second, the sex differences in the subjective experience of ADHD could influence the risk of other psychiatric disorders; or third, the sex difference in health-seeking behavior could influence the risk. A combination of these factors is likely.

A possible true difference between men and women with ADHD which can influence the sex difference in risk of other psychiatric disorders, is the putative "female protective effect". A "female protective effect" suggests that females require a greater exposure to genetic and/or environmental factors associated with ADHD in order to develop the condition (chapter 1.2), (e.g. a higher genetic load)[71,72]. Sex chromosomes,

sex hormones, and gene/environment interactions may influence males and females differently[46]. A higher genetic load suggested in females may also influence the risk of other psychiatric disorders as genetic factors are shown to be shared between ADHD and other psychiatric disorders[83], and this may interact differently in men and women. However, due to low sample sizes and lack of representative sex representation in GWAS of adults with ADHD, this is not yet studied in adults with ADHD. Due to the suggested higher genetic load in females with ADHD, mothers may also have a higher transmission risk of ADHD genes to the offspring, compared to fathers with ADHD. Further, non-transmitted alleles (environmental effect with a genetic component, chapter 1.5.1) may have a larger impact from the mother compared to the non-transmitted alleles from the father, for instance the stronger nurturing effect from the mother on health aspects of the child[137]. A combination of these effects is also possible.

Women with ADHD report more impairment from ADHD symptoms than men[23,63,65]. Women with ADHD also subjectively more often report a negative impact of experienced life events compared to men with ADHD (chapter 1.2)[222]. The larger subjective impairment reported in women with ADHD may be linked to a higher rate of mood disorders in females. Women both with and without ADHD report more depressive symptoms than males[52,66]. The initiation of pharmacological treatment also differs by sex, with later initiation of treatment in females[77,223]. Both the larger reported subjective impairment in females with ADHD, and later initiation of pharmacological treatment towards ADHD may increase the risk for adverse outcomes, including comorbidities like SUD, depression and suicidal behaviour[23,63-65,219,224]. Men with ADHD are more often diagnosed with the combined ADHD phenotype with more externalizing symptoms[9,23,52], and the ADHD-associated novelty seeking and impulsive behaviour may mediate the risk of developing SUD[122]. Further, the larger risk of schizophrenia in men with ADHD may be related to the larger increase in prevalence of SUD, also found in men. Both having ADHD[17,80] and being a male[217,225] increases the risk of SUD, and SUD itself may increase the risk of psychosis[226]. Together, the above-mentioned factors may explain why adult females with ADHD in our studies have a higher increase in prevalence of psychiatric disorders like anxiety,

depression, BD and PD, compared to men with ADHD, while men with ADHD have a higher increase in the prevalence of SUD and SCZ.

The difference in health-seeking behavior among men and women with ADHD can also influence the sex differences we observed in the risk of other psychiatric disorders. In general, relatively more females seek health services as adults compared to males[52,227,228], and by this, they may "catch up" with the males with regards to the ADHD diagnosis, explaining the more equal male-female ratio in adulthood[52]. Contact with health service in adulthood is more dependent on self-referral due to own experienced symptoms than in childhood, where referral is more dependent on others, like parents and teachers[51,52] (chapter 1.2). In addition, females seek health-service to a larger degree due to reproductive health issues and screening programs (at least in Norway). Because of increased contact with health service on a more regular basis compared to males, it may be easier for females to ask for help also for psychiatric symptoms. All these factors may lead to an increased risk of being diagnosed with psychiatric comorbid disorders. Sex differences in health-seeking behavior can also partly explain the larger maternal parent-offspring recurrence risk of ADHD, as mothers may recognize own symptoms in their children, and seek help with regards to both their own and their children's symptoms[52].

Absolute versus relative scales

Our main analyses of differences in psychiatric comorbidity by sex in *paper I* were based on effect measures on the absolute scale, supplemented by effect measures on the relative scale (see chapter 3.4.2), while results in *paper II* were based on effect measures on the relative scale, supplemented by absolute effect measures when assessing sex differences. In *paper III*, we focused mainly on relative effect measures for evaluating parent-offspring recurrence risk.

The sex differences were dependent on the scale of our effect measures. Effect measures on the absolute scale are informative for clinical and public health questions, because it may indicate which subgroups need to be prioritized for preventive measures and interventions, while effect measures on the relative scale are often used to assess

the causality aspect[190]. In our studies, when evaluating the measures on the absolute scale, females seem to have the largest burden of ADHD and other psychiatric disorders, or at least who seek health service and are registered with these disorders. Further, in *paper III*, also on the absolute scale, sons to parents with ADHD had as much as 41.5% risk of ADHD when both parents were diagnosed with ADHD. These very high prevalence rates indicate that clinicians are aware of the possibility of ADHD in the children of affected parents, and either indicate that boys may be more predisposed or that there is a diagnostic bias towards boys.

Further research is needed to disentangle whether the sex differences in risk of psychiatric comorbidity in adults with ADHD and parent-offspring recurrence risk of ADHD observed in this study are true sex differences, due to sex differences in self-experience of ADHD symptoms, due to differences in health-seeking behavior between men and women (with ADHD), or a combination of these factors.

5.2.2 Differences between ADHD and ASD

One of our aims by comparing risk of psychiatric comorbidities between adults with ADHD and ASD (and ADHD+ASD), was to gain knowledge on similarities and/or differences that could inform clinicians about the differing risk of psychiatric comorbidities, and also inform further research in mechanisms behind these neurodevelopmental disorders. In *paper II,* we chose to compare the pattern of psychiatric comorbidities in adults with ADHD, with the corresponding pattern in adults with ASD. As described in chapter 1.3.1, ADHD and ASD are both neurodevelopmental disorders, often co-occur and share underlying genetic factors[97,99-103]. However, even if significant genetic correlations between phenotype-specific traits for ADHD and ASD have been demonstrated[98,105,106], the phenotypic characteristics for these two neurodevelopmental disorders remain quite different[3,4,98]. Therefore, we hypothesized that the pattern of psychiatrc comorbidities could also be different.

We observed significant differences in the associations with all psychiatric comorbidities examined, and with estimates being consistent with previous studies [17,90,102,107,114,116,122,229]. To our knowledge, only one other population-based study

reported the prevalence of psychiatric disorders among individuals with ADHD, ASD or ADHD+ASD compared with unaffected individuals in the same population[123]. However, this population was young (mean age ranging from 13.6 to 18.3 years) and thus had not reached the typical age of onset for most psychiatric disorders[82]. Therefore, the reported estimates were likely biased.

The high prevalences of psychiatric comorbidities observed both in individuals with ADHD, ASD or ADHD+ASD, could reflect that there are "common genetic factors for several phenotypic different psychiatric disorders" as recently reported[83]. Interestingly, the most marked differences were found for schizophrenia and SUD, in which schizophrenia was more common in adults with ASD and SUD was more common in adults with ADHD. The combined group, ADHD+ASD followed the ASD group with regards to schizophrenia, but the ADHD group with regards to the other psychiatric disorders. Further, the combined group had the strongest associations for several of the studied psychiatric disorders, indicating more severe impairment than for ADHD or ASD alone[107,230,231]. *Paper III* provides robust and representative estimates of differences in psychiatric comorbidities among adults diagnosed with ADHD or ASD. Together with the results from genetic correlations, these findings contribute to our understanding of these disorders as being distinct neurodevelopmental disorders with partly shared common genetic factors. Similarities, as well as differences between ADHD and ASD, can be further and more specifically evaluated by examining their symptom dimensions, each of which may have independent and different explanatory values for the clinical diagnoses of ADHD, ASD and their comorbidities[98]. Both diagnostic factors, and behavioural patterns can explain the differences we observe in *paper III*. The distinct comorbidity patterns may provide further information regarding etiologic research on biological mechanisms underlying the pathophysiology of these neurodevelopmental disorders.

5.2.1 The "C-word", a note on causality

The question of causality in observational studies is important to address. From the first preliminary findings of the association between maternal smoking and ADHD in offspring to the recent proven causal relation between small for gestational age and

ADHD[130], there have been several studies showing associations that later have been proven to be caused by other factors (e.g. unmeasured confounding[153]). This underscores the challenge in addressing causality in observational data, and emphasizes the importance of using proper designs, and preferably a combination of several designs (triangulation) [211,232,233].

The causal relationship between ADHD and other neurodevelopmental or psychiatric disorders is difficult to address using registries with a cross-sectional design. However, having information about socio-economic covariates (like parental attained education, maternal marital status, etc), and perinatal factors (like the individual's gestational age in weeks and gestational age- and sex-specific birthweight z-scores), and parental psychiatric disorders, gives the possibility to adjust for possible confounding variables that could influence and bias the effect measures. As ADHD is a multi-factorial etiological disorder, both genetics and environmental factors are important in the causal thinking of ADHD leading to other psychiatric disorders: either mediated by common genetic factors, by other behavioural traits as a consequence of ADHD, or by misclassification. However, adding genetic correlations between ADHD and ASD and other psychiatric traits, and finding of similar patterns, strengthens our results in the observational data where we find distinct patterns between adults with ADHD or ASD (*paper II*)[211]. In *paper III*, we strengthen our results by using generational data, and estimates from data on reproduction which also confirm our first results of higher parent-offspring risk from mothers with ADHD.

6. Conclusions

We found evidence for sex differences in adults with ADHD/ASD:

- Differences in prevalence between adults with and without ADHD were significantly larger in women compared to men for all main psychiatric disorders except schizophrenia and substance use disorder (SUD), indicating the larger potential for introducing preventive measures in women with ADHD.
- Also, between adults with and without ASD or ADHD+ASD we observed significantly larger differences in prevalence in women compared to men for several of the studied psychiatric disorders.
- The present population-based transgenerational study demonstrated a stronger recurrence risk of ADHD from mother to offspring than from father to offspring, and strongest to female offspring. This was true on both the relative and absolute scales.

We found significantly higher risk of psychiatric disorders in adults with ADHD/ASD:

- Both men and women with ADHD had a 4-9 times higher prevalence of anxiety, depression, BD, PD, schizophrenia, and SUD than the remaining adult population.
- A considerable proportion of cases of anxiety, depression, BD, PD, schizophrenia, and SUD in the population can be attributed to an underlying ADHD.
- In epidemiological data, we found statistically significant differences in risk of psychiatric comorbidities between adults diagnosed with ADHD, ASD or ADHD+ASD.
- We found common patterns in differences between ADHD and ASD based on genetic and epidemiological data regarding the six psychiatric comorbidities, although only two of the studied traits showed statistically significant differences between ADHD and ASD.
- Adults with both ADHD and ASD were more vulnerable to higher levels of psychiatric comorbidity.

7. Future perspectives

In this thesis, we have contributed with new knowledge and evidence of sex differences in adults with ADHD both in the risk of psychiatric comorbidities and in parent-offspring recurrence risk. The observed sex differences in *papers I-III* underline the importance of further future research disentangling the contribution of the sex-variable in epidemiological data, and in all research where sex is considered relevant. For this purpose, both large-scaled GWAS, family data, and the combination of genetic and population-based epidemiological data are necessary. It is important to focus on the incorporation of relevant theoretical frameworks, adequate representation of both sex in study samples, and attention to biases in samples and assessment methods[52].

Khramtsova and colleagues recommend that GWAS of complex traits in the future include sex-stratified, gene-by sex interaction, and heritability analyses including sex-chromosomes to determine the role of sex in the genetic basis of complex traits[46]. Large cohorts of genotyped and phenotyped data, biobanks, population-based registries, and associated genomic data, are necessary sources for future studies[46]. More is also necessary to know about the effect of sex hormones, e.g. how menopause affects women with ADHD, thus the effect of sex chromosomes/hormones in the development and influence on ADHD in a life-course perspective.

As commented by Turner in an editorial accompanied by the final version of *paper II*, the study provides the field of epidemiology "with a roadmap for the use of comorbidity patterns to inform understanding of both overlap and non-overlap of ASD and ADHD in a large adult cohort from one country". In the future to come, epidemiological, clinical, and genetic data combined in large population-based datasets will improve the understanding of neurodevelopmental and psychiatric disorders and shared factors. Further, if it is possible to add information about environmental exposures and social determinants, this may contribute to more detailed knowledge about causation and personalized interventions[234].

However, our current diagnostic criteria are based on clinically observed aggregates of symptoms but may not relate to distinct underlying biological pathways. Hence, well-

powered GWAS on clearly defined specific psychiatric phenotypes and narrower symptom domains are needed to uncover the biological mechanisms underlying the multifaceted etiologies of ADHD and ASD. On the contrary, Hyman and colleagues argue of the strengths by using broad categories/large groupings/broad clusters of diagnostic categories, which confer an advantage and are less likely than individual diagnoses to result in artifactual comorbidity[235]. The use of large groupings/clusters of disorders/broad categories of disorders, even with several limitations, is likely to limit confounding factors of existing diagnostic categories[235]. Further, a recent publication of cross-disorder GWAS meta-analysis for ADHD, ASD, obsessive-compulsive disorder, and Tourette syndrome identified 21 genes significantly associated with these conditions, and indicates an increased power in the cross-disorder comparisons[236]. Therefore, a combination of several different strategies may be necessary to complement the puzzle of etiological factors contributing to the development of ADHD (and other neurodevelopmental disorders).

