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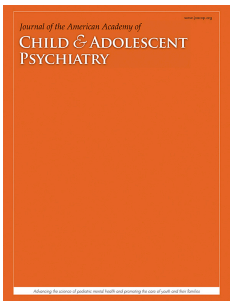

Gender Differences in Associations Between Attention-Deficit/Hyperactivity Disorder and Substance Use Disorder

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Gender Differences in Associations Between Attention-Deficit/Hyperactivity Disorder and Substance Use Disorder

RH: Gender Differences in ADHD With SUD

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ABSTRACT

Objective: To examine gender differences in the association between attention-deficit/hyperactivity disorder (ADHD) and substance use disorder (SUD), and to explore the impact of comorbid psychiatric conditions.

Method: This was a cohort study of all children born in Denmark in 1990-2003 (n=729,560). By record linkage across nationwide registers, we merged data on birth characteristics, socioeconomic status, familial psychiatric history, and diagnoses of ADHD, comorbidities, and SUD. Hazard ratios (HR) with 95% CIs were estimated by Cox regression and adjusted for a range of variables.

Results: ADHD increased the risk of alcohol abuse ($HR_{females}$=1.72 [1.42-2.08], HR_{males}=1.57 [1.37-1.79]), cannabis abuse ($HR_{females}$=2.72 [2.12-3.47], HR_{males}=2.24 [1.86-2.70]) and other illicit substance abuse ($HR_{females}$=2.05 [1.54-2.73], HR_{males}=2.42 [1.98-2.96]), compared to individuals without ADHD. In the overall estimates, no gender differences were found. Among individuals with ADHD without comorbidities, females had higher SUD risk than males, as did females with ADHD and conduct disorder (CD). Comorbid CD, depression, bipolar disorder, and schizophrenia further increased the risk of SUD in ADHD, compared to non-ADHD. Autism spectrum disorder in males with ADHD lowered the SUD risk.

Conclusion: ADHD increased the risk of all SUD outcomes. Individuals with ADHD without comorbidities were also at increased risk and some comorbid disorders further increased the risk. Females and males with ADHD had comparable risks of SUD, although females had higher risk of some SUDs than males. Females with ADHD may be perceived as less impaired than males, but they are at equally increased risk of SUD.

Key words: ADHD; substance abuse; alcohol abuse; gender

INTRODUCTION

Substance use disorders (SUD), including alcohol, cannabis, and illicit substance use, abuse, and dependence are often complicated by psychiatric conditions.[1,2] In individuals seeking treatment for SUD, attention-deficit/hyperactivity disorder (ADHD) is highly prevalent.[3,4] Similarly, childhood ADHD is commonly associated with an increased risk of developing SUD in adolescence and young adulthood.[5-13] Still, the majority of studies examining the association between ADHD and different types of SUD at different severity levels (use, abuse, or dependence) were based on either highly selected study populations or small sample sizes and only a few studies included females with ADHD.

The longest prospective follow-up study found that at a mean age of 31 years, individuals with ADHD (N=208) were 5 times more likely to have developed SUD than controls.[7] Females with ADHD had

much higher risks of SUD than males with ADHD, and comorbid conduct disorder (CD) in childhood significantly increased the risk further. The study only included 25 females with ADHD, and although no participants were lost to attrition during the long-term follow-up and the gender differences were statistically significant, estimates on SUD risks in females with ADHD had broad confidence intervals.

The Multimodal Treatment Study of children with ADHD found 2-fold increased rates of substance use in boys with ADHD, but not in girls with ADHD, compared to controls.[8]

A follow-up study of 208 children and adolescents with ADHD found a 1.5-fold increased risk of alcohol abuse and a 2.7-fold risk of drug use disorders at age 21 in ADHD, compared to controls.[9] When adjusted for the effect of comorbid CD, ADHD still predicted drug use disorders but no longer alcohol abuse. The study included 96 girls and 112 boys with ADHD and found no interaction with gender on risk of SUD. However, significantly more females than males with ADHD from the original sample were lost to follow-up.

