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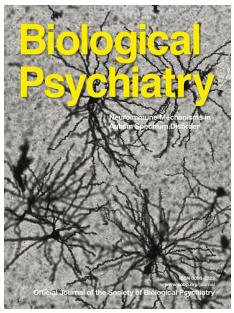

Patterns of psychiatric comorbidity and genetic correlations provide new insights into differences between attention-deficit/hyperactivity disorder and autism spectrum disorder

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TITLE PAGE

Patterns of psychiatric comorbidity and genetic correlations provide new insights into differences between attention-deficit/hyperactivity disorder and autism spectrum disorder

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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 analysed 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=7,528; 0.4%) and both diagnoses (n=1,467; 0.1%), compared to 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) between 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, both in men and women. The relative prevalence increase of substance use disorder (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, $p<0.001$), 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, $p<0.001$). Genetic correlations supported these patterns, but were significantly different between ADHD and ASD only for the SUD-proxies and personality traits ($p<0.006$ for all).

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

INTRODUCTION

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).

Both individuals with ADHD or ASD have a 65-90% 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, schizophrenia spectrum disorder (14-16), while adult ADHD is reported to co-occur with anxiety and major depressive disorders (17-19), bipolar disorder (11, 19-22), personality disorders (18, 19, 23), schizophrenia spectrum disorder (19, 22, 24, 25) and substance use disorder (19, 20, 26). ADHD and ASD share genetic factors with the above mentioned psychiatric disorders (27), and significant genetic 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 ASD alone, however, comparable studies in adults are lacking (31, 32). Only one single population-based study has directly compared individuals with either ADHD alone, ASD alone or both combined to 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, both ADHD and ASD, and adults without ADHD or ASD, and supplemented these analyses with the estimation of genetic correlations between the studied disorders.

METHODS AND MATERIALS

The 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 (MBRN) 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 (NUDB) from Statistics Norway (37, 38) (see Supplemental 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 (STROBE) (39).

Study Population and exposure groups

The study included 1,701,206 individuals born in Norway between 1967- 1997, 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 2004–2015 (NorPD) or had an ADHD-diagnosis (International Classification of Diseases (*ICD-10*) code F90), but no ASD-diagnosis, registered in the NPR during 2008–2015, all 18 years or older. The ADHD medications were methylphenidate, racemic amphetamine, dexamphetamine and atomoxetine. Individuals prescribed central stimulants for narcolepsy were excluded (see Supplemental 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), also 18 years or older and registered in the NPR during 2008–2015 and with no ADHD-diagnosis. Adults (18 years or older) with both ADHD and ASD as defined above constituted the combined group (ADHD+ASD).

The remaining population included all adults who were not dispensed ADHD medication nor had an ADHD or ASD diagnosis in the NPR. Parents of adults with and without ADHD/ASD were also identified through the MBRN and included in the analyses to account for parental factors associated with ADHD, ASD and other psychiatric disorders (e.g. socio-demographic factors, pregnancy-related factors and parental psychiatric disorders), and to account for 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 or more: anxiety disorder (ICD-10 codes; F40-F42), major depressive disorder (MDD; F32-F33), bipolar disorder (BD; F30-F31), personality disorders (PD; F60-F61), with a separate analysis on anti-social personality disorder (F60.2) (only included in the main analyses because of a small number of cases),

schizophrenia spectrum disorder (SCZ; F20-F29) and substance use disorder (SUD; F10-F19). For BD, we also included those who were dispensed lithium during 2004-2015, according to NorPD.

Summary Statistics from large-scale GWAS

Summary statistics from the large-scale GWAS for the psychiatric disorders examined (10, 43-51), were downloaded from the LDHub GWAS share centre (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 GWAS on ADHD and ASD, respectively, would result in associations heavily biased towards the larger study. Thus, we analysed ADHD and ASD only separately.

Since not all data are publically available, and no large-scale, well-powered GWAS were performed on all disorders examined, we used some proxy traits. In lack of adequate genetic data on personality disorders, we combined the data from the five GWAS on the five NEO-personality traits (Neuroticism, Extraversion, Openness to experience, Agreeableness and Conscientiousness) (53) using the inverse variance method in METAL software (54). Since all five NEO-personality traits were analyzed in the same-sized samples, there was no bias towards any of the traits. We also used the trait "anti-social behavior" as a proxy for anti-social personality disorder (49). As proxies for SUD, we used smoking behavior (ever vs never smoked) (51) and alcohol dependence (AD) (50).

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

Statistical Analyses

We estimated prevalence ratios (PR) 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, including the following covariates; Model I: 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 gestational age- and sex-specific birthweight z-scores (56); Model II: covariates of Model I and mothers' and fathers' psychiatric diagnoses, including ADHD or any other psychiatric diagnosis from NPR, 2008-2015 (for details about the covariates, see footnotes beneath the Tables/Figures and in Supplementary). 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 either ADHD, ASD or ADHD+ASD using predicted prevalences 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 Poisson regression models with and without the interaction term (gender x ADHD) included, tested by likelihood ratio tests, and interaction by sex on the additive scale was evaluated using relative excess risk due to interaction (RERI) (57).

Two-sided tests with a significance threshold of $p<0.05$ were employed in all analyses.

Analyses were carried out with PASW Statistics 23 (58) and STATA intercooled v.14 (59) from November 3, 2017 to March 13, 2019.

Genetic correlations (r_g) were calculated using linkage disequilibrium score regression (LDSC) that quantifies the similarities in genetic architecture between two traits by evaluating the relationship between SNP association strengths and genetic linkage disequilibrium (8). Due 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 "rg1" estimate and "b" refers to SE of "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 0.05, bringing the adjusted significance threshold to 0.00625.

Sensitivity Analyses

We conducted several sensitivity analyses to evaluate the robustness of our results. We re-ran all the analyses 1) excluding individuals with a diagnosis of intellectual disability, 2) excluding all with comorbid SCZ when analysing BD and SUD, 3) excluding all individuals with SUD when analysing SCZ, and 4) only including individuals who had their psychiatric diagnosis registered at least twice in the NPR. Missing values in covariates (6% for gestational age and birthweight z-scores, < 1% for other variables) were handled by list-wise deletion in the main analyses. In the sensitivity analyses, we also used multiple imputation with chained equations (60) to evaluate possible bias due to missing information in gestational age when adjusting for

covariates. The outcome variables, all specified covariates and also birthweight, maternal preeclampsia 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, 7,528 (0.4%; 27.9% women) with ASD, 1,467 (0.1%; 28.8% women) with ADHD+ASD and 1,653,575 (97.2%; 49% women) adults in the remaining population. In 2015, the mean ages of the ADHD, ASD and ADHD+ASD groups were 31, 26 and 27 years, respectively, compared to 33 years 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 to the ADHD group and the remaining population, likely explained by mothers to individuals with ASD/ADHD+ASD being born later in our study period, in a time where high 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 to the remaining population (Table 1).

Psychiatric comorbidity in adults with either ADHD, ASD or ADHD+ASD

Comorbid psychiatric disorders were two 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 with MDD the weakest in adults with ADHD (PRs: 7.1; 95% CI 6.8-7.4 and 3.7; 95% CI 3.6-3.8, respectively),

while the association with SCZ was the strongest and with SUD the weakest in adults with ASD (PRs 13.9; 95% CI 12.7-15.2 and 1.9; 95% CI 1.7-2.2, respectively) (Table 2, model II). The associations with anxiety, BD, MDD, PD and SUD were significantly stronger in adults with ADHD than with ASD (p<0.001 for all), with SUD revealing a particularly pronounced difference (PR_{ADHD}: 6.2 versus PR_{ASD}: 1.9). The association with SCZ, however, was stronger in adults with ASD than with ADHD (PRs 13.9 versus 4.4, p <0.001).

In the ADHD+ASD group, the PRs ranged from 3.6 (95% CI 3.2-4.0) for MDD to 12.5 (95% CI 10.3-15.1) for SCZ (Table 2, model II). For all disorders, except MDD and SUD, associations with ADHD+ASD were significantly stronger than for those with ADHD. For SCZ, associations with ADHD+ASD and ASD were similar and both significantly stronger than with ADHD; $PR_{ADHD+ASD}$ 12.5 (95% CI 10.3-15.1), PR_{ASD} 13.9 (95% CI 12.7-15.2) and PR_{ADHD} 4.4 (95% CI 4.1-4.7, p<0.001).