In the short term, it is possible to continue to do research based on the existing available registry-data, focusing on sex differences. Further, to disentangle the contribution of a genetic effect in the parent-offspring effect by sex, enough data to perform GWAS with the non-transmitted allele is needed. This may gain insight into pathways through which the effect of an individual variant is manifested, and highlights the importance of utilizing family/generational data, which is used in *paper III*[137]. Thus, it is possible to do genetic analyses (polygenic risk scores) in data on parents/trios from multigenerational cohorts, such as Avon Longitudinal Study of Parents and Children (ALSPAC)[237,238] or the Norwegian Mother, Father and Child Cohort Study (MoBa)[239], to come closer to the observed sex difference in the parent-offspring recurrence risk.

In the longer run, it is important, although more expensive, to generate large-scaled prospective studies, to track males and females through a life-span, and thereby, gain knowledge on sex-specific development of ADHD regarding symptoms, prevalence, persistence, comorbidities, and adverse life events. Further, in addition to etiological research utilizing the epidemiological and genetic data available, it is also important to examine the sex difference in health-seeking behavior as an important explanatory

factor of the differences in psychiatric diagnoses between men and women. If relevant information about health-seeking behavior is available, data from large Norwegian health surveys may be utilized for this; the MoBa study, Hordaland Health Studies (HUSK)[240], and the HUNT Study (an acronym for the Norwegian name: Helseundersøkelsen i Nord-Trøndelag)[241].

Related to *paper III*, more studies using generational data, sibling design, and family design with longer follow-up and linking of several registries will increase the possibility of going further into the parent-offspring recurrence risk of ADHD, and further alleviate the strong associations found in *paper III*.

In the question of causal inference/causality regarding psychiatric comorbidities, Krieger and Davey Smith have emphasized the use of "triangulation" of different designs with different biases and assumptions providing greater confidence in the robustness of the results[233].

Our understanding of the etiology and pathogenesis of ADHD is still limited. The main aim of the research should always be to the best of individuals with ADHD, toward personalized and ultimately precision medicine. Also, to better focus on a lifespan perspective, we should aim to unify research from both child/adolescent and adult psychiatry.

8. References

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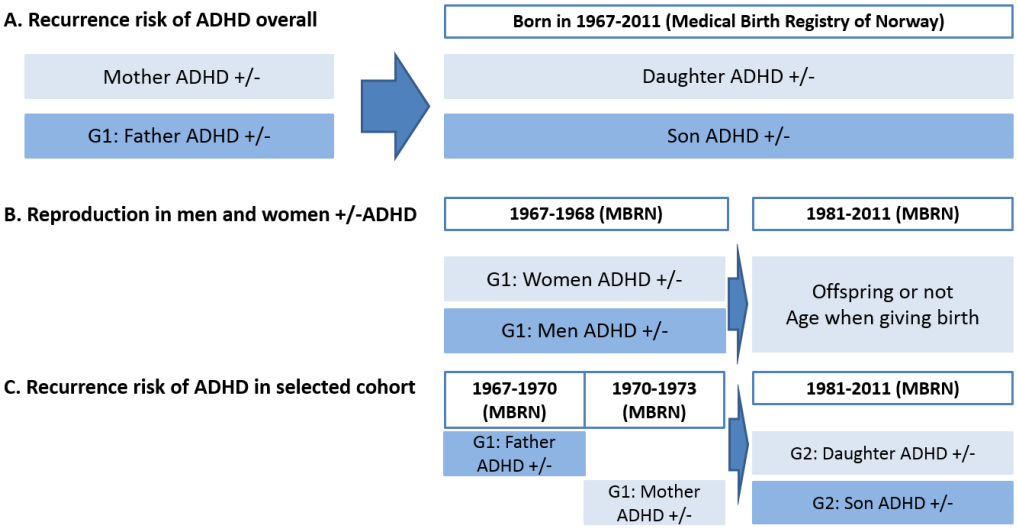
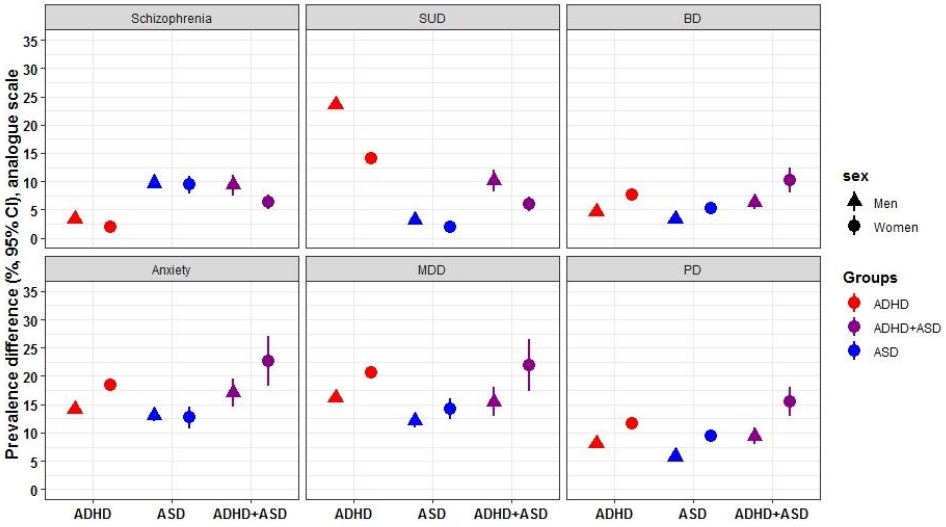
9. Appendices

Appendix 1. *Overview of the different parent-offspring recurrence analyses (A, C) and calculation of reproduction (B). All alive at record linkage in 2015.*



Appendix 2. *Prevalence difference of psychiatric disorders in adults with ADHD, ASD and ADHD+ASD relative to the remaining population, by sex*



Abbreviations: Schizophrenia= Schizophrenia Spectrum Disorder, SUD= Substance Use Disorder, BD= Bipolar Disorder, MDD= Major Depression Disorder, PD= Personality Disorder. Prevalence difference, 95% CI error bars, analogue scale. Adjusted for birth year (5-year groups, from 1967 to 1997).

Appendix 3. *Reprinted with permission from Elsevier. Turner TN. Large-Scale Population-Based Assessment of Psychiatric Comorbidities in Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder. Biological psychiatry. 2019;86(8):e25-e27. Copyright Elsevier.*

Table 1. Summary of Relative Prevalence Differences for Psychiatric Comorbidities in Individuals With ADHD and/or ASD and in the Remaining Population

Psychiatric Comorbidity	Remaining Population	ADHD	ASD	ADHD and ASD
Anxiety Disorder	♀ > ♂	♀ > ♂	♀ ≈ ♂[a]	♀ > ♂
Bipolar Disorder	♀ ≈ ♂	♀ > ♂[a]	♀ > ♂[a]	♀ > ♂[a]
Major Depressive Disorder	♀ > ♂	♀ > ♂	♀ > ♂	♀ > ♂
Personality Disorder	♀ ≈ ♂	♀ > ♂[a]	♀ > ♂[a]	♀ > ♂[a]
Schizophrenia	♀ ≈ ♂	♀ < ♂[a]	♀ ≈ ♂	♀ < ♂[a]
Substance Use Disorder	♀ < ♂	♀ < ♂	♀ < ♂	♀ < ♂

Summary values are derived from Solberg *et al.*'s (7) Supplemental Table S4. ♀ > ♂ indicates that the prevalence is greater in females than in males, ♀ < ♂ indicates that the prevalence is greater in males than in females, and ♀ ≈ ♂ indicates that the prevalence is about equal in males and females.

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.

[a]Categories in which there is a difference when compared with the remaining population.

10. Papers I-III

I

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Gender differences in psychiatric comorbidity: a population-based study of 40 000 adults with attention deficit hyperactivity disorder

Solberg BS, Halmøy A, Engeland A, Igland J, Haavik J, Klungsøyr K. Gender differences in psychiatric comorbidity: a population-based study of 40 000 adults with attention deficit hyperactivity disorder.

Objective: We aimed at determining whether gender modified associations between ADHD and psychiatric comorbidities in adults.
Method: We identified adults with ADHD by linking Norwegian national registries and compared them with the remaining adult population (born 1967–1997, ADHD and bipolar during 2004–2015, other psychiatric disorders 2008–2015). Prevalence differences (PDs) and prevalence ratios (PRs) of psychiatric disorders were determined by Poisson regression. Interaction by gender was evaluated on additive (PDs) and multiplicative (PRs) scales. Proportions of psychiatric disorders attributable to ADHD were calculated.
Results: We identified 40 103 adults with ADHD (44% women) and 1 661 103 adults (49% women) in the remaining population. PDs associated with ADHD were significantly larger in women than in men for anxiety, depression, bipolar and personality disorders, for example depression in women: 24.4 (95% CI, 23.8–24.9) vs. in men: 13.1 (12.8–13.4). PDs were significantly larger in men for schizophrenia and substance use disorder (SUD), for example SUD in men: 23.0 (22.5–23.5) vs. in women: 13.7 (13.3–14.0). Between 5.6 and 16.5% of psychiatric disorders in the population were attributable to ADHD.
Conclusion: The association between ADHD and psychiatric comorbidities differed significantly among men and women. Clinicians treating adults with ADHD should be aware of these frequent and gender-specific comorbidities, such that early treatment can be offered.

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Key words: attention deficit hyperactivity disorder; gender; epidemiology; psychiatric disorders; comorbidity

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Significant outcomes

- Both men and women with ADHD had a 4–9 times higher prevalence of anxiety, depression, bipolar and personality disorders, schizophrenia and substance use disorder (SUD) than the remaining adult population.
- Differences in prevalence between ADHD and non-ADHD adults were significantly larger in women than in men for all psychiatric disorders except schizophrenia and SUD, indicating the larger potential for introducing preventive measures in women with ADHD.
- A considerable proportion of cases of anxiety, depression, bipolar and personality disorders, schizophrenia and SUD in the population can be attributed to an underlying comorbid ADHD.

Limitations

- This study employed a cross-sectional design, limiting the possibility of making causal conclusions.
- Information on ADHD and psychiatric comorbid disorders was based on data registered in the Norwegian Prescription Database from 2004 to 2015 and in the Norwegian Patient Registry from 2008 to 2015, limiting the study of temporal relations.
- Information on psychiatric comorbid disorders was based on diagnoses registered in secondary health care, missing comorbidities registered in primary care.

Introduction

Attention deficit hyperactivity disorder (ADHD) (1, 2) is an impairing and prevalent childhood-onset disorder that frequently persists into adulthood (3–5). Based on an estimated worldwide prevalence of 2.5% among adults, ADHD affects millions of individuals across the world and is of major public health concern (3, 6, 7). The strong male predominance among children with ADHD decreases with age; further, comorbidity with other psychiatric disorders is the rule rather than the exception, particularly in adults with ADHD (8–12). It is also known that women with ADHD are more frequently diagnosed with the inattentive subtype, as defined in DSM-IV/DSM-5 (1, 13), with more internalizing comorbid disorders such as depression and anxiety. Women also report more impairment than men (11, 14–17), and a study based on self-reports among adults showed that women with ADHD, more often than men, reported a history of treatment for other psychiatric disorders than ADHD (8). The combined subtype, with more externalizing symptoms, is more frequent in men (17). This subtype is more often linked to antisocial personality disorder and substance use disorder (SUD) (11, 18).

Several studies have focused on psychiatric comorbidity in adults with ADHD, for example anxiety and major depressive disorder (depression) (3, 11), bipolar disorder (9–11, 19), personality disorders (20, 21), schizophrenia spectrum disorders (schizophrenia) (19, 22, 23) and SUD (11, 24). However, existing studies of gender differences in such comorbidity have shown conflicting results in adults with ADHD, possibly because of varying outcome measures, sample characteristics and methodologies. To gain a better understanding of gender differences is important in order to be in a position to provide suitable treatment and prevention strategies for both men and women with ADHD (18, 25). Few studies have investigated whether these comorbidities differ between men and women (26, 27), and large epidemiological studies of good quality are still lacking (7, 18).

In the present work, we use the term 'gender' instead of 'sex' because the study concerns adults, and 'gender' is shaped by environment and experience in addition to the biological characteristics determined by sex (28).

Aims of the study

We aimed at determining whether gender modified associations between ADHD and psychiatric comorbidities. We also aimed at determining the proportion of psychiatric disorders among men and women in the population that could be attributed to a comorbid ADHD.

Method

Study population

We conducted a cross-sectional analysis in a cohort of adults in Norway, by linking information from four nationwide, population-based registries: The Medical Birth Registry of Norway (MBRN), established in 1967 (29), the Norwegian Prescription Database (NorPD) (30), established in 2004, the Norwegian Patient Registry (NPR) (31), with data from 2008, and the National Educational Database (NUDB) from Statistics Norway (32, 33). See Appendix S1 for Supporting Information and details about the registries. The study included all individuals born between 1967 and 1997, alive and resident in Norway at record linkage in 2015 (n = 1 701 206). Record linkage was established using the national identification number unique to every Norwegian resident.

The study was approved by the Regional Ethics Committee in Norway (2011/2272). No informed consent was required for the analysis of anonymized registry data.

We defined adults with ADHD as those who had been dispensed their last prescription of ADHD medication at 18 years of age or more

during 2004–2015 (NorPD), or with an ADHD diagnosis registered at 18 years or higher in the period 2008–2015 (NPR). The ADHD medications identified were the central stimulants: methylphenidate, racaemic amphetamine and dexamphetamine, and the non-stimulant drug atomoxetine, see Appendix S2 for ADHD medication used for narcolepsy.