A large population-based study found strong associations between ADHD and later SUD.[6] However, the study did not report specific risks of SUD in females with ADHD, and although the study used Cox regression in some sub-analyses, simple descriptive and unadjusted analyses of the prevalence of SUD were applied, which did not account for the large differences in the time of follow-up of individuals (time at risk) or confounding effects.

A meta-analysis from 2011 of thirteen prospective studies of childhood ADHD published between 1984 and 2007 found a 1.4-fold increased risk for alcohol use disorder in young adulthood.[14] Another meta-analysis also from 2011 included 27 prospective studies and found childhood ADHD to be associated with a 2–3-fold increased risk of alcohol abuse/dependence, cannabis use and abuse/dependence, and cocaine abuse/dependence.[15] The meta-analysis found moderately consistent evidence for effects of comorbid oppositional defiant disorder (ODD)/CD and concluded that such comorbid problems likely increase the risk of SUD, which is consistent with results from two recent prospective follow-up studies.[6,7] To further examine effects of ODD/CD, a meta-analysis from 2013 included 15 studies of individuals with ADHD assessed for ODD/CD and found that ADHD itself was not associated with an increased risk of SUD when controlling for the effect of comorbid CD.[16]

None of these meta-analyses calculated specific estimates for the risk of SUD in females with ADHD, and in general, few studies have examined the outcome of females with ADHD. Nonetheless, some follow-up studies have suggested that females with ADHD may have higher risks of adverse outcomes than

males with ADHD, such as a higher risk of SUD,[7] developing more severe psychiatric disorders,[17] including schizophrenia,[18] and increased mortality.[19]

Several mechanisms might confer the increased risk for SUD in ADHD. Neurobiological models point towards an imbalance in the dopaminergic neurotransmission, and dysfunctional circuitries in ventrolateral and dorsolateral prefrontal cortex, and basal ganglia regions, in both disorders.[20-23] Self-medication for ADHD symptoms or higher perceived benefits of drug use on response inhibition in individuals with ADHD compared to in individuals without ADHD may also be possible explanations.[24] Common environmental and genetically influenced risk factors for both disorders, such as low socioeconomic status (SES),[25-27] parental alcohol abuse or other SUD,[28-30] and family history of psychiatric disorders,[31-33] could also explain the association.

Hence, this prospective cohort study aims to examine the gender differences in the association between ADHD and alcohol, cannabis, and other illicit substance use, abuse, and dependence, adjusted for the effect of comorbidities, SES, and family history of psychiatric disorders and SUD, accessing nationwide health registers.

METHOD

Data Sources and Study Population

This register-based, prospective cohort study used data derived from the Danish Civil Registration System (CRS),[34] the Danish Medical Birth Register (MBR),[35] the Integrated Database for Labour Market Research (IDA),[36] the Danish Psychiatric Central Research Register (DPCRR),[37] and the Danish National Patient Register (DNPR).[38] Using CRS we identified all children born in Denmark to Danish-born parents between 1990 and 2003 (n=729,560) and identified their parents and siblings. All individuals born in Denmark are assigned a unique identification number (the CPR number) at birth. This identification number was used to identify individuals across registers and obtain and accurately merge information from the five registers. We obtained data on birth weight, 5 minute APGAR score, gestational age, maternal and paternal age, paternal income, maternal level of education (at the time the child was born), and psychiatric diagnoses in participants, parents, siblings, and half-siblings. Data on psychiatric diagnoses and SUD were treated as time-dependent variables.

In Denmark, the *International Classification of Diseases – Eighth Revision (ICD-8)* was used until 1994, after which the tenth revision (*ICD-10*) was used.[39] Psychiatric diagnoses in the registers only include

those made by psychiatrists at hospital departments. We identified diagnoses of ADHD in participants, parents and siblings (*ICD-8*: 308.01 and *ICD-10:* F90, F98.8), thereby including diagnoses equivalent to all ADHD subtypes. For the main analyses, we collapsed SUD outcomes according to three most prevalent types of substances[40] into three groups: alcohol (*ICD-10*: F10), cannabis (*ICD-10*: F12), and other illicit substances (*ICD-10*: F11, 13-16, and 18-19). For additional analyses we divided SUD into three severity groups: use (*ICD-10*: F1x.0), abuse (*ICD-10*: F1x.1, F1x.8 and F1x.9), and dependence (*ICD-10*: F1x.2, F1x.3, F1x.4, F1x.5, F1x.6, and F1x.7). Nicotine was not included in any of these analyses, as its prevalence is highly underestimated in the registers.