Sex-specific results

When stratifying on sex, patterns of psychiatric comorbidity corresponded to those in the total sample (Figure 1/ Supplemental, Table S2/S3). In both men and women, PR estimates for SCZ were significantly larger in ASD or ADHD+ASD than in ADHD, while for SUD, estimates were significantly larger for ADHD or ADHD+ASD than for ASD. For anxiety, 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 between women and men with ADHD for all the disorders studied, while only for three disorders in adults with ASD (Figure 2/Supplemental, Table S4). Further, the associations were reversed, and prevalence

of most psychiatric disorders increased more in women than men in all exposure groups except for SUD and SCZ, where 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 3B/Supplemental, Table S5). For SCZ, the r_g estimate with ASD was almost twice as large as that with ADHD ($r_{g(ASD+SCZ)}$: 0.211 (SE: 0.048, p<0.0001), $r_{g(ADHD+SCZ)}$: 0.127 (SE: 0.036, p=0.0004)), but this difference was not statistically significant (p=0.16). The differences in genetic correlations between ADHD and ASD with the examined comorbid disorders were only statistically significant 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, where the PR for SCZ increased slightly (PR_{crude} 15.1; 95% CI 13.9-16.4 to $PR_{sensitivity}$ 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, Table S6/Table S7).

DISCUSSION

In this first nationwide population-based study combining epidemiological data on adults with ADHD only, ASD only or both diagnoses, 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 confer severe additional psychiatric morbidity relative to adults with either ADHD or ASD alone.

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, where SCZ was more common in adults with ASD, and SUD more common in adults with ADHD. Associations with anxiety, BD and personality disorders were strongest in adults with both ADHD and ASD, indicating that this group of adults suffers from more severe impairments than those with ADHD or ASD only (61). This is supported by previous studies in children (32, 62). Further, we found that adults with both ADHD and ASD had a similar increase in risk for SCZ as adults with ASD only, which, as far as we know, has not been shown before. To our knowledge, only one other population-based study reports on prevalences of psychiatric disorders among individuals with either ADHD, ASD or ADHD+ASD compared to 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-5 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, 63).

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 and colleagues, 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 behaviours (ASD) and a weak correlation with social interaction and communication) (28). 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 in order 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, 64). 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 (65). Further, on a more psychological level, even if individuals with ADHD or ASD often experience peer-rejection and relational problems (66, 67), individuals with ASD are diagnostically defined by their struggle to communicate and are hence less able to communicate their problems in spite of large impairments (68, 69). 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, both on the relative and absolute scales. The present findings for adults with ADHD are also presented in our previous publication (19), and confirmed by a recent Swedish study (70). Sex differences are strongly dependent on the scale used for analyses; with stronger associations for most psychiatric comorbidities in men than women on the relative scale, and stronger in women than 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 (71, 72).

The behavioural 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 behaviour, increasing the risk of developing SUD to a larger degree in ADHD than in ASD, where a rigid and norm-abiding behaviour, with limited social contact, may be relatively

protective (30, 73, 74). 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, and thereby modify the risk to 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, 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, ASD alone or both combined, 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 were not based solely on symptom scores or self-reports. We chose to identify the ADHD-cases by either a dispensed prescription of ADHD-medication from the NorPD or by an ADHD-diagnosis from the NPR, similarly to other Scandinavian studies (22, 75-77). ASD, BD and SCZ diagnoses in the NPR have been validated with good results (36, 78), 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 during 2004-2015 (NorPD) and 2008-2015 (NPR), preventing the examination of temporal relations. However, since 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 that of ADHD according to DSM-IV and ICD-10 (79, 80). 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, as growing evidence supported the importance of diagnosing both conditions when present in order 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 (81). However, all adults with severe psychiatric disorders are likely to be in touch with secondary health care throughout life, independent of underlying neurodevelopmental disorders (82).

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 GWAS 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 GWAS 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 between 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 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 further provide information to etiologic research on biological mechanisms underlying the pathophysiology of these neurodevelopmental disorders.

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Figure title, Figure 1:

Figure 1. Prevalence ratios of psychiatric disorders in adults with ADHD, ASD or ADHD+ASD relative to the remaining population, by sex

Figure legend, Figure 1:

Abbreviations: Schizophrenia= Schizophrenia Spectrum Disorder, SUD= Substance Use Disorder, BD= Bipolar Disorder, MDD= Major Depression Disorder, PD= Personality Disorder. Log-scale, 95% CI 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 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).

Figure title, Figure 2:

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

Figure legend, Figure 2:

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).

Figure title, Figure 3:

Figure 3. A)The pattern of prevalence ratios of psychiatric comorbidity in adults with ADHD or ASD observed in this study (ADHD; n=38,636, ASD; n=7,528) and B) genetic correlations (r_g) calculated from genome wide association studies

Figure legend, Figure 3 A and 3 B:

A. Prevalence ratio, model II, log-scale, 95% CI 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 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).
B. Genetic correlations, r_g, linear scale, SE error bars. 'ever_vs_never_smoked' and 'Alcohol Dependence' as proxies for smoking, 'NEO-5-personality traits' as proxy for personality disorder.

Table 1. Sample characteristics of the 1,701,206 adults in the study population, all born from 1967 to 1997 and followed to 2015.

Variables	ADHD No. (%)	ASD No. (%)	ADHD+ASD No. (%)	Remaining population No. (%)
No. (%)	38,636 (2.3)	7,528 (0.4)	1,467 (0.1)	1,653,575 (97.2)
Gender	*P<0.001*[a]	*P=491*[b]	*P<0.001*[c]	*P<0.001*[d]
Women	17, 393 (45.0)	2,099 (27.9)	422 (28.8)	809,962 (49.0)
M:F ratio	1.22	2.58	2.48	1.04
Mean age in 2015, years (SD)	*P<0.001*[a]		*P=0.99*[c]	*P<0.001*[d]
	31.3 (8.3)	26.2 (7.9)	26.8 (7.1)	33.2 (9.3)
Maternal age at birth	*P<0.001*[a]	*P<0.001*[b]	*P<0.001*[c]	*P<0.001*[d]
<20	4,417 (11.4)	372 (4.9)	107 (7.3)	112,674 (6.8)
20-24	13,587 (35.2)	1,936 (25.7)	435 (29.7)	498,264 (30.1)
25-29	11,865 (30.7)	2,539 (33.7)	525 (35.8)	575,743 (34.8)
30-34	6,144 (15.9)	1,747 (23.2)	279 (19.0)	327,637 (19.8)
35-39	2,215 (5.7)	774 (10.3)	102 (7.0)	116,139 (7.0)
40+	408 (1.1)	160 (2.1)	19 (1.3)	23,118 (1.4)
Paternal age at birth	*P<0.001*[a]	*P<0.001*[b]	*P<0.001*[c]	*P<0.001*[d]
<20	1,054 (2.7)	75 (1.0)	21 (1.4)	24,546 (1.5)
20-24	9,013 (23.3)	1,093 (14.5)	267 (18.2)	302,939 (18.3)
25-29	12,941 (33.5)	2,242 (29.8)	484 (33.0)	563,896 (34.1)
30-34	8,728 (22.6)	2,120 (28.2)	392 (26.7)	432,678 (26.2)
35-39	4,086 (10.6)	1,154 (15.3)	182 (12.4)	207,833 (12.6)
40-44	1,621 (4.2)	519 (6.9)	78 (5.3)	76,947 (4.7)
45-49	489 (1.3)	171 (2.3)	25 (1.7)	24,796 (1.5)
50+	183 (0.5)	70 (0.9)	3 (0.2)	8,741 (0.5)
Missing	521 (1.4)	84 (1.1)	15 (1.0)	11,199 (0.7)
Maternal marital status[d]	*P<0.001*[a]	*P=0.007*[b]	*P=0.016*[c]	*P<0.001*[d]
Single	6,483 (16.8)	909 (12.1)	225 (15.3)	151,975 (9.2)
Married/cohabitant	31,122 (80.6)	6,508 (86.5)	1,220 (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)	2,761 (0.2)
Maternal education status[e]	*P<0.001*[a]	*P=0.169*[b]	*P<0.001*[c]	*P<0.001*[d]
Low	13,498 (34.9)	1,904 (25.3)	394 (26.9)	430,874 (26.1)
Middle	16,478 (42.7)	3,022 (40.1)	583 (39.7)	768,773 (46.5)
High	8,415 (21.8)	2,565 (34.1)	488 (33.3)	447,380 (27.1)
Missing	245 (0.6)	37 (0.5)	2 (0.1)	6,548 (0.4)
Paternal education status[e]	*P<0.001*[a]	*P<0.001*[b]	*P<0.001*[c]	*P<0.001*[d]
Low	12,501 (32.4)	1,639 (21.8)	388 (26.5)	381,154 (23.1)
Middle	18,626 (48.2)	3,486 (46.3)	694 (47.3)	834,541 (50.5)
High	6,475 (16.8)	2,237 (29.7)	352 (24.0)	414,399 (25.1)
Missing	1,034 (2.7)	166 (2.2)	33 (2.3)	23,481 (1.4)
Maternal psychiatric disorder[f]	*P=0.073*[a]	*P<0.001*[b]	*P=0.001*[c]	*P<0.001*[d]
None	28,140 (72.8)	5,557 (73.8)	1,009 (68.8)	1,432,294 (86.6)
Paternal psychiatric disorder[f]	*P<0.001*[a]	*P=0.010*[b]	*P=0.492*[c]	*P<0.001*[d]
None	31,478 (82.7)	6,289 (84.7)	1,189 (82.0)	1,479,367 (90.2)