The remaining population included all adults (18 years or older by record linkage) who had neither been dispensed ADHD medication nor had an ADHD diagnosis, in the NorPD and NPR respectively. Parents to adults with and without ADHD were also identified through the MBRN, to evaluate the influence of factors known to be associated with both ADHD and other psychiatric disorders (sociodemographic variables, pregnancy-related risk factors and parental psychiatric disorders).

Measures

We analysed the association between ADHD and psychiatric disorders among men and women, ADHD being our 'exposure', and evaluated effect modification by gender. Our main aim was to evaluate psychiatric comorbidity in adults with ADHD, and for this analysis, no confounding variables are relevant; thus, we only adjusted for age (birth year; 5-year groups from 1967 to 1997, with 1967–1973 as the reference period). To evaluate how risk factors for both ADHD and other psychiatric disorders influenced the prevalence ratios, we ran two regression models, including the following covariates that all have been documented as risk factors for ADHD and psychiatric disorders (34–41): Model 1: birth year, maternal marital status (single, married/cohabiting (reference category), other), maternal age (<20, 20–24, 25–29 (reference value), 30–34, 35–39, 40+) and paternal age (<20, 20–24, 25–29, 30–34 (reference value), 35–39, 40–44, 45–49, 50+) at delivery, parent's highest attained educational level at record linkage (low (<10 years of education), middle (10–12 years of education) and high level (>12 years of education (reference category)), the individual's gestational age in weeks (<27, 28–31, 32–34, 35–36, 37–41 (reference value), 42+) and gestational age- and sex-specific birthweight z-scores (<-2.0; −2.0 to −0.51; −0.5 to 0.5 (reference value); 0.51 to 2.0; 2.01+).

Model 2 further included mothers' and fathers' psychiatric diagnoses (yes/no), including ADHD or any other psychiatric diagnosis from NPR, 2008–2015.

We studied the following major comorbid psychiatric disorders, typically diagnosed in late adolescence and adulthood, and all registered at 18 years or more: anxiety (ICD-10 codes; F40-F42), depression (F32-F33), bipolar (F30-F31) and personality disorders (F60-F61), schizophrenia (F20-F29) and SUD (F10-F19).

To define bipolar disorder, we used data from the NorPD in addition to the NPR including individuals who had been prescribed and dispensed either lithium during 2004–2015 or anti-epileptic drugs with mood disorders as the indication during 2008–2015 (indications for psychotropic medications are only available in the NorPD since 2008).

Statistical analysis

Absolute prevalence differences (PD) of psychiatric disorders between persons with and without ADHD among men and women were calculated using predicted prevalences from a Poisson regression model with adjustment for birth year (5-year periods). Significance of interaction by gender on the additive scale was evaluated using relative excess risk due to interaction (RERI) (42). While it has been suggested that effect measures and interactions on the multiplicative scale are better suited to 'assess causality', risk differences and interactions on the additive scale are the most important to assess public health relevance, indicating which group may benefit the most from treatment or preventive measures (42). To examine the association between ADHD and other psychiatric disorders on a multiplicative scale, we estimated prevalence ratios (PR) using Poisson regression with robust standard errors (43). Significance of interaction by gender on the multiplicative scale was evaluated by comparing Poisson regression models with and without the interaction term (gender x ADHD) included, as tested by likelihood ratio tests. Finally, we estimated the proportion of psychiatric comorbidities attributable to ADHD among men and women with ADHD (attributable fractions in the exposed—AFE) and in the population (population attributable fractions—PAF) (44). Two-sided tests with a significance level of 0.05 were used in all analyses. Analyses were carried out with PASW Statistics 23 (45) and STATA intercooled v.14 (46) from 3 January 2016 to 24 July 2017.

Sensitivity analysis

We conducted several sensitivity analyses to test the robustness of the results, see Appendix S3 in Supporting Information for details: for all psychiatric disorders, we excluded individuals with a diagnosis of mental retardation, and when analysing prevalences of bipolar disorder, we excluded

individuals with comorbid schizophrenia. We repeated analyses including only individuals with one psychiatric comorbid diagnosis alone. Analyses were also repeated requiring the psychiatric diagnosis to be registered at least twice in the NPR. Finally, when adjusting for covariates, we used multiple imputation with chained equations (MICE) (47) to evaluate possible biases due to missing information for gestational age. In the main analyses, missing values in covariates (6% for gestational age and birthweight z-scores, other variables <1%) were handled by listwise deletion. To impute for missing values in gestational age and z-scores, we ran sensitivity analyses using MICE, where the outcome variables, all specified covariates and also birthweight, maternal preeclampsia and mother's chronic diseases (yes/no), were used for information.

Results

Study groups

We identified a total of 40 103 adults with ADHD (2.4% of the population), 17 815 women (44.4%), with a total mean age of 31 years in 2015. The remaining population consisted of 1 661 103 adults, 812 061 women (48.9%) and a mean age for the total sample of 33 years in 2015. The male : female ratio in the ADHD group was 1.3 : 1. As shown in Table 1, more mothers of ADHD adults than remaining mothers had the lowest educational level (34.9% vs. 26.2%) and were single when giving birth (16.8% vs. 9.2%). Also, parents of ADHD adults had significantly more psychiatric disorders than parents of the remaining population (mothers: 27.3 vs. 13.4%; fathers: 17.3 vs. 9.9%).

Table 1. Sample characteristics of the study population, 1 701 206 adults in Norway

Variable	ADHD, No. (%)	Non-ADHD, No. (%)	ADHD Women, No. (%)	ADHD Men, No. (%)
No. (%)	40 103 (2.4)	1 661 103 (97.6)	17 815 (44.4)	22 288 (55.6)
Gender				
Women	17 815 (44.4)	812 061 (48.9)		
Men	22 288 (55.6)	849 042 (51.1)		
M:F ratio	1.25	1.05		
Mean age in 2015 (years) (SD)		$P < 0.001$*		$P < 0.001$**
	31.2 (8.3)	33.1 (9.3)	31.4 (8.4)	31.0 (8.2)
Gestational age (weeks)		$P < 0.001$*		$P < 0.001$**
<27	113 (0.3)	2464 (0.2)	43 (0.3)	70 (0.3)
28–31	283 (0.8)	7835 (0.5)	101 (0.6)	182 (0.9)
32–34	677 (1.9)	22 239 (1.4)	270 (1.7)	407 (2.0)
35–36	1313 (3.6)	49 624 (3.2)	532 (3.3)	781 (3.8)
37–41	28 552 (77.9)	1 250 422 (80.3)	12 660 (77.8)	15 892 (78.1)
42+	5701 (15.6)	223 779 (14.4)	2661 (16.4)	3040 (14.9)
Missing	3464 (8.6)	104 740 (6.3)	1548 (8.7)	1916 (8.6)
Maternal marital status		$P < 0.001$*		$P = 0.9$**
Married/cohabitant	32 342 (80.9)	1 489 193 (89.8)	14 354 (80.8)	17 988 (80.9)
Single	6708 (16.8)	152 884 (9.2)	2996 (16.9)	3712 (16.7)
Other	944 (2.4)	16 250 (1.0)	419 (2.4)	525 (2.4)
Missing	109 (0.3)	2776 (0.2)	46 (0.3)	63 (0.3)
Maternal educational status		$P < 0.001$*		$P = 0.8$**
Low	13 892 (34.9)	432 778 (26.2)	6197 (35.0)	7695 (34.7)
Middle	17 061 (42.8)	771 795 (46.7)	7629 (43.1)	9432 (42.6)
High	8903 (22.3)	449 945 (27.2)	3877 (21.2)	5026 (22.7)
Missing	247 (0.6)	6585 (0.4)	112 (0.6)	135 (0.6)
Paternal educational status		$P < 0.001$*		$P = 0.006$**
Low	12 889 (33.0)	382 793 (23.4)	5695 (32.8)	7194 (33.2)
Middle	19 320 (49.5)	838 027 (51.2)	8746 (50.4)	10 574 (48.8)
High	6827 (17.5)	416 636 (25.4)	2914 (16.8)	3913 (18.1)
Missing	1067 (2.7)	23 647 (1.4)	460 (2.6)	607 (2.7)
Maternal psychiatric disorder		$P < 0.001$*		$P = 0.99$**
None	29 149 (72.7)	1 437 851 (86.6)	12 977 (72.8)	16 172 (72.6)
Any, including ADHD	10 953 (27.3)	223 216 (13.4)	4838 (27.2)	6115 (27.4)
Paternal psychiatric disorder		$P < 0.001$*		$P = 0.06$**
None	32 667 (82.7)	1 485 656 (90.1)	14 609 (83.2)	18 058 (82.2)
Any, including ADHD	6848 (17.3)	162 779 (9.9)	2941 (16.8)	3907 (17.8)

*P-value (Pearson's chi-square test and t-test for equality of means) for the difference in ADHD total relative to the comparison population.

**P-value (Pearson's chi-square test and t-test for equality of means) for the difference in men with ADHD vs. women with ADHD.

Association between ADHD and psychiatric comorbidities in men and women

Adults with ADHD had a much higher prevalence of additional psychiatric disorders compared to the remaining population, as shown in Fig. 1. As many as 53.5% of women and 48.5% of men with ADHD had one or more of the six studied psychiatric comorbidities, compared to 13.7% of women and 9.1% of men in the remaining population. Women with ADHD had the highest prevalence of all disorders except schizophrenia and SUD (Fig. 1).

Evaluated on an absolute scale, the prevalence differences (PD) between adults with and without ADHD were statistically significant for all the psychiatric disorders and ranged from 2.1% (95% CI 2.0–2.3) for schizophrenia to 24.4% (23.8–24.9) for depression, both in women, see Table 2.

Evaluated on a multiplicative scale, adult ADHD was most closely associated with bipolar disorder, personality disorders and SUD, with PR estimates ranging from 7.2 (95% CI, 7.0–7.5) for SUD in women to 8.9 (8.5–9.3) for bipolar and personality disorders in men. Associations with anxiety, depression and schizophrenia were weaker, though still strong, with a four to five times higher prevalence of these disorders in both men and women with ADHD than those without, see Table 3.

Interaction by gender

Interaction by gender was tested both on the additive and the multiplicative scales, see Tables 2 and 3. When testing for interaction by gender on an additive scale, the PDs were significantly larger in women than in men for all psychiatric comorbidities except schizophrenia and SUD, where the PDs were larger in men. On the multiplicative scale, the associations with ADHD were significantly stronger in men than in women for anxiety, depression, bipolar and personality disorders, see Table 3.

Attributable proportions

A large proportion of psychiatric disorders among adults with ADHD could be attributed to their existing ADHD condition, with AFE ranging from 72.9% to 87.5% in women and 79.5% to 88.8% in men, see Table 3. The proportions of psychiatric disorders in the adult population that could be attributed to a comorbid ADHD were also high, with PAF ranging from 5.6% to 13.0% in women and from 8.9% to 16.5% in men.

Sensitivity analysis

The results of the sensitivity analyses are shown in Supporting Information, Tables S1–S3. All sensitivity analyses were compatible with the results of the main analyses.

Discussion

This is the first large population-based study performed on adults clinically diagnosed with ADHD to evaluate gender differences in major psychiatric comorbidities and testing for interaction by gender

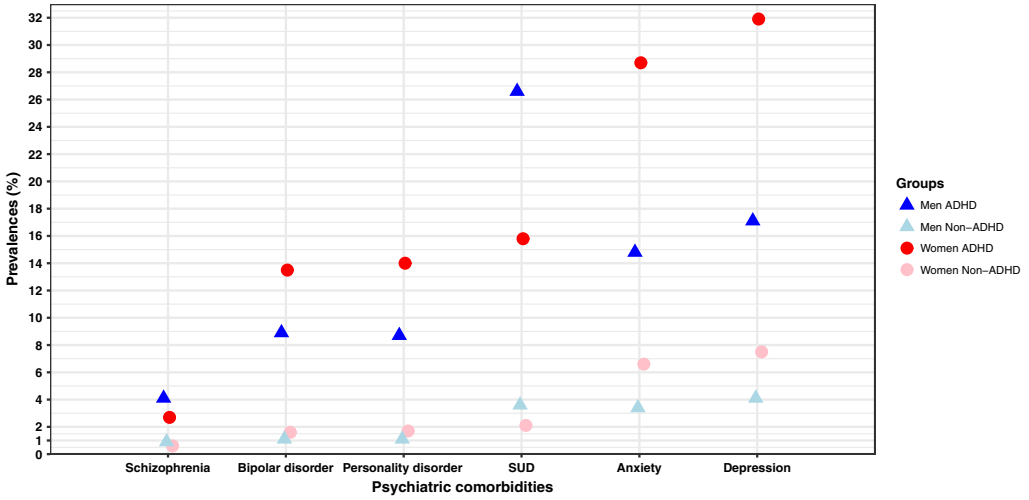

Fig. 1. Adjusted* prevalences of psychiatric disorders in men and women with and without ADHD. *Prevalences was adjusted for birth year, 5-year groups, from 1967 to 1997, with 1967–1973 as the reference. SUD, Substance use disorder.