a. *P*-value (Pearsons chi-square test and t-test for equality of means), the difference between the ADHD and ASD cases
b. *P*-value (Pearsons chi-square test and t-test for equality of means), the difference between the between the ASD and ADHD+ASD cases
c. *P*-value (Pearsons chi-square test and t-test for equality of means), the difference between the ADHD and ADHD+ASD cases
d. *P*-value (Pearsons chi-square test and t-test for equality of means), for the difference between cases relative to the comparison population

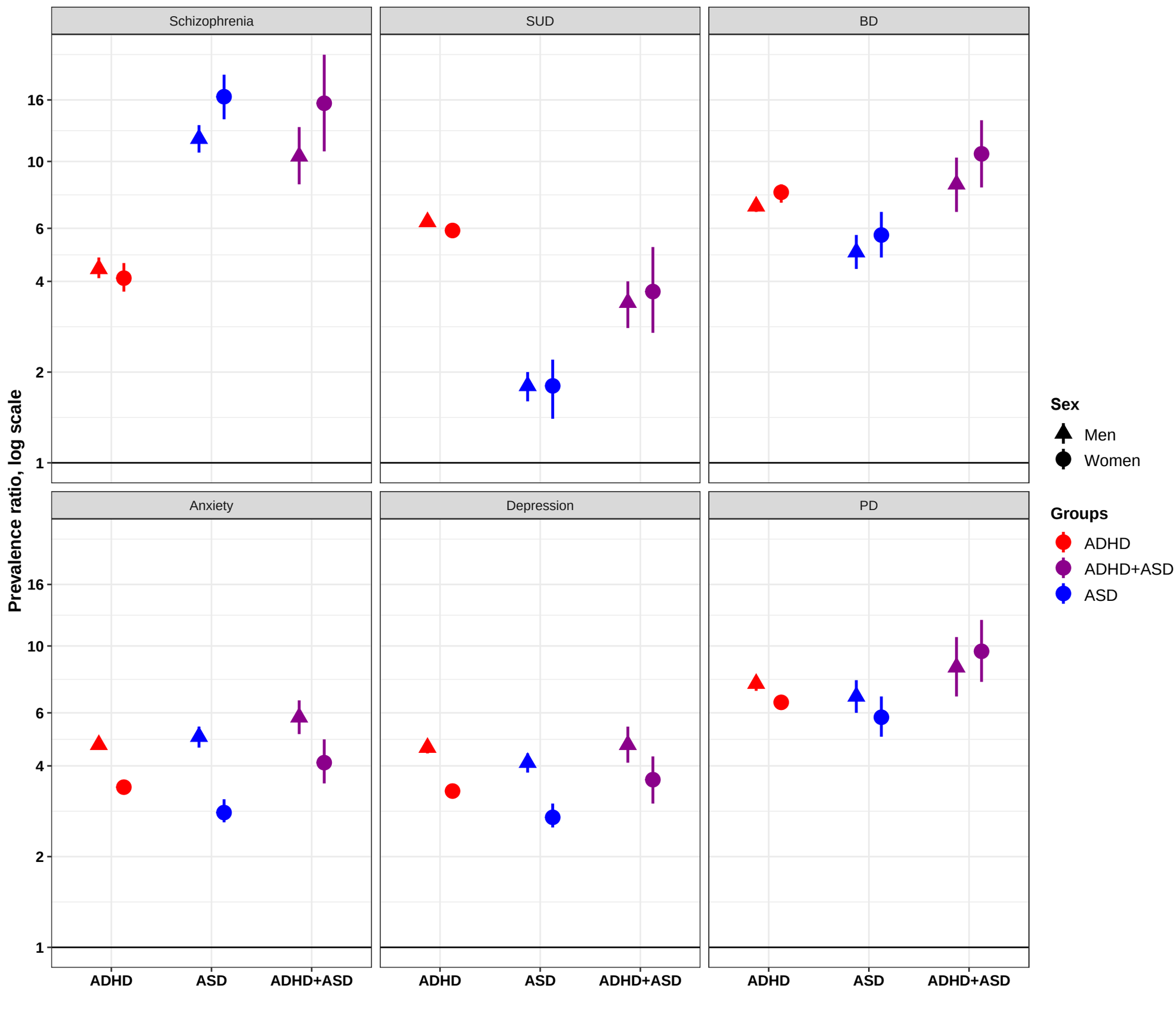
Table 2. Prevalence ratios of psychiatric disorders comparing adults with and without ADHD, ASD or ADHD+ASD. Based on 1.7 million individuals born in Norway (1967-1997), and followed to 2015.