Table 2. Prevalence differences in psychiatric disorders in men and women with and without ADHD. Effect modification by gender evaluated on an additive scale

	Crude prevalences, No. (%)		Prevalence, % (95% CI)*			Additive effect modification†
Psychiatric disorders (*ICD-10*)	ADHD	Non-ADHD	ADHD	Non-ADHD	PD‡ (95% CI)	RERI§ (95% CI)
Anxiety disorders (F40–42)						
Women	4676 (26.3)	54 479 (6.7)	28.7 (28.2–29.3)	6.6 (6.6–6.7)	22.1 (21.6–22.6)	1.4 (1.2–1.7)*¶
Men	4054 (18.2)	28 364 (3.3)	14.8 (14.5–15.1)	3.4 (3.4–3.5)	11.4 (11.1–11.7)	
Bipolar disorder (F30–31 or medication)‖						
Women	2290 (12.9)	13 183 (1.6)	13.5 (13.1–13.9)	1.6 (1.6–1.6)	11.9 (11.5–12.3)	3.4 (2.7–4.0)*
Men	1981 (8.9)	9009 (1.1)	8.9 (8.7–9.2)	1.1 (1.0–1.1)	7.9 (7.6–8.1)	
Major depressive disorder (F32–33)						
Women	5138 (28.8)	61 880 (7.6)	31.9 (31.4–32.5)	7.5 (7.5–7.6)	24.4 (23.8–24.9)	1.3 (1.1–1.5)*
Men	4516 (20.3)	33 733 (4.0)	17.1 (16.8–17.5)	4.1 (4.0–4.1)	13.1 (12.8–13.4)	
Personality disorder (F60–61)						
Women	2428 (13.6)	14 079 (1.7)	14.0 (13.6–14.5)	1.7 (1.7–1.7)	12.3 (11.9–12.7)	3.8 (3.2–4.4)*
Men	2030 (9.1)	8909 (1.1)	8.7 (8.4–8.9)	1.1 (1.0–1.1)	7.6 (7.3–7.9)	
Schizophrenia spectrum disorder (F20–29)						
Women	444 (2.5)	4621 (0.6)	2.7 (2.5–2.8)	0.6 (0.5–0.6)	2.1 (2.0–2.3)	−1.8 (−2.2; −1.3)*
Men	928 (4.2)	7352 (0.9)	4.1 (3.9–4.3)	0.9 (0.8–0.9)	3.3 (3.0–3.5)	
Substance use disorder (F10–19)						
Women	2878 (16.2)	17 200 (2.1)	15.8 (15.4–16.1)	2.1 (2.1–2.1)	13.7 (13.3–14.0)	−2.9 (−3.1; −2.7)*
Men	6135 (27.5)	30 233 (3.6)	26.6 (26.1–27.1)	3.6 (3.5–3.6)	23.0 (22.5–23.5)	

ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision, World Health Organization; CI, confidence interval; PD, prevalence difference; RERI, relative excess in risk due to interaction.

*Prevalence adjusted for birth year (5-year groups, from 1967 to 1997, with 1967–1973 as the reference period).

†Female gender as reference group.

‡Prevalence Difference (PD) between adults with and without ADHD, adjusted for birth year as above.

§Relative Excess in Risk due to Interaction (RERI) adjusted for birth year as above.

¶*P-value* of interaction on an additive scale, all $P < 0.001$.

‖Medication: lithium during 2004–2015 or anti-epileptic drugs with mood disorders as the indication during 2008–2015.

Table 3. Prevalence ratios of psychiatric disorders men and women with and without ADHD. Effect modification by gender evaluated on a multiplicative scale

	Crude prevalences, No. (%)		Prevalence ratios (95% CI)			Attributable fraction (95% CI)	
Psychiatric disorders	ADHD	Non-ADHD	Crude†	Model 1‡	Model 2§	AFE¶	PAF‖
Anxiety Disorders			$P < 0.001$**	$P < 0.001$	$P < 0.001$	††	
Women	4676 (26.3)	54 479 (6.7)	3.7 (3.7–3.8)	3.6 (3.5–3.7)	3.4 (3.3–3.5)	73.3 (72.6–74.0)	5.8 (5.6–6.0)
Men	4054 (18.2)	28 364 (3.3)	5.3 (5.2–5.5)	5.1 (4.9–5.2)	4.7 (4.5–4.8)	81.2 (80.6–81.7)	10.2 (9.8–10.5)
Bipolar Disorder			$P = 0.03$	$P = 0.03$	$P = 0.07$		
Women	2290 (12.9)	13 183 (1.6)	8.0 (7.7–8.3)	7.8 (7.5–8.2)	7.2 (6.8–7.5)	87.5 (87.0–88.0)	13.0 (12.4–13.5)
Men	1981 (8.9)	9009 (1.1)	8.9 (8.5–9.3)	8.9 (8.5–9.4)	8.1 (7.7–8.5)	88.8 (88.2–89.3)	16.0 (15.3–16.7)
Major depressive disorder			$P < 0.001$	$P < 0.001$	$P < 0.001$		
Women	5138 (28.8)	61 880 (7.6)	3.7 (3.6–3.8)	3.6 (3.5–3.7)	3.3 (3.2–3.4)	72.9 (72.2–73.5)	5.6 (5.4–5.8)
Men	4516 (20.3)	33 733 (4.0)	5.1 (5.0–5.3)	4.9 (4.8–5.0)	4.5 (4.4–4.6)	80.5 (79.9–81.0)	9.5 (9.2–9.8)
Personality disorder			$P = 0.001$	$P = 0.008$	$P = 0.02$		
Women	2428 (13.6)	14 079 (1.7)	7.7 (7.3–8.0)	7.1 (6.8–7.4)	6.5 (6.2–6.8)	86.9 (86.4–87.5)	12.8 (12.3–13.3)
Men	2030 (9.1)	8909 (1.1)	8.9 (8.5–9.3)	8.1 (7.7–8.5)	7.3 (6.9–7.7)	88.8 (88.2–89.3)	16.5 (15.8–17.2)
Schizophrenia spectrum disorder			$P = 0.08$	$P = 0.07$	$P = 0.1$		
Women	444 (2.5)	4621 (0.6)	4.5 (4.1–4.9)	4.5 (4.1–5.0)	4.1 (3.7–4.6)	77.7 (75.4–79.7)	6.8 (6.0–7.6)
Men	928 (4.2)	7352 (0.9)	4.9 (4.6–5.2)	4.8 (4.5–5.2)	4.3 (4.0–4.7)	79.5 (78.0–80.8)	8.9 (8.2–9.6)
Substance use disorder			$P = 0.4$	$P = 0.7$	$P = 0.98$		
Women	2878 (16.2)	17 200 (2.1)	7.2 (7.0–7.5)	6.3 (6.1–6.6)	5.8 (5.6–6.0)	86.2 (85.7–86.7)	12.4 (11.9–12.8)
Men	6135 (27.5)	30 233 (3.6)	7.6 (7.4–7.8)	6.6 (6.5–6.8)	6.1 (6.0–6.3)	86.8 (86.5–87.1)	14.6 (14.3–15.0)

CI, Confidence interval; ADHD, adults with ADHD; non-ADHD, remaining population without ADHD; AFE, attributable fraction among the exposed; PAF, population attributable fraction.

†Adjusted for birth year (5-year groups from 1967 to 1997, with 1967–1973 as the reference period).

‡Model 1: Adjusted for birth year, maternal marital status (single, married/cohabiting (reference category), other), maternal and paternal education (low (<10 years of education), middle (10–12 years of education and high level (>12 years of education (reference category)), maternal age (<20, 20–24, 25–29 (reference value), 30–34, 35–39, 40+) and paternal age (<20, 20–24, 25–29, 30–34 (reference value), 35–39, 40–44, 45–49, 50+) at delivery, gestational age (<27, 28–31, 32–34, 35–36, 37–41 (reference value), 42+), gestational age and sex-specific birthweight z-scores (<−2.0; −2.0 to −0.51; −0.5 to 0.5 (reference value); 0.51–2.0; 2.01+).

§Model 2: As in Model 1 and additionally adjusted for maternal and paternal psychiatric disorders (yes/no).

¶Attributable fraction among the exposed (AFE) (%) (=ADHD population), based on crude model.

‖Population attributable fraction (PAF) (%), based on crude model.

**P-value of the interaction between ADHD and sex on a multiplicative scale.

††Statistical significant difference between men and women with ADHD based on non-overlapping 95% confidence intervals.

on both multiplicative and additive scales. Both men and women with ADHD had 4–9 times higher prevalences of all the studied psychiatric disorders than the remaining adult population. However, on an absolute scale, differences in prevalence between ADHD and non-ADHD adults were significantly larger in women than in men for all psychiatric disorders except schizophrenia and SUD, indicating the larger potential for preventive measures in women with ADHD. The proportions of psychiatric disorders in the population attributable to a comorbid ADHD were large for both genders.

In line with previous studies in the literature, we found higher prevalences of all the studied comorbidities in adults with ADHD than in those without (3, 10). However, few previous studies have evaluated gender differences in comorbidity among adults with ADHD, and results from existing studies are conflicting. A study of 219 clinically diagnosed adults with ADHD, including 37.4% women, found no gender difference in risk of anxiety, bipolar disorder, depression, SUD and antisocial personality disorder, but that study was in all likelihood underpowered (11). One of the largest population-based studies until now, a twin-study using self-reported symptom scores for both ADHD and other psychiatric disorders, studied anxiety, bipolar disorder, depression and alcohol dependence. Similar relative risk estimates for anxiety and bipolar disorder as in our study were reported, but gender differences were not found (26). In another recent twin-study based on self-reported symptom scores, a high risk of comorbid SUD in adults with ADHD was reported, but this did not report finding any gender differences (24). Among studies showing high risk of comorbid bipolar disorder, one was large and population-based, but involved both children and adults (19); another study was small with low female representation (11). Both studies considered gender differences, but none were found. A large Swedish study analysed risk of comorbid schizophrenia, but did not focus on adults and did not evaluate gender differences (19). A smaller Danish study found the same relative risk of comorbid psychosis as observed here, but in adults diagnosed with ADHD as children. The study only included a small proportion of women, and an evaluation of gender differences was thus not possible (22). A large study from Taiwan with over 70 000 individuals with ADHD diagnosed in childhood reported a five times higher risk of developing some form of psychotic disorder. The male proportion was 80%, and mean age at diagnosed psychosis was only 15 years. An increased risk for psychosis in women with ADHD was, however, found (23). The number of studies on ADHD and different personality disorders is smaller and mostly performed on young adults and adolescents, where ADHD was diagnosed in childhood. Hazard ratios of 5.8 for personality disorders 'not specified' and 3.1 for antisocial personality disorder have been reported without specification of gender (21, 48).

Most previous studies have their limitations: they have either relied on self-reported diagnosis of ADHD diagnosis or screening questionnaires, many studies are small, and most of them have a low proportion of females or include individuals younger than 18 years at the time of comorbid diagnosis. Few studies have been population-based or focused specifically on gender differences in risk of comorbidities in adults.

In a recent narrative meta-analysis of gender differences in adult ADHD, Williamson and Johnston found that only three of 11 studies included appropriate comparison groups (18). However, the most important difference, and novelty of the present study, is that we tested for interaction by gender on an additive scale, thus using the prevalence differences to estimate the prevention potential. We also calculated the proportion of major psychiatric disorders that could be attributed to ADHD in the adult population.

Testing for interaction on the additive scale is informative for clinical and public health questions, because it may indicate which subgroups need to be prioritized such that preventive measures and interventions can be introduced (42). We found that differences in prevalences of anxiety, depression, bipolar and personality disorders between adults with and without ADHD were significantly larger for women than for men, while the opposite was true for SUD and schizophrenia. Previous investigations have failed to show these gender differences in psychiatric comorbidities, and none have evaluated interactions on an additive scale. Women with ADHD have been shown to report more symptoms and impairments resulting from their condition than men, thus possibly predisposing them to a higher level of psychiatric comorbidity (11, 14–16, 49). Our results show that there is a relatively higher increase in prevalence of most psychiatric comorbidities associated with ADHD in women with ADHD fitting this. Detecting and treating ADHD in girls and women may prove to be an important preventive measure in order to reduce the risk of future psychiatric comorbidity. Paying more attention towards girls and women with ADHD, who have less hyperactivity and therefore may go undiagnosed during childhood years, may thus be warranted, both among clinicians and researchers (25). The larger

increase in SUD and schizophrenia associated with ADHD in men is also of importance, and clinicians treating adults with ADHD should be aware of the gender-specific comorbidities described in our study, both with respect to detection and the offer of early treatment following diagnosis.

The larger increase in prevalence of schizophrenia associated with ADHD in men might be related to the larger increase in prevalence of SUD, also found in men. Both having ADHD (10, 24) and being a male (50, 51) increase the risk of SUD, and SUD itself may increase the risk of psychosis (52). To test this hypothesis, we excluded all individuals with SUD in the study population (n = 62 434) and reran the PD analyses for schizophrenia. The PDs of schizophrenia in women with and without ADHD changed from 2.1 (95% CI, 2.1–2.1) to 1.1 (1.0–1.3) and in men from 3.3 (3.0–3.5) to 1.4 (1.2–1.6). The gender difference was still statistically significant (RERI −0.66, 95% CI, −1.3 – −0.07). We therefore believe that the increased risk of schizophrenia in men with ADHD may be partly, although not fully explained, by a comorbid SUD. The apparent increased vulnerability to schizophrenia in men with ADHD could be of clinical importance. In contrast, when excluding all cases with SUD, the PD for women was no longer significant when compared to women without ADHD.