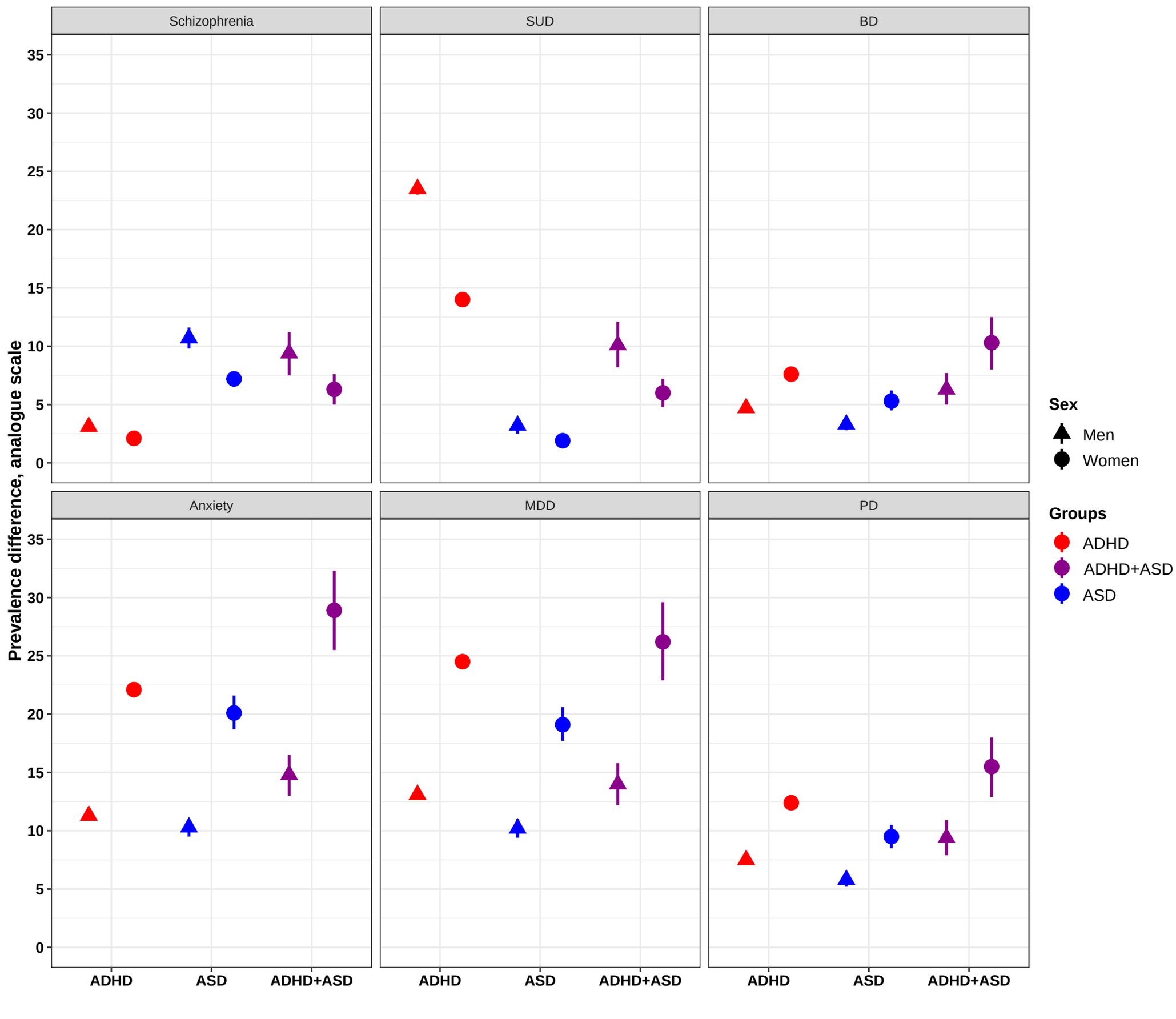
Psychiatric disorders (ICD-10)	Prevalence ratio (PR), crude (95% CI)[a]				PR model I, (95% CI)[b]			PR model II, (95% CI)[c]		
	Remaining population	**ADHD**	**ASD**	**ADHD+ASD**	**ADHD**	**ASD**	**ADHD+ASD**	**ADHD**	**ASD**	**ADHD+ASD**
		P<0.001[d]	*P*<0.001[e]	*P*=0.001[f]	*P*=0.020[d]	*P*<0.001[e]	*P*<0.001[f]	*P*=0.023[d]	*P*<0.001[e]	*P*<0.001[f]
Anxiety Disorders (F40-42)	1 (ref)	4.2 (4.2-4.3)	3.5 (3.3-3.7)	4.7 (4.3-5.2)	4.1 (4.0-4.2)	3.6 (3.4-3.8)	4.7 (4.2-5.2)	3.8 (3.7-3.9)	3.4 (3.2-3.6)	4.3 (3.9-4.7)
		P<0.001	*P*<0.001	*P*=0.006	*P*<0.001	*P*<0.001	*P*=0.020	*P*<0.001	*P*<0.001	*P*=0.021
Bipolar Disorder (F30-31 or medication[g])	1 (ref)	7.8 (7.5-8.1)	5.3 (4.7-6.0)	9.4 (7.7-11.4)	7.8 (7.4-8.1)	5.4 (4.7-6.2)	9.3 (7.6-11.5)	7.1 (6.8-7.4)	5.0 (4.4-5.7)	8.4 (6.8-10.3)
		P<0.001	*P*<0.001	*P*=0.801	*P*<0.001	*P*=0.001	*P*=0.886	*P*<0.001	*P*=0.001	*P*=0.898
Major Depressive Disorder (F32-33)	1 (ref)	4.2 (4.1-4.2)	3.1 (2.9-3.3)	4.0 (3.6-4.4)	4.0 (3.9-4.1)	3.2 (3.0-3.3)	3.9 (3.5-4.3)	3.7 (3.6-3.8)	3.0 (2.8-3.1)	3.6 (3.2-4.0)
		P<0.001	*P*<0.001	*P*=0.009	*P*<0.001	*P*<0.001	*P*=0.014	*P*=0.001	*P*<0.001	*P*=0.015
Personality Disorder (F60-61)	1 (ref)	8.1 (7.9-8.4)	5.9 (5.4-6.5)	8.1 (7.9-10.6)	7.4 (7.2-7.7)	6.0 (5.5-6.6)	8.6 (7.3-10.1)	6.8 (6.5-7.0)	5.6 (5.1-6.2)	7.7 (6.5-9.1)
		P<0.001	*P*<0.001	*P*=0.215	*P*<0.001	*P*<0.001	*P*=0.070	*P*<0.001	*P*<0.001	*P*=0.070
Anti-social PD (F60.2)	1 (ref)	20.7 (18.4-23.2)	4.1 (2.4-7.2)	24.8 (15.4-40.0)	17.2 (15.1-19.7)	4.1 (2.3-7.5)	24.0 (14.4-40.1)	15.4 (13.5-17.7)	3.8 (2.1-6.9)	21.1 (12.6-35.2)
		P<0.001	*P*=0.194	*P*<0.001	*P*<0.001	*P*=0.470	*P*<0.001	*P*<0.001	*P*=0.424	*P*<0.001
Schizophrenia Spectrum Disorder (F20-29)	1 (ref)	4.8 (4.6-5.1)	15.1(13.9-16.4)	13.3 (11.1-16.0)	4.8 (4.5-5.1)	14.9 (13.6-16.2)	13.8 (11.4-16.8)	4.4 (4.1-4.7)	13.9 (12.7-15.2)	12.5 (10.3-15.1)
		P<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001
Substance Use Disorder (F10-19)	1 (ref)	7.8 (7.6-7.9)	2.1(1.9-2.3)	4.2 (3.7-4.9)	6.8 (6.6-7.0)	2.1 (1.9-2.3)	4.1 (3.5-4.8)	6.2 (6.1-6.4)	1.9 (1.7-2.2)	3.7 (3.2-4.3)

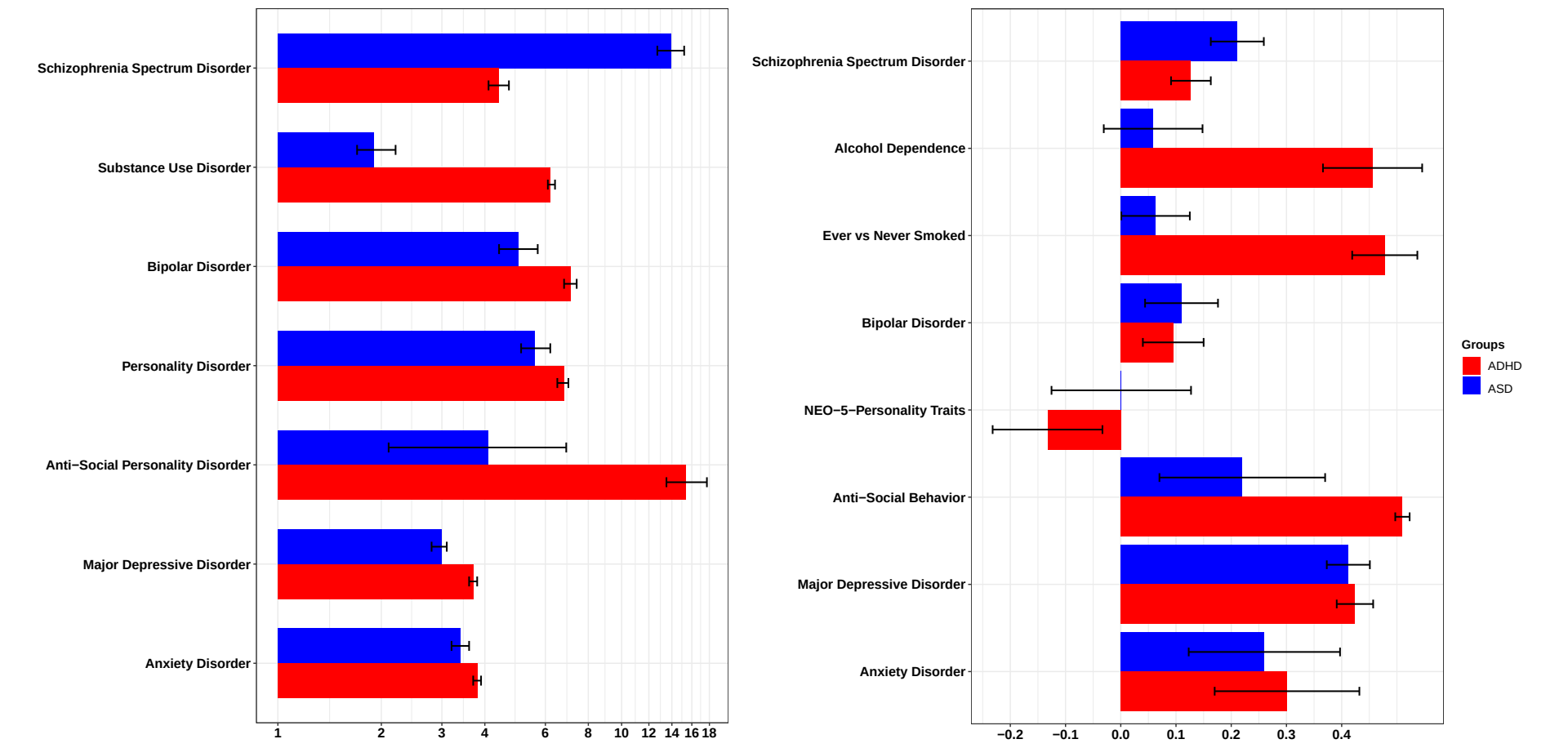
Abbreviations: PR: Prevalence ratio, CI: confidence interval, ref: reference population, PD: Personality Disorder