The relatively increased risk of anxiety and depression in men with ADHD on the multiplicative scale may partly be explained by the low prevalence of these disorders in men without ADHD, who generally have lower health-seeking behaviour (53). Men with ADHD are already in contact with the health services and may therefore get these comorbid disorders diagnosed more easily than their non-ADHD counterparts. Although both men and women with ADHD are in contact with the health services, women, independently of ADHD, are generally in closer contact with the health services than men, due to, for example, maternal health issues (fertility regulation, pregnancy and childbirth) (54). This may partly explain why disorders such as depression and anxiety are more easily detected in women than in men in the general population (50, 55).

The gender-specific pattern of psychiatric disorders that we find among adults with ADHD in our study is similar to the pattern found in the general population (50, 51, 56). The absolute prevalence rates are, however, much higher for both men and women with ADHD, as shown in Fig. 1. Although the presence of ADHD enhances the trend among men and women in the general population, it is evident that the magnitude of this enhancement differs between men and women and is also dependent on the specific disorder.

To evaluate how associations between ADHD and psychiatric comorbidities were influenced by common risk factors for both ADHD and other psychiatric disorders, we adjusted for socioeconomic and perinatal risk factors (Model 1). This hardly changed the PR estimates. When also including psychiatric disorders of the parents in the model (Model 2), the estimates were slightly attenuated, suggesting that genetic predisposition or problems linked to having parents suffering from psychiatric diseases are important, see Table 3. This calls for increased attention regarding children of parents being treated for psychiatric disorders.

Strengths and limitations

Our study has several strengths. We used data from nationwide health registries of good quality and with mandatory, prospective reporting, minimizing selection bias and loss to follow-up and eliminating recall bias. Bipolar disorder and schizophrenia registration in the NPR have been validated with good results (31). Due to the large study population with almost 45% women with ADHD, we could evaluate less prevalent disorders, such as schizophrenia, and compare psychiatric comorbidity in men and women with representative numbers in both groups. We had prospectively registered data on perinatal factors (birthweight and gestational age) for the whole study population, and we had information on psychiatric diagnoses, including ADHD, for the parents. Therefore, we could adjust for these covariates to evaluate whether these risk factors explained the increased prevalence of psychiatric comorbidities in adults with ADHD.

Unlike some other large Scandinavian population-based studies, we did not use ADHD symptom ratings or self-reports to define ADHD. ADHD medication is restricted in Norway, and medical treatment in adults is initiated only after thorough assessment by a specialist in psychology or psychiatry. Therefore, we believe that a prescribed and dispensed prescription of ADHD medication is a good proxy for a clinical ADHD diagnosis. Calculating PDs and testing for interaction by gender on the additive scale give relevant information concerning which comorbid diagnoses clinicians should be especially aware of when following men and women with ADHD. Our estimates of attributable risk of comorbid disorders in men and women with ADHD underscore the gender-specific prevention potential.

We are aware that our study also has some limitations: analyses were cross-sectional and based on data registered in the NorPD from 2004–15 and in the NPR from 2008–15, limiting the study of temporal relations. However, as ADHD is defined as a neuropsychiatric disorder with onset in childhood, we may assume that ADHD was present before the comorbid psychiatric disorders, which all are typically diagnosed in late adolescence and adulthood. Since the NorPD was established in 2004, adults diagnosed and treated for ADHD only before 2004 and not after will be undetected. However, ADHD was not understood as a disorder of adulthood before the late 1990s, and during 1997–2005, adults in Norway were only allowed to receive medical treatment with central stimulants after a thorough evaluation by one of three regional diagnostic committees (8). Further, some ADHD patients will not receive medication because of contraindications or other causes; these patients are identified in the NPR, but only from 2008 and onwards. During 2008–2015, a total of 9346 (23.3%) adults with ADHD were registered with ADHD in the NPR without receiving medication.

The NPR was the data source for defining psychiatric comorbidities. In Norway, many psychiatric patients are followed in primary health care after diagnosis, and treatment is established in secondary care, for example patients with bipolar disorder who are stable on medication. A recent study from Sweden reported that almost 80% of the most common mental disorders were treated in primary care (57). For bipolar disorder, we therefore used the NorPD as an additional data source. It is likely that patients with the more severe disorders such as schizophrenia (31) and severe personality disorders will likely have some contact with specialist health care throughout life and should therefore be captured by the NPR.

As discussed above, it may be argued that adults with ADHD could more easily be diagnosed with other psychiatric disorders because they are already in contact with the health services (55). This may be true, especially for depression and anxiety in men, who in general have little contact with the health service before old-age (54). However, adults with bipolar disorder, schizophrenia, personality disorders and SUD are likely to be referred to secondary health care also in the non-ADHD population.

To conclude, a large proportion of both men and women with ADHD have comorbid psychiatric disorders, and a considerable proportion of anxiety, bipolar disorder, depression, schizophrenia, SUD and personality disorders in the population can be attributed to an underlying comorbid ADHD. The differences in prevalence of anxiety, depression, bipolar and personality disorders in adults with and without ADHD are larger for women than for men. Clinicians treating women with ADHD should be aware of these comorbidities, to both detect the conditions and offer early treatment if diagnosed. Similarly, the possibility of a comorbid SUD or schizophrenia spectrum disorder is particularly relevant when treating men with ADHD. Importantly, clinicians should also be aware of a possible underlying ADHD when adults present with symptoms of other psychiatric disorders. Identifying children and adolescents with ADHD at earlier stages may be an important preventive measure to reduce the risk of future psychiatric comorbidity. This may be particularly important in girls and women with ADHD, who often have a lower degree of hyperactivity and are therefore at an increased risk of being undiagnosed in childhood, with a higher risk of developing other psychiatric disorders as a possible consequence.

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Declaration of interests

J.H. has served as a speaker for Eli-Lilly, HB Pharma and Shire. The other authors declare no conflict of interests.

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Supporting Information

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

Table S1. Prevalence ratio of psychiatric disorders comparing adults with and without ADHD when (a) mental retardation is excluded and (b) schizophrenia is excluded from bipolar.

Table S2. Prevalence ratio of psychiatric disorders comparing adults with and without ADHD when (a) all individuals have only one (additional) psychiatric disorder or (b) psychiatric disorders registered at least twice in the Norwegian Patient Registry (NPR).

Table S3. Prevalence ratio of psychiatric disorders comparing adults with and without ADHD, using missing imputation for gestational age and sex-specific birthweight by gestational age z-scores.

Appendix S1. Registries.

Appendix S2. Narcolepsy.

Appendix S3. Sensitivity Analysis.

II

Archival Report

Biological Psychiatry: Celebrating 50 Years

Patterns of Psychiatric Comorbidity and Genetic Correlations Provide New Insights Into Differences Between Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder

Berit S. Solberg, Tetyana Zayats, Maj-Britt Posserud, Anne Halmøy, Anders Engeland, Jan Haavik, and Kari Klungsøyr

ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) share common genetic factors but seem to have specific patterns of psychiatric comorbidities. There are few systematic studies on adults; therefore, we compared psychiatric comorbidities in adults with these two neurodevelopmental disorders using population-based data and analyzed their genetic correlations to evaluate underlying factors.

METHODS: Using data from Norwegian registries, we assessed patterns of psychiatric disorders in adults with ADHD (n = 38,636; 2.3%), ASD (n = 7528; 0.4%), and both diagnoses (n = 1467; 0.1%) compared with the remaining adult population (n = 1,653,575). We calculated their prevalence ratios (PRs) and differences using Poisson regression, also examining sex-specific relations. Genetic correlations (r_g) among ADHD, ASD, and the examined psychiatric disorders were calculated by linkage disequilibrium score regression, exploiting summary statistics from relevant genome-wide association studies.

RESULTS: For all psychiatric comorbidities, PRs differed between ADHD and ASD. Associations were strongest in individuals with ADHD and ADHD+ASD for most comorbidities, in both men and women. The relative prevalence increase of substance use disorder was three times larger in ADHD than in ASD (PR_{ADHD}, 6.2; 95% confidence interval [CI], 6.1–6.4; PR_{ASD}, 1.9; 95% CI, 1.7–2.2; $p < .001$); however, the opposite was true for schizophrenia (PR_{ASD}, 13.9; 95% CI, 12.7–15.2; PR_{ADHD}, 4.4; 95% CI, 4.1–4.7; $p < .001$). Genetic correlations supported these patterns but were significantly different between ADHD and ASD only for the substance use disorder proxies and personality traits ($p < .006$ for all).

CONCLUSIONS: Adults with ADHD, ASD, or both ADHD and ASD have specific patterns of psychiatric comorbidities. This may partly be explained by differences in underlying genetic factors.

Keywords: ADHD, ASD, Genetics, Psychiatric comorbidity, Schizophrenia, SUD

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Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are highly heritable neurodevelopmental conditions and major contributors to human suffering worldwide (1,2). There is emerging evidence of polygenicity and environmental factors contributing to both disorders (3,4). Genetic, epidemiological, and twin studies show that ADHD and ASD often co-occur and share common underlying genetic factors (5–8), but with different phenotypic characteristics. The shared genetic factors are believed to affect the structure and function of molecular networks in the brain, possibly involved in the etiology of ADHD (9) and ASD (10).

Individuals with either ADHD or ASD have a 65% to 90% risk of developing concomitant psychiatric disorders (11–13), but with seemingly different patterns of comorbidity. Adults with ASD present high rates of co-occurring anxiety, depression (13), bipolar disorder (BD), and schizophrenia spectrum disorder (SCZ) (14–16), while adult ADHD is reported to co-occur with anxiety disorder and major depressive disorder (MDD) (17–19), BD (11,19–22), personality disorders (PDs) (18,19,23), SCZ, (19,22,24,25), and substance use disorder (SUD) (19,20,26).

ADHD and ASD share genetic factors with the above-mentioned psychiatric disorders (27), and significant genetic

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correlations between different phenotype-specific traits for ADHD and ASD have been demonstrated (28).

Nonetheless, except for a couple of small clinical studies, patterns of psychiatric comorbidities have not been systematically compared between adults with ASD or ADHD (29,30). Further, previous studies have reported that children with both ADHD and ASD may have more severe impairments than those with ASD alone; however, comparable studies in adults are lacking (31,32). Only one single population-based study has directly compared individuals with ADHD alone, ASD alone, or both ADHD and ASD with unaffected individuals, but this was in a population too young to be diagnosed with adult-onset psychiatric disorders (33).

We aimed at evaluating similarities and differences in psychiatric comorbidity between ADHD and ASD in adulthood, both clinically and genetically. Therefore, we compared the prevalence of psychiatric disorders in adults with ADHD alone, ASD alone, and both ADHD and ASD with adults without ADHD or ASD and supplemented these analyses with the estimation of genetic correlations between the studied disorders.

METHODS AND MATERIALS

Registries

We conducted cross-sectional analyses in a cohort of adults by linking information from four nationwide, population-based registries, all with compulsory notification: the Medical Birth Registry of Norway, established in 1967 (34); the Norwegian Prescription Database (NorPD) (35), established in 2004; the Norwegian Patient Registry (NPR) (36), with data since 2008; and the National Educational Database from Statistics Norway (37,38) (see Supplement for more details).

Individual records from the registries were linked by means of the unique national identification numbers, given to all individuals residing in the country. The Regional Ethics Committee in Norway approved the study (2011/2272). No informed consent was required for the analyses, as the records were anonymized. To guide the reporting of this study, we used the Strengthening the Reporting of Observational Studies in Epidemiology statement (39).

Study Population and Exposure Groups

The study included 1,701,206 individuals born in Norway between 1967 and 1997 who were alive and living in Norway in 2015, the year of data linkage. This population consists of individuals mainly of European descent, with 8.2% of births registered to mothers from non-European countries by 2015. We defined adults with ADHD only (ADHD) as those who were dispensed ADHD medication at any time between 2004 and 2015 (NorPD) or had an ADHD diagnosis (ICD-10 code F90), but no ASD diagnosis, registered in the NPR during 2008 to 2015, and who were 18 years of age or older. The ADHD medications were methylphenidate, racemic amphetamine, dexamphetamine, and atomoxetine. Individuals prescribed central stimulants for narcolepsy were excluded (see Supplement for details).

Adults with ASD only (ASD) were defined as individuals with an ASD diagnosis (ICD-10 codes F84.0–1+F84.5+F84.8–9) (40,41) who were 18 years of age or older, were registered in the NPR during 2008 to 2015, and had no ADHD diagnosis. Adults (18 years of age or older) with both ADHD and ASD as defined above comprised the combined group (ADHD+ASD).

The remaining population included all adults who were neither dispensed ADHD medication registered in the NorPD nor had an ADHD or ASD diagnosis registered in the NPR. Parents of adults with and without ADHD/ASD were also identified through the Medical Birth Registry of Norway and included in the analyses to account for parental factors associated with ADHD, ASD, and other psychiatric disorders (e.g., sociodemographic factors, pregnancy-related factors, parental psychiatric disorders) and relatedness.

Outcome Diagnoses

We studied the following major comorbid psychiatric disorders typically diagnosed in late adolescence and adulthood (42), all registered in the NPR, at 18 years of age or older: anxiety disorders (ICD-10 codes F40–F42); MDD (F32–F33); BD (F30–F31); PDs (F60–F61), with a separate analysis on antisocial personality disorder (F60.2) (only included in the main analyses because of a small number of cases); SCZ (F20–F29); and SUD (F10–F19). For BD, we also included those individuals who were dispensed lithium during 2004 to 2015, according to NorPD.

Summary Statistics From Large-Scale Genome-wide Association Studies

Summary statistics from the large-scale genome-wide association studies (GWASs) for the psychiatric disorders examined (10,43–51) were downloaded from the LD Hub GWAS share center (http://ldsc.broadinstitute.org/gwashare/) (52). To date, no GWAS has examined the genetics of individuals diagnosed with both ADHD and ASD. Combining the existing data from individual GWASs on ADHD and ASD, respectively, would result in associations heavily biased toward the larger study. Thus, we analyzed ADHD and ASD separately.

As not all data are publicly available, and no large-scale, well-powered GWASs were performed on all disorders examined, we used some proxy traits. Owing to the lack of adequate genetic data on PDs, we combined the data from the five GWASs on the five traits in the NEO Personality Inventory (NEO) (neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness) (48,53) using the inverse variance method in METAL software (54). As all five NEO personality traits were analyzed in same-sized samples, there was no bias toward any of the traits. We also used the trait "antisocial behavior" as a proxy for antisocial personality disorder (49). As proxies for SUD, we used smoking behavior (ever smoked vs. never smoked) (51) and alcohol dependence (50).

In all analyses, we restricted the examined data to single nucleotide polymorphisms of good imputation quality (INFO $\geq$0.8), minor allele frequency $\geq$1% (common variation), and the data were derived from individuals of European descent only.

Statistical Analyses

We estimated prevalence ratios (PRs) using Poisson regression with robust standard errors (55) to examine the

associations of ADHD, ASD, and ADHD+ASD with other psychiatric disorders, using the remaining adult population as reference. To adjust for potential confounders, we performed two regression models, which included the following covariates: 1) model I, which included birth year, maternal marital status, maternal age and paternal age in years at delivery, parents' highest attained level of education at record linkage, the individual's gestational age in weeks, and the individual's gestational age- and sex-specific birth weight *Z* scores (56); and 2) model II, which included covariates of model I and mothers' and fathers' psychiatric diagnoses, including ADHD or any other psychiatric diagnosis from the NPR from 2008 to 2015 (for details about the covariates, see footnotes beneath the tables and figures and in the Supplement). To account for correlations between siblings, we used mother's identification number as a cluster variable in the analyses.

Analyses were performed on the total sample and stratified by sex. Our main analyses were based on the multiplicative scale using relative effect measures; however, when assessing sex differences, we supplemented the analyses with absolute effect measures. For this, we estimated prevalence differences of psychiatric disorders between men and women with and without ADHD, ASD, or ADHD+ASD using predicted prevalence from a Poisson regression model with adjustment for birth year (5-year periods). Significance of interaction by sex on the multiplicative scale was evaluated by comparing the Poisson regression models with and without the interaction term (sex × ADHD) included, tested by likelihood ratio tests, and significance of interaction by sex on the additive scale was evaluated using relative excess risk due to interaction (57).

Two-sided tests with a significance threshold of $p < .05$ were employed in all analyses.

Analyses were carried out with SPSS version 22.0 (IBM Corp., Armonk, NY) and STATA intercooled version 14 (StataCorp, College Station, TX) from November 3, 2017, to March 13, 2019.

Genetic correlations (r_g) were calculated using linkage disequilibrium score regression, which quantifies the similarities in genetic architecture between two traits by evaluating the relationship between single nucleotide polymorphism association strengths and genetic linkage disequilibrium (8). Owing to sample overlap between the examined datasets, the correlations were calculated without constraining the intercept. To calculate if the genetic correlations in the ADHD group were significantly different from those in the ASD group, we applied the following formula: $\frac{rg1 - rg2}{\sqrt{a^2 + b^2}}$, where rg1 refers to the genetic correlation between a comorbidity and ADHD, rg2 refers to the genetic correlation between the same comorbid disorder and ASD, *a* refers to SE of the rg1 estimate, and *b* refers to the standard error of the rg2 estimate. The significance was calculated using a two-tailed *Z* test. To account for multiple testing, Bonferroni correction was applied to the significant threshold of .05, bringing the adjusted significance threshold to .00625.

Sensitivity Analyses

We conducted several sensitivity analyses to evaluate the robustness of our results. We reran all the analyses 1) excluding individuals with a diagnosis of intellectual disability, 2) excluding all with comorbid diagnoses of SCZ when analyzing BD and SUD, 3) excluding all individuals with SUD when analyzing SCZ, and 4) including only individuals who had their psychiatric diagnosis registered at least twice in the NPR. Missing values in covariates (6% for gestational age and birth weight *Z* scores, <1% for other variables) were handled by listwise deletion in the main analyses. In the sensitivity analyses, we also used multiple imputation with chained equations (58) to evaluate possible bias due to missing information in gestational age when adjusting for covariates. The outcome variables, all specified covariates, and also birth weight, maternal pre-eclampsia, and mother's chronic diseases (yes/no) were used for this information.

RESULTS

Study Population

Among the 1,701,206 individuals included in the study, we identified 38,636 adults (2.3% of the population; 45% women) with ADHD, 7528 adults (0.4%; 27.9% women) with ASD, 1467 adults (0.1%; 28.8% women) with ADHD+ASD, and 1,653,575 adults (97.2%; 49% women) in the remaining population. In 2015, the mean ages of individuals in the ADHD, ASD, and ADHD+ASD groups were 31, 26, and 27 years of age, respectively, compared with 33 years of age in the remaining population (Table 1). Among parents, significantly more mothers of individuals with ASD and ADHD+ASD had the highest level of education compared with the ADHD group and the remaining population, likely explained by the mothers of individuals with ASD/ADHD+ASD having been born later in our study period, in a time during which higher education was more common. In addition, being diagnosed with at least one psychiatric disorder was more prevalent among parents of individuals in all exposure groups, compared with the remaining population (Table 1).

Psychiatric Comorbidity in Adults With ADHD, ASD, or ADHD+ASD

Comorbid psychiatric disorders were 2 to 14 times more common in adults with ADHD, ASD, or ADHD+ASD than in the remaining population (Table 2). Overall, the PRs differed significantly between adults with ADHD and ASD for all psychiatric disorders studied. Relative to the remaining population, the association with BD was the strongest and the association with MDD was the weakest in adults with ADHD (PR_{BD}, 7.1; 95% confidence interval [CI], 6.8–7.4; PR_{MDD}, 3.7; 95% CI, 3.6–3.8), while the association with SCZ was the strongest and the association with SUD was the weakest in adults with ASD (PR_{SCZ}, 13.9; 95% CI, 12.7–15.2; PR_{SUD}, 1.9; 95% CI, 1.7–2.2) (Table 2, model II). The associations with anxiety disorders, BD, MDD, PDs, and SUD were significantly stronger in adults with ADHD than in adults with ASD ($p < .001$ for all), with SUD revealing a particularly pronounced difference (PR_{ADHD}, 6.2 vs. PR_{ASD}, 1.9). The association with SCZ, however, was stronger in adults with ASD than in adults with ADHD (PR_{ASD}, 13.9 vs. PR_{ADHD}, 4.4; $p < .001$).

In the ADHD+ASD group, the PRs ranged from 3.6 for MDD (95% CI, 3.2–4.0) to 12.5 for SCZ (95% CI, 10.3–15.1) (Table 2, model II). For all disorders, except MDD and SUD, associations with ADHD+ASD were significantly stronger than for those

Table 1. Sample Characteristics of the 1,701,206 Adults in the Study Population, All Born From 1967 to 1997 and Followed Until 2015

Variable	ADHD	ASD	ADHD+ASD	Remaining Population
Population	38,636 (2.3)	7528 (0.4)	1467 (0.1)	1,653,575 (97.2)
Women	17,393 (45.0), $p < .001$[a]	2099 (27.9), $p = .491$[b]	422 (28.8), $p < .001$[c]	809,962 (49.0), $p < .001$[d]
Male/Female Ratio	1.22	2.58	2.48	1.04
Age in 2015, Years	31.3 ± 8.3, $p < .001$[a]	26.2 ± 7.9, $p = .99$[b]	26.8 ± 7.1, $p < .001$[c]	33.2 ± 9.3, $p < .001$[d]
Maternal Age at Birth	$p < .001$[a]	$p < .001$[b]	$p < .001$[c]	$p < .001$[d]
<20 years	4417 (11.4)	372 (4.9)	107 (7.3)	112,674 (6.8)
20–24 years	13,587 (35.2)	1936 (25.7)	435 (29.7)	498,264 (30.1)
25–29 years	11,865 (30.7)	2539 (33.7)	525 (35.8)	575,743 (34.8)
30–34 years	6144 (15.9)	1747 (23.2)	279 (19.0)	327,637 (19.8)
35–39 years	2215 (5.7)	774 (10.3)	102 (7.0)	116,139 (7.0)
40+ years	408 (1.1)	160 (2.1)	19 (1.3)	23,118 (1.4)
Paternal Age at Birth	$p < .001$[a]	$p < .001$[b]	$p < .001$[c]	$p < .001$[d]
<20 years	1054 (2.7)	75 (1.0)	21 (1.4)	24,546 (1.5)
20–24 years	9013 (23.3)	1093 (14.5)	267 (18.2)	302,939 (18.3)
25–29 years	12,941 (33.5)	2242 (29.8)	484 (33.0)	563,896 (34.1)
30–34 years	8728 (22.6)	2120 (28.2)	392 (26.7)	432,678 (26.2)
35–39 years	4086 (10.6)	1154 (15.3)	182 (12.4)	207,833 (12.6)
40–44 years	1621 (4.2)	519 (6.9)	78 (5.3)	76,947 (4.7)
45–49 years	489 (1.3)	171 (2.3)	25 (1.7)	24,796 (1.5)
50+ years	183 (0.5)	70 (0.9)	3 (0.2)	8741 (0.5)
Missing	521 (1.4)	84 (1.1)	15 (1.0)	11,199 (0.7)
Maternal Marital Status[d]	$p < .001$[a]	$p < .007$[b]	$p = .016$[c]	$p < .001$[d]
Single	6483 (16.8)	909 (12.1)	225 (15.3)	151,975 (9.2)
Married/cohabiting	31,122 (80.6)	6508 (86.5)	1220 (83.2)	1,482,685 (89.7)
Other	924 (2.4)	96 (1.3)	20 (1.4)	16,154 (1.0)
Missing	107 (0.3)	15 (0.2)	2 (0.1)	2761 (0.2)
Maternal Education Status	$p < .001$[a]	$p = .169$[b]	$p < .001$[c]	$p < .001$[d]
Low	13,498 (34.9)	1904 (25.3)	394 (26.9)	430,874 (26.1)
Middle	16,478 (42.7)	3022 (40.1)	583 (39.7)	768,773 (46.5)
High	8415 (21.8)	2565 (34.1)	488 (33.3)	447,380 (27.1)
Missing	245 (0.6)	37 (0.5)	2 (0.1)	6548 (0.4)
Paternal Education Status	$p < .001$[a]	$p < .001$[b]	$p < .001$[c]	$p < .001$[d]
Low	12,501 (32.4)	1639 (21.8)	388 (26.5)	381,154 (23.1)
Middle	18,626 (48.2)	3486 (46.3)	694 (47.3)	834,541 (50.5)
High	6475 (16.8)	2237 (29.7)	352 (24.0)	414,399 (25.1)
Missing	1034 (2.7)	166 (2.2)	33 (2.3)	23,481 (1.4)
Maternal Psychiatric Disorder	$p = .073$[a]	$p < .001$[b]	$p = .001$[c]	$p < .001$[d]
None	28,140 (72.8)	5557 (73.8)	1009 (68.8)	1,432,294 (86.6)
Paternal Psychiatric Disorder	$p < .001$[a]	$p = .010$[b]	$p = .492$[c]	$p < .001$[d]
None	31,478 (82.7)	6289 (84.7)	1189 (82.0)	1,479,367 (90.2)

Values are *n* (%) or mean ± SD.
ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder.
[a]Difference between the ADHD and ASD cases (Pearson chi-square test and *t* test for equality of means).
[b]Difference between the ASD and ADHD+ASD cases (Pearson chi-square test and *t* test for equality of means).
[c]Difference between the ADHD and ADHD+ASD cases (Pearson chi-square test and *t* test for equality of means).
[d]Difference between cases relative to the comparison population (Pearson chi-square test and *t* test for equality of means).

with ADHD. For SCZ, associations with ADHD+ASD and ASD were similar, and both were significantly stronger than associations with ADHD ($PR_{ADHD+ASD}$, 12.5; 95% CI, 10.3–15.1; PR_{ASD}, 13.9; 95% CI, 12.7–15.2; PR_{ADHD}, 4.4; 95% CI, 4.1–4.7; $p < .001$).