a. Crude: Adjusted for birth year (5-year groups, from 1967 to 1997, with 1967-1973 as the reference period)
b. Model I: Adjusted for birth year, 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+)
c. Model II: Adjusted for covariates as in model I and additionally adjusted for maternal and paternal psychiatric disorders (yes/no)
d. *P*-value for the difference between the ADHD and the ASD cases (likelihood-ratio test)
e. *P*-value for the difference between the ASD and the ADHD+ASD cases (likelihood-ratio test)

f. *P*-value for the difference between the ADHD and the ADHD+ASD cases (likelihood-ratio test)
g. Medication: Lithium from Norwegian Prescription Database (2004-2015)


Schizophrenia
SUD
BD
Anxiety
Depression
PD
Prevalence ratio, log scale
16
10
6
4
2
1
ADHD
ASD
ADHD+ASD
Sex
Men
Women
Groups
ADHD
ADHD+ASD
ASD


Schizophrenia
SUD
BD
Anxiety
MDD
PD
Prevalence difference, analogue scale
0
5
10
15
20
25
30
35
ADHD
ASD
ADHD+ASD
Sex
Men
Women
Groups
ADHD
ADHD+ASD
ASD


Schizophrenia Spectrum Disorder
Substance Use Disorder
Bipolar Disorder
Personality Disorder
Anti−Social Personality Disorder
Major Depressive Disorder
Anxiety Disorder
1
2
3
4
6
8
10
12
14
16
18
Schizophrenia Spectrum Disorder
Alcohol Dependence
Ever vs Never Smoked
Bipolar Disorder
NEO−5−Personality Traits
Anti−Social Behavior
Major Depressive Disorder
Anxiety Disorder
−0.2
−0.1
0.0
0.1
0.2
0.3
0.4
Groups
ADHD
ASD

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

Supplementary Information

Contents:

Supplemental Text

Description of the registries

The nationwide Medical Birth Registry of Norway (MBRN) was established in 1967 and contains information about all births in Norway, including spontaneous abortions and stillbirths from 16 weeks of gestation (1). The aim of the registry is to clarify 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 data on maternal health before and during pregnancy, labour complications and interventions, and birth outcomes. Information on the father is also included in the registry.

The Norwegian Prescription Database (NorPD) contains data about all prescribed and dispensed drugs in Norway since 2004. The aim of the NorPD is to collect and process data on drug consumption. Drugs that are purchased without prescription are not included, and medication given to an individual during a hospital stay is not available at the individual level. For reimbursed medications, information about the indication is also included; however, for psychiatric disorders, this is only available from 2008 (2). The medications are classified by the Anatomical Therapeutic Chemical (ATC) classification system.

The Norwegian Patient Registry (NPR) is a health registry containing information about diagnoses given to individuals treated in secondary health care, both in hospitals and out-patient clinics. 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. NPR was established in 1997, but has only had data available for linkage on an individual level from 2008.

The Personal Health Data Filing System Act (3, 4) which is further specified in registry-specific regulations, provide the legal basis for the health registries.

The National Educational Database (NUDB), established in 1970, contains information about the level of education of every Norwegian inhabitant from the age of 16 years, from

completed lower secondary education to tertiary education including PhD level, and is updated every year (3, 5).

Statistical analyses

To adjust for potential confounders, we performed two regression models, including the following covariates; Model I: Birth year (5-year groups, from 1967 to 1997), maternal marital status (single, married/cohabiting (reference), other), 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+) in years at delivery, parents' highest attained level of education at record linkage (low (<10 years of education), middle (10-12 years of education) and high level (>12 years of education (reference)), the individual's gestational age in weeks (<28, 28-31, 32-34, 35-36, 37-41 (reference), 42+) and gestational age- and sex-specific birthweight z-scores (<-2.0; -2.0 to -0.51; -0.5 to 0.5 (reference); 0.51-2.0; 2.01+) (6); Model II: covariates of Model I and mothers' and fathers' psychiatric diagnoses (yes/no), including ADHD or any other psychiatric diagnosis from NPR, 2008-2015. To account for correlations between siblings, we used mother's identification number as a cluster variable in the analyses.

Narcolepsy

ADHD medication may also be used for narcolepsy (*ICD-10* code G47 or ICPC P06). Using the reimbursement codes in NorPD (available from 2008), we found that 789 individuals (0.05%) of the adult population were prescribed stimulants exclusively for narcolepsy in the period 2008-2015, and these were excluded from the group of individuals with ADHD. Thus, for patients who were dispensed medication in the period 2004-2008 only, there may be a small number of individuals with narcolepsy left in the adult ADHD case-groups.

Supplemental Tables

Table S1. Prevalence differences of psychiatric disorders in adults with ADHD, ASD or ADHD+ ASD, based on the study population

Psychiatric disorders (ICD-10)	Crude prevalences, No. (%)				Prevalence, % (95% CI)[a]				Prevalence Differences, % (95% CI)[a]		
	Remaining population	ADHD	ASD	ADHD+ASD	Remaining population	ADHD	ASD	ADHD+ASD	ADHD	ASD	ADHD+ASD
Anxiety Disorders (F40-42)	81 781 (5.0)	8 422 (21,8)	1 062 (14.2)	308 (21.0)	4.9 (4.9-5.0)	21.0 (20.6-21.4)	17.4 (16.5-18.4)	23.2 (21.0-25.4)	16.0 (15.6-16.4)	12.5 (11.5-13.4)	18.3 (16.1-20.5)
Bipolar Disorder (F30-31 or medication[b])	14 629 (0.9)	2 595 (6.7)	239 (3.2)	92 (6.3)	0.9 (0.9-0.9)	6.9 (6.6-7.1)	4.7 (4.1-5.3)	8.3 (6.7-9.9)	6.0 (5.7-6.2)	3.8 (3.2-4.4)	7.4 (5.8-9.0)
Major Depressive Disorder (F32-33)	94 538 (5.7)	9 361 (24.2)	1 075 (14.3)	293 (20.0)	5.7 (5.7-5.7)	23.8 (23.4-24.2)	17.8 (16.8-18.7)	22.6 (20.4-24.8)	18.1 (17.7-18.5)	12.1 (11.1-13.0)	16.9 (14.7-19.1)
Personality Disorder (F60-61)	22 556 (1.4)	4 311 (11.2)	432 (5.7)	147 (10.0)	1.4 (1.3-1.4)	11.0 (10.7-11.4)	8.1 (7.4-8.8)	12.4 (10.6-14.3)	9.7 (9.4-10.0)	6.7 (6.0-7.5)	11.1 (9.2-12.9)
Anti-social PD (F60.2)	919 (0.06)	454 (1.2)	13 (0.2)	17 (1.2)	0.06 (0.05-0.06)	1.1 (1.0-1.3)	0.2 (0.1-0.4)	1.4 (0.7-2.0)	1.1 (1.0-1.2)	0.2 (0.05-0.3)	1.3 (0.7-2.0)
Schizophrenia Spectrum Disorder (F20-29)	11 432 (0.7)	1 268 (3.3)	541 (7.2)	104 (7.1)	0.7 (0.7-0.7)	3.3 (3.2-3.5)	10.4 (9.6-11.3)	9.2 (7.5-10.9)	2.6 (2.5-2.8)	9.7 (8.9-10.6)	8.5 (6.8-10.2)
Substance Use Disorder (F10-19)	47 061 (2.9)	8 850 (22.9)	372 (4.9)	163 (11.1)	2.8 (2.8-2.9)	22.1 (21.7-22.5)	5.9 (5.4-6.5)	12.0 (10.3-13.8)	19.3 (18.9-19.7)	3.1 (2.5-3.7)	9.2 (7.5-10.9)