Sex-Specific Results

When stratifying on sex, patterns of psychiatric comorbidity corresponded with those in the total sample (Figure 1; Supplemental Tables S2, S3). In both men and women, PR estimates for SCZ were significantly larger in ASD or

Table 2. Prevalence Ratios of Psychiatric Disorders Comparing Adults With and Without ADHD, ASD or ADHD+ASD, Based on 1.7 Million Individuals Born in Norway (1967–1997) and Followed Until 2015

Psychiatric Disorders (ICD-10 Codes)	Remaining Population	Crude PR (95% CI)[a]			PR Model I (95% CI)[b]			PR Model II (95% CI)[c]		
		ADHD	ASD	ADHD+ASD	ADHD	ASD	ADHD+ASD	ADHD	ASD	ADHD+ASD
Anxiety Disorders (F40–F42)	1 (ref)	4.2 (4.2–4.3), $p < .001$[d]	3.5 (3.3–3.7), $p < .001$[e]	4.7 (4.3–5.2), $p = .001$[f]	4.1 (4.0–4.2), $p = .020$[d]	3.6 (3.4–3.8), $p < .001$[e]	4.7 (4.2–5.2), $p < .001$[f]	3.8 (3.7–3.9), $p = .023$[d]	3.4 (3.2–3.6), $p < .001$[e]	4.3 (3.9–4.7), $p < .001$[f]
Bipolar Disorder (F30–F31 or Medication[g])	1 (ref)	7.8 (7.5–8.1), $p < .001$	5.3 (4.7–6.0), $p < .001$	9.4 (7.7–11.4), $p = .006$	7.8 (7.4–8.1), $p < .001$	5.4 (4.7–6.2), $p < .001$	9.3 (7.6–11.5), $p = .020$	7.1 (6.8–7.4), $p < .001$	5.0 (4.4–5.7), $p < .001$	8.4 (6.8–10.3), $p = .021$
Major Depressive Disorder (F32–F33)	1 (ref)	4.2 (4.1–4.2), $p < .001$	3.1 (2.9–3.3), $p < .001$	4.0 (3.6–4.4), $p = .801$	4.0 (3.9–4.1), $p < .001$	3.2 (3.0–3.3), $p = .001$	3.9 (3.5–4.3), $p = .886$	3.7 (3.6–3.8), $p < .001$	3.0 (2.8–3.1), $p = .001$	3.6 (3.2–4.0), $p = .898$
Personality Disorders (F60–F61)	1 (ref)	8.1 (7.9–8.4), $p < .001$	5.9 (5.4–6.5), $p < .001$	8.1 (7.9–10.6), $p = .009$	7.4 (7.2–7.7), $p < .001$	6.0 (5.5–6.6), $p < .001$	8.6 (7.3–10.1), $p = .014$	6.8 (6.5–7.0), $p = .001$	5.6 (5.1–6.2), $p < .001$	7.7 (6.5–9.1), $p = .015$
Antisocial Personality Disorder (F60.2)	1 (ref)	20.7 (18.4–23.2), $p < .001$	4.1 (2.4–7.2), $p < .001$	24.8 (15.4–40.0), $p = .215$	17.2 (15.1–19.7), $p < .001$	4.1 (2.3–7.5), $p < .001$	24.0 (14.4–40.1), $p = .070$	15.4 (13.5–17.7), $p < .001$	3.8 (2.1–6.9), $p < .001$	21.1 (12.6–35.2), $p = .070$
Schizophrenia Spectrum Disorder (F20–F29)	1 (ref)	4.8 (4.6–5.1), $p < .001$	15.1 (13.9–16.4), $p = .194$	13.3 (11.1–16.0), $p < .001$	4.8 (4.5–5.1), $p < .001$	14.9 (13.6–16.2), $p = .470$	13.8 (11.4–16.8), $p < .001$	4.4 (4.1–4.7), $p < .001$	13.9 (12.7–15.2), $p = .424$	12.5 (10.3–15.1), $p < .001$
Substance Use Disorder (F10–F19)	1 (ref)	7.8 (7.6–7.9), $p < .001$	2.1 (1.9–2.3), $p < .001$	4.2 (3.7–4.9), $p < .001$	6.8 (6.6–7.0), $p < .001$	2.1 (1.9–2.3), $p < .001$	4.1 (3.5–4.8), $p < .001$	6.2 (6.1–6.4), $p < .001$	1.9 (1.7–2.2), $p < .001$	3.7 (3.2–4.3), $p < .001$

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval; ICD-10, International Classification of Diseases of the World Health Organization, 10th ed.; PR, prevalence ratio; ref, reference population.

[a]Adjusted for birth year (5-year groups, from 1967 to 1997, with 1967–1973 as the reference period).

[b]Adjusted for birth year, maternal marital status (single, married/cohabiting [reference], other), maternal and paternal education (low [<10 years], middle [10–12 years], and high [>12 years] [reference]), maternal age (<20, 20–24, 25–29 [reference], 30–34, 35–39, 40+ years of age) and paternal age (<20, 20–24, 25–29, 30–34 [reference], 35–39, 40–44, 45–49, 50+ years of age) at delivery, gestational age (<28, 28–31, 32–34, 35–36, 37–41 [reference], 42+ weeks of age), and gestational age- and sex-specific birth weight *Z* scores (<−2.0; −2.0 to −0.51; −0.5 to 0.5 [reference]; 0.51 to 2.0; 2.01+).

[c]Adjusted for covariates as in model I and additionally adjusted for maternal and paternal psychiatric disorders (yes/no).

[d]Difference between the ADHD and the ASD cases (likelihood ratio test).

[e]Difference between the ASD and the ADHD+ASD cases (likelihood ratio test).

[f]Difference between the ADHD and the ADHD+ASD cases (likelihood ratio test).

[g]Lithium, from the Norwegian Prescription Database (2004–2015).

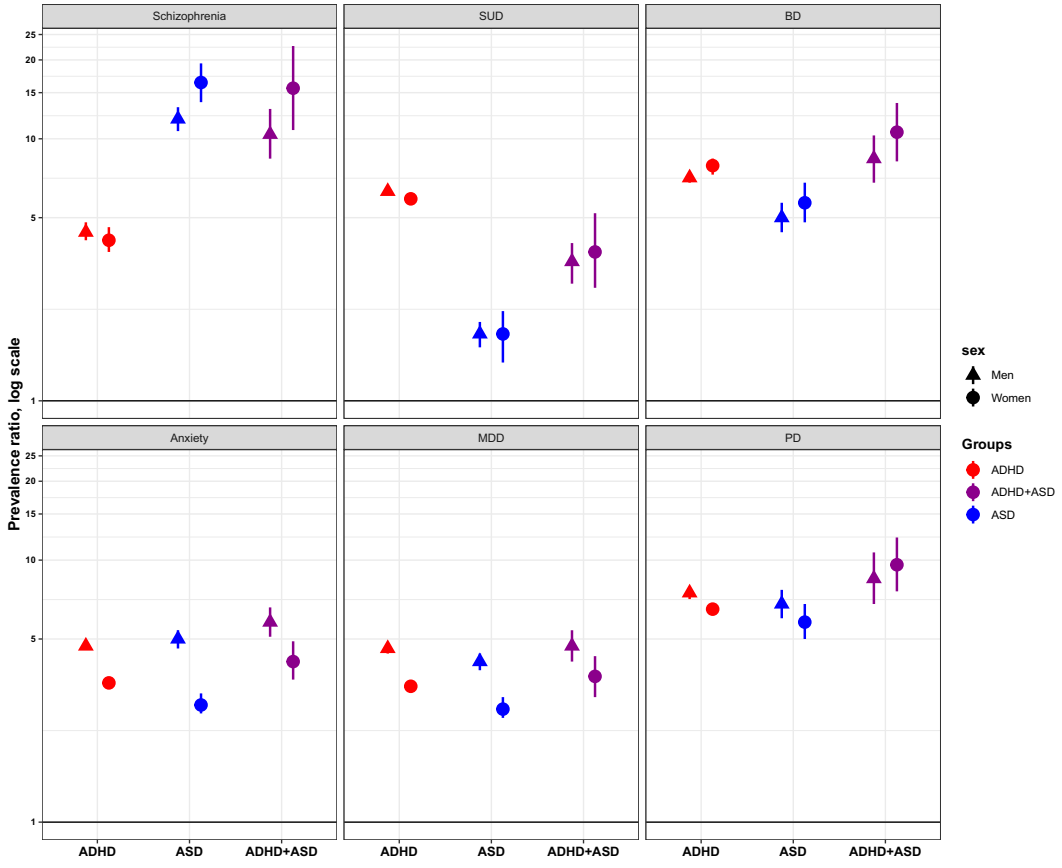

Figure 1. Prevalence ratios of psychiatric disorders in adults with attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), or ADHD+ASD relative to the remaining population, by sex. Log scale, 95% confidence interval, error bars. Adjusted for birth year (5-year groups, from 1967 to 1997, with 1967–1973 as the reference), maternal marital status (single, married/cohabiting [reference], other), maternal and paternal education (low [<10 years], middle [10–12 years] and high [>12 years] [reference]), maternal age (<20, 20–24, 25–29 [reference], 30–34, 35–39, 40+ years of age) and paternal age (<20, 20–24, 25–29, 30–34 [reference], 35–39, 40–44, 45–49, 50+ years of age) at delivery, gestational age (<28, 28–31, 32–34, 35–36, 37–41 [reference], 42+ weeks of age), gestational age- and sex-specific birth weight *Z* scores (<−2.0; −2.0 to −0.51; −0.5 to 0.5 [reference]; 0.51 to 2.0; 2.01+), and maternal and paternal psychiatric disorders (yes/no). BD, bipolar disorder; MDD, major depressive disorder; PD, personality disorders; schizophrenia, schizophrenia spectrum disorder; SUD, substance use disorder.

ADHD+ASD than in ADHD, while for SUD, estimates were significantly larger for ADHD or ADHD+ASD than for ASD. For anxiety disorders, the PR estimates were significantly larger in men than in women for all exposure groups, and for SCZ, the PR was significantly larger in women with ASD than in men with ASD.

When evaluating associations and interactions on the additive scale, sex differences were more pronounced, and the prevalence difference estimates were significantly different for all the disorders in women and men with ADHD but for only three disorders in men and women with ASD (Figure 2; Supplemental Table S4). Further, the associations were reversed, and prevalence of most psychiatric disorders increased more in women than in men in all exposure groups except SUD and SCZ, in which men in all exposure groups showed the highest prevalence increase.

Genetic Correlations

As shown in Figure 3, the patterns of genetic correlations (r_g) were similar to those of the PRs for psychiatric comorbidities based on the epidemiological data. The two proxies for SUD revealed significantly stronger correlations with ADHD than with ASD (Figure 3, right panel; Supplemental Table S5). For

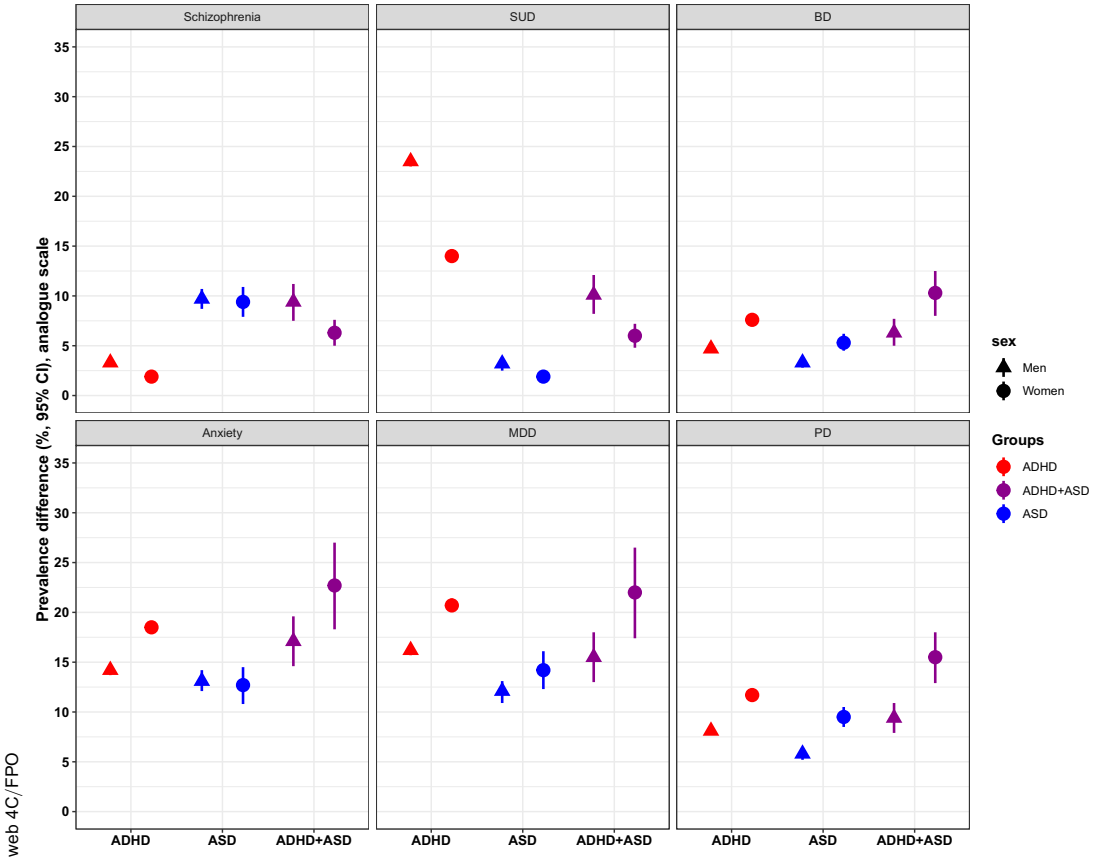

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Figure 2. Prevalence difference of psychiatric disorders in adults with attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), ADHD+ASD relative to the remaining population, by sex. Prevalence difference, 95% confidence interval, error bars, analog scale. Adjusted for birth year (5-year groups, from 1967 to 1997). BD, bipolar disorder; MDD, major depressive disorder; PD, personality disorders; schizophrenia, schizophrenia spectrum disorder; SUD, substance use disorder.