Abbreviations: ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision, World Health Organization, CI: confidence interval, PD: Personality Disorder

a. Adjusted for birth year (5-year groups)
b. Medication: Lithium from the Norwegian Prescription Database (2004-2015)

Table S2. Crude and adjusted prevalences of psychiatric disorders in adults with and without ADHD, ASD or ADHD+ASD, by sex

Psychiatric disorders (ICD-10)	Crude prevalences, No. (%)				Prevalence, % (95% CI)[a]			
	Remaining population	ADHD	ASD	ADHD+ASD	Remaining population	ADHD	ASD	ADHD+ASD
Anxiety Disorders (F40-42)								
Women	54,139 (6.7)	4,561 (26.2)	340 (16.2)	115 (27.3)	6.7 (6.6-6.7)	25.2 (24.6-25.8)	19.3 (17.5-21.2)	29.3 (25.0-33.7)
Men	27,642 (3.3)	3,861 (18.2)	722 (13.3)	193 (18.5)	3.3 (3.2-3.3)	17.5 (17.0-18.0)	16.4 (15.3-17.5)	20.4 (17.9-22.9)
Bipolar Disorder (F30-31 or medication)[b]								
Women	8,944 (1.1)	1,446 (8.3)	95 (4.5)	34 (8.1)	1.1 (1.1-1.1)	8.7 (8.3-9.0)	6.4 (5.6-7.3)	11.4 (9.1-13.6)
Men	5,685 (0.7)	1,149 (5.4)	144 (2.7)	58 (5.6)	0.7 (0.7-0.7)	5.4 (5.1-5.6)	4.0 (3.5-4.5)	7.0 (5.6-8.4)
Major Depressive Disorder (F32-33)								
Women	61,501 (7.6)	5,025 (28.9)	379 (18.1)	113 (26.8)	7.6 (7.5-7.7)	28.3 (27.7-29.0)	21.8 (19.9-23.7)	29.6 (25.0-34.1)
Men	33,037 (3.9)	4,336 (20.4)	696 (12.8)	180 (17.2)	3.9 (3.9-4.0)	20.1 (19.6-20.6)	15.9 (14.8-17.0)	19.4 (16.9-21.9)
Personality Disorder (F60-61)								
Women	13,913 (1.7)	2,361 (13.6)	166 (7.9)	67 (15.9)	1.7 (1.7-1.7)	13.4 (12.9-13.9)	11.2 (10.2-12.2)	17.2 (14.6-19.7)
Men	8,643 (1.0)	1,950 (9.2)	266 (4.9)	80 (7.7)	1.0 (1.0-1.1)	9.1 (8.7-9.5)	6.8 (6.2-7.4)	10.4 (8.9-12.0)
Schizophrenia Spectrum Disorder (F20-29)								
Women	4,472 (0.6)	415 (2.4)	149 (7.1)	29 (6.9)	0.6 (0.5-0.6)	2.4 (2.2-2.6)	9.9 (8.4-11.4)	6.8 (5.6-8.1)
Men	6,960 (0.8)	853 (4.0)	392 (7.2)	75 (7.2)	0.8 (0.8-0.8)	4.1 (3.8-4.4)	10.5 (9.5-11.5)	10.2 (8.3-12.1)
Substance Use Disorder (F10-19)								
Women	17,124 (2.1)	2,841 (16.3)	76 (3.6)	37 (8.8)	2.1 (2.1-2.1)	16.1 (15.7-16.4)	4.0 (3.6-4.4)	8.1 (7.0-9.3)
Men	29,937 (3.6)	6,009 (28.3)	296 (5.5)	126 (12.1)	3.6 (3.5-3.6)	27.1 (26.6-27.6)	6.7 (6.0-7.4)	13.7 (11.7-15.6)

Abbreviations: ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision, World Health Organization, CI: confidence interval

a. Adjusted for birth year (5-year groups, from 1967 to 1997, with 1967-1973 as the reference)
b. Medication: Lithium in the Norwegian Prescription Database (2004-2015)

Table S3. Prevalence ratios of psychiatric disorders comparing adults with and without ADHD, ASD or ADHD+ASD, based on the study population, by sex

Psychiatric disorders (ICD-10)	Prevalence ratio (PR), (95% CI)[a]				PR model I, (95% CI)[b]			PR model II, (95% CI)[c]		
	Remaining population	ADHD	ASD	ADHD+ASD	ADHD	ASD	ADHD+ASD	ADHD	ASD	ADHD+ASD
Anxiety Disorders (F40-42)		***P*<0.001**	***P*<0.001**	***P*<0.001**	***P*<0.001**	***P*<0.001**	***P*=0.001**	***P*<0.001**	***P*<0.001**	***P*=0.004**
Women	1 (ref)	3.8 (3.7-3.8)	2.9 (2.6-3.2)	4.4 (3.8-5.1)	3.6 (3.5-3.7)	3.0 (2.7-3.3)	4.4 (3.7-5.1)	3.4 (3.3-3.5)	2.8 (2.6-3.1)	4.1 (3.5-4.9)
Men	1 (ref)	5.4 (5.2-5.6)	5.2 (4.9-5.5)	6.4 (5.7-7.3)	5.1 (5.0-5.3)	5.3 (4.9-5.7)	6.4 (5.6-7.3)	4.7 (4.6-4.9)	5.0 (4.6-5.4)	5.8 (5.1-6.6)
Bipolar Disorder (F30-31 or medication[d])		*P*=0.086	*P*=0.992	*P*=0.418	*P*=0.056	*P*=0.756	*P*=0.397	*P*=0.089	*P*=0.687	*P*=0.561
Women	1 (ref)	7.5 (7.2-8.0)	5.7 (4.7-6.9)	9.0 (6.6-12.4)	7.4 (7.0-7.9)	5.9 (4.8-7.2)	8.8 (6.2-12.4)	7.9 (7.3-8.4)	5.7 (4.8-6.8)	10.6 (8.2-13.7)
Men	1 (ref)	8.5 (7.9-9.0)	6.2 (5.3-7.3)	11.9 (9.3-15.2)	8.7 (8.1-9.3)	6.2 (5.2-7.3)	12.0 (9.3-15.6)	7.1 (6.8-7.4)	5.0 (4.4-5.7)	8.4 (6.8-10.3)
Major Depressive Disorder (F32-33)		***P*<0.001**	***P*<0.001**	***P*=0.016**	***P*<0.001**	***P*<0.001**	***P*=0.027**	***P*<0.001**	***P*<0.001**	*P*=0.067
Women	1 (ref)	3.7 (3.6-3.8)	2.8 (2.6-3.1)	3.8 (3.3-4.5)	3.6 (3.5-3.7)	2.9 (2.6-3.1)	3.8 (3.2-4.5)	3.3 (3.3-3.4)	2.7 (2.5-3.0)	3.6 (3.0-4.3)
Men	1 (ref)	5.2 (5.1-5.4)	4.3)4.0-4.6)	5.3 (4.6-6.0)	5.0 (4.8-5.1)	4.4 (4.0-4.7)	5.2 (4.6-6.0)	4.6 (4.4-4.7)	4.1 (3.8-4.4)	4.7 (4.1-5.4)
Personality Disorder (F60-61)		***P*<0.001**	*P*=0.379	*P*=0.249	***P*=0.001**	*P*=0.761	*P*=0.206	***P*=0.003**	*P*=0.802	*P*=0.120
Women	1 (ref)	7.7 (7.4-8.0)	6.0 (5.2-6.9)	10.7 (8.6-13.2)	7.1 (6.8-7.4)	6.2 (5.4-7.2)	10.3 (8.2-13.0)	6.5 (6.2-6.8)	5.8 (5.0-6.8)	9.6 (7.6-12.2)
Men	1 (ref)	9.1 (8.7-9.6)	7.4 (6.5-8.3)	10.2 (8.3-12.6)	8.3 (7.9-8.7)	7.3 (6.4-8.3)	9.7 (7.7-12.1)	7.5 (7.1-7.9)	6.8 (6.0-7.7)	8.5 (6.8-10.7)
Schizophrenia Spectrum Disorder (F20-29)		***P*=0.042**	***P*<0.001**	*P*=0.128	***P*=0.038**	***P*=0.002**	*P*=0.165	*P*=0.051	***P*=0.002**	*P*=0.105
Women	1 (ref)	4 .4 (4.0-4.9)	18.4 (15.7-21.5)	16.0 (11.3-22.6)	4.4 (4.0-4.9)	17.3 (14.7-20.5)	16.6 (11.5-23.9)	4.1 (3.7-4.6)	16.4 (13.8-19.4)	15.6 (10.8-22.6)
Men	1 (ref)	4.9 (4.6-5.3)	12.8 (11.6-14.1)	11.3 (9.1-14.1)	4.9 (4.5-5.3)	12.8 (11.5-14.2)	11.8 (9.5-14.8)	4.4 (4.1-4.8)	11.9 (10.7-13.2)	10.4 (8.4-13.0)
Substance Use Disorder (F10-19)		*P*=0.118	*P*=0.614	*P*=0.307	*P*=0.321	*P*=0.497	*P*=0.334	*P*=0.497	*P*=0.474	*P*=0.241
Women	1 (ref)	7.3 (7.0-7.6)	1.9 (1.5-2.3)	4.2 (3.1-5.7)	6.4 (6.1-6.7)	1.9 (1.5-2.4)	4.0 (2.9-5.7)	5.9 (5.6-6.1)	1.8 (1.4-2.2)	3.7 (2.7-5.2)
Men	1 (ref)	7.8 (7.6-8.0)	1.9 (1.7-2.2)	3.8 (3.3-4.5)	6.8 (6.6-7.0)	1.9 (1.7-2.2)	3.7 (3.2-4.4)	6.3 (6.1-6.4)	1.8 (1.6-2.0)	3.4 (2.8-4.0)