SCZ, the r_g estimate for ASD was almost twice as large as that for ADHD ($r_{g(ASD+SCZ)}$: 0.211 [SE: 0.048, $p < .0001$]; $r_{g(ADHD+SCZ)}$: 0.127 [SE: 0.036, $p = .0004$]), but this difference was not statistically significant ($p = .16$). The differences in genetic correlations between ADHD and ASD with the examined comorbid disorders were statistically significant only for the SUD proxies and for the NEO personality dimensional traits (Supplemental Table S5).

Sensitivity Analyses

When we excluded individuals with intellectual disability, the results changed only for ASD, in which the PR for SCZ increased slightly (PR_{crude}, 15.1; 95% CI, 13.9–16.4; $PR_{sensitivity}$, 16.5; 95% CI, 15.1–18.1). For the ADHD and the ADHD+ASD groups, there were no substantial changes. All the other sensitivity analyses yielded results that were very similar to those of the main analyses (Supplemental Tables S6, S7).

DISCUSSION

In this first nationwide, population-based study combining epidemiological data on adults with ADHD only, ASD only, or both ADHD and ASD, together with corresponding genetic data, we found different patterns of psychiatric comorbidities between the groups, overall and also when stratifying by sex. These patterns were also reflected in the genetic correlations; however, only proxies for two of the six traits showed a significant difference between ADHD and ASD. We also found that adults with both ADHD and ASD have severe additional psychiatric morbidity relative to adults with either ADHD or ASD alone.

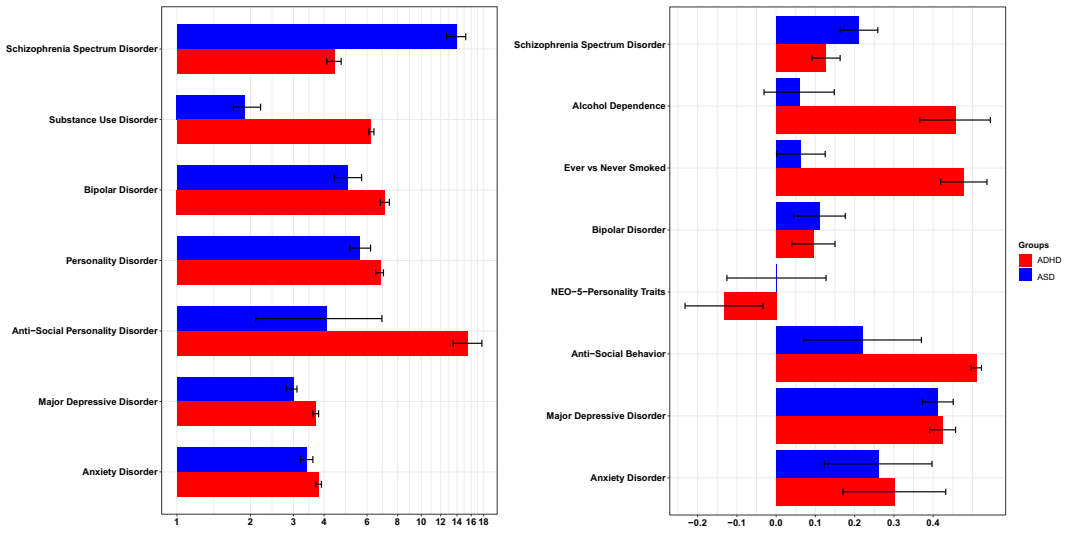

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Figure 3. (Left panel) The pattern of prevalence ratios of psychiatric comorbidity in adults with attention-deficit/hyperactivity disorder (ADHD) (n = 38,636) or autism spectrum disorder (ASD) (n = 7528) observed in this study and (right panel) genetic correlations (r_g) calculated from genome-wide association studies. (Left panel) Prevalence ratio, model II, log-scale, 95% confidence interval, error bars. Adjusted for birth year (5-year groups, from 1967 to 1997, with 1967–1973 as the reference), maternal marital status (single, married/cohabiting [reference], other), maternal and paternal education (low [<10 years], middle [10–12 years] and high [>12 years] [reference]), maternal age (<20, 20–24, 25–29 [reference], 30–34, 35–39, 40+ years of age) and paternal age (<20, 20–24, 25–29, 30–34 [reference], 35–39, 40–44, 45–49, 50+ years of age) at delivery, gestational age (<28, 28–31, 32–34, 35–36, 37–41 [reference], 42+ weeks of age), gestational age- and sex-specific birth weight Z scores (<−2.0; −2.0 to −0.51; −0.5 to 0.5 [reference]; 0.51 to 2.0; 2.01+), and maternal and paternal psychiatric disorders (yes/no). (Right panel) Genetic correlations, r_g, linear scale, SE bars, with "Ever vs Never Smoked" and "Alcohol Dependence" as proxies for substance use disorder, and "NEO–5–Personality Traits" as proxy for personality disorder.

When comparing ADHD and ASD in our epidemiological data, we observed significant differences in the associations with all psychiatric comorbidities examined, with individual estimates being consistent with previous studies (11–13,15,24,30–32). The most marked differences were found for SCZ and SUD, in which SCZ was more common in adults with ASD and SUD was more common in adults with ADHD. Associations with anxiety disorders, BD, and PDs were strongest in adults with both ADHD and ASD, indicating that this group of adults has more severe impairments than those with ADHD or ASD only (59). This is supported by previous studies in children (32,60). Further, we found that adults with both ADHD and ASD had a similar increase in risk for SCZ as that for adults with ASD only, which, as far as we know, has not been shown before. To our knowledge, only one other population-based study reported the prevalence of psychiatric disorders among individuals with ADHD, ASD, or ADHD+ASD compared with unaffected individuals in the same population (33). However, this population was young (mean age ranging from 13.6 to 18.3 years) and had not reached the typical age of onset for most psychiatric disorders (42). The reported estimates were, therefore, likely to be biased.

With regard to the genetic correlations, the patterns were similar to those we observed in the epidemiological data, and two—the SUD proxies and NEO personality traits—revealed significant differences in their correlations with ADHD and ASD. The genetic correlation (r_g) between ADHD and ASD has been estimated to be 0.36 (10), indicating shared genetic etiology between them. Nonetheless, it is conceivable that their polygenic architecture is still different, as supported by our epidemiological observation of significantly different patterns of comorbidities between these two disorders. It has also been shown that individuals with various clinical manifestations of ASD reveal distinct loads of genetic variants associated with this disorder (10,61).

Etiological similarities, as well as differences between ADHD and ASD, can be further and more specifically evaluated by examining their symptom dimensions, each of which may have independent and different explanatory values for the clinical diagnoses of ADHD, ASD, and their comorbidities. Ghirardi *et al.* (28), for example, have reported that the symptoms of hyperactivity/impulsivity (ADHD) show different levels of genetic correlation with symptoms of ASD (e.g., a strong genetic correlation with repetitive and restricted behaviors [ASD] and a weak correlation with social interaction and communication). Our current diagnostic criteria are based on clinically observed aggregates of symptoms but may not relate to distinct underlying biological pathways. Hence, well-powered GWASs on clearly defined specific psychiatric phenotypes and narrower symptom domains are needed to uncover the biological mechanisms underlying the multifaceted etiologies of ADHD and ASD.

Apart from genetics, the observed differences in patterns of comorbidities between ADHD and ASD may also be explained

by diagnostic factors. Diagnosing psychiatric comorbidities in adults with ASD is difficult, as many diagnostic tools are not customized for these individuals (31,62). In addition, clinicians may not look for additional psychiatric disorders in ASD patients and explain their symptoms as part of the underlying ASD (32), i.e., diagnostic overshadowing (63). Further, on a more psychological level, even if individuals with ADHD or ASD often experience peer rejection and relational problems (64,65), individuals with ASD are diagnostically defined by their struggle to communicate and hence are less able to communicate their problems because of their large impairments (66,67). This may contribute to a lower level of diagnosed psychiatric comorbidities in individuals with ASD.

The sex differences in risk of psychiatric comorbidities were different among adults with ADHD and ASD, on both the relative and absolute scales. The present findings for adults with ADHD are also presented in our previous publication (19) and were confirmed by a recent Swedish study (68). Sex differences are strongly dependent on the scale used for analyses, with stronger associations for most psychiatric comorbidities in men than in women on the relative scale and stronger associations in women than in men on the absolute scale. This may be explained by the lower prevalence in psychiatric disorders among men than women in the reference group, which has a profound influence on the relative effect measures but not on the risk differences. We suggest that the smaller sex differences observed in adults with ASD than ADHD may partly be explained by the larger male/female ratio in adults with ASD and partly by women with ASD struggling more to communicate internalizing symptoms than women with ADHD (69,70).

The behavioral patterns in the individuals of the two phenotypically different disorders also lead to different interactions with their environments. The differences in the associations with SUD between ADHD and ASD may partly be due to the ADHD-associated novelty seeking and impulsive behavior, increasing the risk of developing SUD to a larger degree in ADHD than in ASD, in which a rigid and norm-abiding behavior, with limited social contact, may be relatively protective (30,71,72). Thus, both genetic and environmental risk factors, as well as their interactions, may alter the expression of genes and affect the structure and function of molecular networks in the brain, thereby modifying the risk of ADHD and ASD (32).

Strengths and Limitations

To our knowledge, this is the largest population-based study comparing psychiatric comorbidity in adults with ADHD, ASD, or both ADHD and ASD conducted so far. The analyses were also stratified according to sex and included genetic correlations in the interpretation. We used data from nationwide, population-based registries with compulsory notification, thus reducing selection bias to a minimum. As our patient groups were large enough to allow us to study individuals with either ADHD alone or ASD alone, or both ADHD and ASD, we were able to study differences between more homogeneous groups.

We designed our study specifically to examine an adult population, allowing all participants to reach the typical age of diagnosis of the conditions investigated (42). Notably, this study covers the first birth cohort for which ASD became prevalent enough in adulthood to enable such a study to be performed.

In Norway, formal diagnoses of ASD and ADHD, and pharmacological treatment of ADHD, are always based on clinical evaluation by specialists. Thus, identification of ADHD and ASD cases was not based solely on symptom scores or self-reports. We chose to identify the ADHD cases either by a dispensed prescription of ADHD medication from the NorPD or by an ADHD diagnosis from the NPR, similar to other Scandinavian studies (22,73–75). ASD, BD, and SCZ diagnoses in the NPR have been validated with good results (36,76), suggesting acceptable validity for other NPR-registered psychiatric diagnoses as well. However, we cannot exclude a possible misdiagnosis of SCZ and ASD. Our definition of BD was also based on dispensed lithium, a medication mainly used for treating BD.

Limitations include the fact that our analyses were cross-sectional and based on data registered from 2004 to 2015 (NorPD) and from 2008 to 2015 (NPR), preventing the examination of temporal relations. However, as ADHD and ASD are defined as neurodevelopmental disorders with an onset in childhood, we assume that they were present before the comorbid psychiatric disorders, all typically diagnosed in late adolescence and adulthood (42).

Up to 2013, an ASD diagnosis would preclude a diagnosis ADHD according to the DSM-IV and ICD-10 (77,78). This may have affected the diagnostic procedures and hindered clinicians from diagnosing both disorders if the criteria for ASD were fulfilled. However, clinical practice has not adhered strictly to these criteria, as growing evidence supported the importance of diagnosing both conditions when present to provide the best treatment (31).

Further, it may be argued that adults with ADHD or ASD could more easily get other psychiatric diagnoses because they are already in touch with the health care system (79). However, all adults with severe psychiatric disorders are likely to be in touch with secondary health care throughout life, independent of underlying neurodevelopmental disorders (80).

With regard to the genetic correlations, it is important to note that their estimations are highly dependent on the sample size of the utilized GWAS. In addition, because there are no large-scale GWASs with freely available summary statistics for some of the examined comorbidities, proxy phenotypes were examined. Furthermore, patients' comorbidities are not always taken into account in the genetic studies, although individuals with known combined ADHD and ASD were excluded from some studies (43). Currently, psychiatric genetics are lacking GWASs on patients with comorbidities or with specific symptoms of psychiatric disorders, which limits our ability to examine the genetic variability that may be responsible for the diverse clinical landscape of psychiatric disorders.

Conclusions

In conclusion, our study provides robust and representative estimates of differences in psychiatric comorbidities among adults diagnosed with ADHD, ASD, or ADHD+ASD. With the results from analyses of genetic correlations, this finding contributes to our understanding of these disorders as being

distinct neurodevelopmental disorders with partly shared common genetic factors. Clinicians should be aware of the overall high level of comorbidity in adults with ADHD, ASD, or ADHD+ASD and of the distinct patterns of psychiatric comorbidities to detect these conditions and offer early treatment. It is also important to take into account the observed sex differences. The distinct comorbidity patterns may provide further information regarding etiologic research on biological mechanisms underlying the pathophysiology of these neurodevelopmental disorders.

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