Abbreviations: ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision, World Health Organization, CI: confidence interval

P-values: **Bold P for** significant interaction of sex on a multiplicative scale, *P*<0.05 (likelihood-ratio test)

a. Adjusted for birth year (5-year groups, from 1967 to 1997, with 1967-1973 as the reference)
b. Model I: Adjusted for birth year, 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+)
c. Model II: Adjusted for covariates as in model I and additionally adjusted for maternal and paternal psychiatric disorders (yes/no)
d. Medication: Lithium in the Norwegian Prescription Database (2004-2015)

Table S4. Prevalence differences of psychiatric disorders in adults with ADHD, ASD or ADHD+ ASD, by sex

Psychiatric disorders (ICD-10)	Prevalence, % (95% CI)[a]				Prevalence difference, % (95%CI)[a]					
	Remaining population	ADHD	ASD	ADHD+ASD	ADHD	RERI[b]	ASD	RERI[b]	ADHD+ASD	RERI[b]
Anxiety Disorders (F40-42)										
Women	6.7 (6.6-6.7)	25.2 (24.6-25.8)	19.3 (17.5-21.2)	29.3 (25.0-33.7)	18.5 (17.9-19.1)	1.5 (1.2-1.7)[c]	12.7 (10.8-14.5)	-0.08 (-0.7;0.5)	22.7 (18.3-27.0)	1.8 (0.2-3.4)[c]
Men	3.3 (3.2-3.3)	17.5 (17.0-18.0)	16.4 (15.3-17.5)	20.4 (17.9-22.9)	14.2 (13.7-14.7)		13.1 (12.1-14.2)		17.1 (14.6-19.6)	
Bipolar Disorder (F30-31 or medication)[d]										
Women	1.1 (1.1-1.1)	8.7 (8.3-9.0)	6.4 (5.6-7.3)	11.4 (9.1-13.6)	7.6 (7.2-7.9)	3.9 (3.1-4.7)[c]	5.3 (4.5-6.2)	2.9 (1.0-4.7)[c]	10.3 (8.0-12.5)	3.7 (-1.7;9.1)
Men	0.7 (0.7-0.7)	5.4 (5.1-5.6)	4.0 (3.5-4.5)	7.0 (5.6-8.4)	4.7 (4.5-4.9)		3.3 (2.8-3.8)		6.3 (5.0-7.7)	
Major Depressive Disorder (F32-33)										
Women	7.6 (7.5-7.7)	28.3 (27.7-29.0)	21.8 (19.9-23.7)	29.6 (25.0-34.1)	20.7 (20.1-21.4)	1.3 (1.0-1.5)[c]	14.2 (12.3-16.1)	0.6 (0.02-1.1)[c]	22.0 (17.4-26.5)	1.7 (0.4-3.1)[c]
Men	3.9 (3.9-4.0)	20.1 (19.6-20.6)	15.9 (14.8-17.0)	19.4 (16.9-21.9)	16.2 (15.7-16.7)		12.1 (10.9-13.1)		15.5 (13.0-18.0)	
Personality Disorder (F60-61)										
Women	1.7 (1.7-1.7)	13.4 (12.9-13.9)	11.2 (10.2-12.2)	17.2 (14.6-19.7)	11.7 (11.2-12.2)	3.8 (3.1-4.4)[c]	9.5 (8.5-10.5)	2.8 (1.3-4.3)[c]	15.5 (12.9-18.0)	8.6 (4.3-12.9)[c]
Men	1.0 (1.0-1.1)	9.1 (8.7-9.5)	6.8 (6.2-7.4)	10.4 (8.9-12.0)	8.1 (7.7-8.5)		5.8 (5.2-6.4)		9.4 (7.9-10.9)	
Schizophrenia Spectrum Disorder (F20-29)										
Women	0.6 (0.5-0.6)	2.4 (2.2-2.6)	9.9 (8.4-11.4)	6.8 (5.6-8.1)	1.9 (1.6-2.1)	-1.8 (-2.3;-1.4)[c]	9.4 (7.9-10.9)	-0.002 (-2.0;2.0)	6.3 (5.0-7.6)	-0.4 (-4.8;3.9)
Men	0.8 (0.8-0.8)	4.1 (3.8-4.4)	10.5 (9.5-11.5)	10.2 (8.3-12.1)	3.3 (3.0-3.5)		9.7 (8.7-10.7)		9.4 (7.5-11.2)	
Substance Use Disorder (F10-19)										
Women	2.1 (2.1-2.1)	16.1 (15.7-16.4)	4.0 (3.6-4.4)	8.1 (7.0-9.3)	14.0 (13.6-14.3)	-3.1 (-3.3;-2.8)[c]	1.9 (1.5-2.3)	-0.2 (-0.5;0.1)	6.0 (4.8-7.2)	-0.6 (-1.6;0.4)
Men	3.6 (3.5-3.6)	27.1 (26.6-27.6)	6.7 (6.0-7.4)	13.7 (11.7-15.6)	23.5 (23.0-24.0)		3.2 (2.5-3.8)		10.1 (8.2-12.1)	

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

a. Prevalence adjusted for birth year (5-year groups, from 1967 to 1997, with 1967-1973 as the reference)
b. Female sex as reference group
c. *P*<0.05 of the interaction between sex on an additive scale (RERI)
d. Medication: Lithium in the Norwegian Prescription Database (2004-2015)

Table S5. Genetic correlations between ADHD/ASD and different psychiatric comorbidities

Trait	Sample size (cases and controls)		Reference (PubMed ID)	Heritability (SE)	Intercept (SE)	Genetic correlation with ADHD			Genetic correlation with ASD			Difference between genetic correlations with ADHD and ASD
						r_g	SE	*P*-value	r_g	SE	*P*-value	*P*-value
ADHD	20,183	35,191	30478444	0.227(0.015)	1.03(0.01)	NA	NA	NA	0.36	0.051	1.24E-12	NA
ASD	18,381	27,969	30804558	0.194(0.017)	1.01(0.01)	0.360	0.051	1.24E-12	NA	NA	NA	NA
SCZ	36,989	113,075	25056061	0.236(0.009)	1.05(0.01)	0.127	0.036	4.00E-04	0.211	0.048	1.03E-05	0.161
Alcohol Dependence*	14,904	37,944	30482948	0.097(0.018)	1.02(0.01)	0.456	0.089	3.84E-07	0.058	0.0894	0.512	0.002
Ever_vs_never smoked*	41,969	32,066	20418890	0.075(0.007)	0.99(0.01)	0.494	0.062	2.15E-15	0.064	0.0634	0.309	1.34E-06
Bipolar Disorder	7,481	9,250	21926972	0.447(0.041)	1.01(0.01)	0.095	0.055	0.080	0.110	0.066	0.093	0.861
Major Depressive Disorder	135,458	344,901	29700475	0.189(0.012)	0.99(0.01)	0.424	0.033	7.38E-38	0.412	0.039	1.40E-25	0.814
Anxiety Disorders	7,016	14,745	26754954	0.077(0.029)	1.00(0.01)	0.301	0.131	0.022	0.260	0.137	0.057	0.829
Anti-social behavior**	Total sample=16,400		28979981	0.055(0.027)	0.98(0.01)	0.515	0.182	0.005	0.218	0.152	0.151	0.211
NEO-5-personality traits***	Total sample=17,375		21173776	0.104(0.033)	1.08(0.01)	-0.133	0.099	0.182	0.001	0.126	0.994	9.88E-17

Abbreviations: r_g: denotion of genetic correlation; SE: Standard Error; *P: P*-value

* proxy for substance use disorder (SUD)

**proxy for anti-social personality disorder

***NEO-5-personality traits; Neuroticism, Extraversion, Openness to experience, Agreeableness and Conscientiousness

Table S6. Prevalence ratios of psychiatric disorders in different sensitivity analyses comparing adults with and without ADHD, ASD or ADHD+ASD

Psychiatric disorder	Prevalence No. (%)				Prevalence ratios (95% CI)[a]		
	Remaining population	ADHD	ASD	ADHD+ASD	ADHD	ASD	ADHD+ASD
Mental retardation (F70-F79) is excluded							
Anxiety Disorders	81 215 (4.9)	8 303 (22.0)	950 (15.3)	284 (22.2)	4.3 (4.2-4.4)	3.9 (3.7-4.1)	5.0 (4.5-5.5)
Bipolar Disorder	14 427 (0.9)	2 562 (6.8)	174 (2.8)	74 (5.8)	7.9 (7.6-8.2)	4.9 (4.2-5.7)	8.7 (7.0-10.8)
Major Depressive Disorder	94 028 (5.7)	9 236 (24.5)	989 (15.9)	276 (21.6)	4.2 (4.1-4.3)	3.5 (3.4-3.7)	4.3 (3.9-4.7)
Personality Disorder	22 349 (1.4)	4 252 (11.3)	412 (6.6)	142 (11.1)	8.2 (7.9-8.5)	7.1 (6.5-7.8)	10.1 (8.7-11.7)
Schizophrenia Spectrum Disorder	10 985 (0.7)	1 199 (3.2)	455 (7.3)	92 (7.2)	4.8 (4.5-5.1)	16.5 (15.1-18.1)	13.9 (11.5-16.9)
Substance Use Disorder	46 734 (2.8)	8 709 (23.1)	348 (5.6)	150 (11.7)	7.8 (7.7-8.0)	2.4 (2.2-2.7)	4.5 (3.8-5.2)
Schizophrenia (F20-F29) is excluded							
Bipolar Disorder	12 862 (0.8)	2 345 (6.3)	179 (2.6)	62 (4.6)	8.2 (7.9-8.6)	5.1 (4.4-5.8)	7.9 (6.2-10.1)
Substance Use Disorder	42 979 (2.6)	8 009 (21.4)	268 (3.8)	125 (9.2)	7.9 (7.7-8.1)	1.8 (1.6-2.0)	(3.3-4.5)
SUD (F10-F19) is excluded							
Schizophrenia Spectrum Disorder	7 350 (0.5)	427 (1.4)	437 (6.1)	66 (5.1)	3.4 (3.1-3.8)	20.7 (18.9-22.8)	15.8 (12.5-20.0)
Psychiatric disorders registered at least twice in the NPR							
Anxiety Disorders	74 317 (4.5)	7 727 (20.0)	1 587 (21.1)	360 (24.5)	4.3 (4.2-4.4)	4.7 (4.5-4.9)	5.2 (4.8-5.7)
Bipolar Disorder	12 284 (0.7)	2 143 (5.6)	224 (3.0)	82 (5.6)	7.5 (7.2-7.9)	5.1 (4.4-5.8)	8.9 (7.2-11.0)
Major Depressive Disorder	89 763 (5.4)	8 675 (22.5)	1 462 (19.4)	342 (23.3)	4.1 (4.0-4.1)	3.6 (3.5-3.8)	4.3 (3.9-4.7)
Personality Disorder	20 246 (1.2)	3 724 (9.6)	429 (5.7)	142 (9.7)	7.7 (7.5-8.0)	5.8 (5.2-6.3)	8.9 (7.6-10.4)
Schizophrenia Spectrum Disorder	10 415 (0.6)	1 070 (3.8)	619 (8.2)	98 (6.7)	4.4 (4.2-4.7)	16.4 (15.1-17.7)	12.5 (10.3-15.1)
Substance Use Disorder	36 110 (2.2)	8 000 (20.7)	393 (5.2)	163 (11.1)	9.3 (9.1-9.5)	2.8 (2.5-3.1)	5.5 (4.8-6.4)

Abbreviations: CI: confidence interval

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

Table S7. Prevalence ratios of psychiatric disorders comparing adults with and without ADHD or ASD, using missing imputation for gestational age and sex-specific birth weight by gestational age z-scores

Psychiatric disorders	Crude prevalences, No. (%)				PR non-imputed model II, (95% CI)[a]				PR imputed model II, (95% CI)[a]		
	Remaining population	ADHD	ASD	ADHD+ASD	Remaining population	ADHD	ASD	ADHD+ASD	ADHD	ASD	ADHD+ASD
Anxiety Disorders	81 781 (5.0)	8 422 (21.8)	1 062 (14.2)	308 (21.0)	1 (ref)	4.0 (3.9-4.1)	3.1 (2.9-3.2)	4.2 (3.8-4.7)	4.0 (3.9-4.1)	3.0 (2.8-3.1)	4.1 (3.7-4.6)
Bipolar Disorder	14 629 (0.9)	2 595 (6.7)	239 (3.2)	92 (6.3)	1 (ref)	7.5 (7.1-7.8)	4.5 (3.9-5.1)	8.1 (6.6-10.0)	7.3 (7.0-7.6)	4.4 (3.9-5.0)	8.2 (6.7-10.0)
Major Depressive Disorder	94 538 (5.7)	9 361 (24.2)	1,075 (14.3)	293 (20.0)	1 (ref)	3.9 (3.8-4.0)	2.7 (2.6-2.9)	3.6 (3.2-4.0)	3.9 (3.8-3.9)	2.7 (2.5-2.8)	3.5 (3.2-3.9)
Personality Disorder	22 556 (1.4)	4 311 (11.2)	432 (5.7)	147 (10.0)	1 (ref)	7.2 (7.0-7.5)	4.9 (4.4-5.4)	7.4 (6.3-8.8)	7.1 (6.9-7.4)	4.8 (4.4-5.3)	7.2 (6.1-8.5)
Schizophrenia Spectrum Disorder	11 432 (0.7)	1 268 (3.3)	541 (7.2)	104 (7.1)	1 (ref)	4.7 (4.4-5.0)	12.6 (11.5-13.8)	12.3 (10.2-14.9)	4.6 (4.3-4.9)	11.7 (9.7-14.1)	10.1 (8.0-12.6)
Substance Use Disorder	47 061 (2.9)	8 850 (22.9)	372 (4.9)	163 (11.1)	1 (ref)	6.6 (6.5-6.8)	1.8 (1.6-2.0)	3.7 (3.2-4.3)	6.5 (6.4-6.7)	1.8 (1.6-1.9)	3.5 (3.0-4.1)

Abbreviations: PR: Prevalence ratio, CI: confidence interval

a. Model II: Adjusted for birth year, 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)

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