All children were followed from the date of their fifth birthday until they received a diagnosis of SUD or were censored on the date of death, emigration, or end of follow-up on December 31, 2012, whichever came first. Children who received a diagnosis of ADHD before age 3 or an SUD diagnosis before the age of 5 were excluded.

Comorbid psychiatric disorders (ASD, mental retardation, depression, ODD/CD, anxiety, tic, bipolar, eating disorder, and personality disorder, and schizophrenia spectrum disorder [in the following termed schizophrenia]) were classified according to *ICD-8* and *ICD-10* (see Table S1, available online).

Statistical Analyses

We calculated crude incidence rates of SUD in the total cohort for covariates by Poisson regression (see Table S2, available online). Cox regression was used to estimate the gender-specific hazard ratios (HRs) and 95% CIs for each of the three subgroups of SUD, in females and males with ADHD, compared to females and males without ADHD, respectively.

In the overall analyses, four adjustment models were applied. Crude analyses were adjusted for calendar time. Model 1 was adjusted for calendar time, maternal educational level, paternal income level, maternal and paternal age, Apgar score, birth weight, and gestational age. Model 2 was adjusted for the covariates in Model 1 and in addition the history of psychiatric disorders, in the mother, father, siblings and half-siblings. Model 3 was adjusted for the covariates in Model 2 and in addition comorbid CD, ODD, depression, anxiety disorder, ASD, tic disorder, mental retardation, bipolar disorder, schizophrenia spectrum disorder, personality disorders, and eating disorders.

RESULTS

We identified 729,560 children born between 1990 and 2003. We excluded 16,167 children (2.2%) due to missing information on one or more covariates (n=13,998), diagnosis of ADHD before the age of 3 (n=218), diagnosis of any kind of substance abuse before age of 5 (n=152), or loss to follow-up due to death or emigration before entry to the study (n=1,799), leaving us with a total of 717,501 children in the study cohort (51% male). Included individuals contributed with more than 8 million person years of follow-up for SUD outcomes, and individuals in the study cohort were followed for a mean period of 13.3 years (SD=4.4) from their 5th birthday.

Within the study cohort, we identified 19,645 individuals with ADHD. Of these, 5,144 (26.2%) were females. The mean age of ADHD diagnosis was 13.02 years (SD=4.4) for females and 11.03 years (SD=4.11) for males. The most prevalent comorbidities among females with ADHD were anxiety disorder (13.6%), ODD/CD (13.1%) and ASD (11.7%), whereas the most prevalent comorbidities among males with ADHD were ASD (19.3%), ODD/CD (18.4%), and mental retardation (9.8%). For distribution of variables within the study cohort, stratified on gender and ADHD status, see Table S3, available online.

ADHD and Gender Differences in Risk of SUD

Within the entire study cohort, the IRs per 10,000 person years were 11.3 for alcohol abuse, 2.6 for cannabis abuse, and 2.3 for abuse of other illicit substances. In individuals with ADHD, the IR's were 44.3 for alcohol abuse, 25.0 for cannabis abuse, and 28.7 for abuse of other illicit substances. The risks of the three types of SUD in females and males with ADHD are shown in Table 1.

(Insert Table 1 about here)

ADHD significantly increased the risk of all three types of SUD, in both males and females, compared to individuals without ADHD. In females with ADHD, the highest increased risk was for cannabis abuse (HR=2.72 [2.12-3.47]), whereas in males with ADHD, the highest increased risk was for abuse of other illicit substances (HR=2.42 [1.98-2.96]), compared to females and males without ADHD, respectively.

No gender differences were identified in the fully adjusted analyses (Model 3) of increased risks of any of the three SUDs in individuals with ADHD, compared to individuals without ADHD. However, in analyses not adjusted for the effect of comorbid psychiatric disorders (Model 2), females with ADHD had significantly higher risks of alcohol (p=.005) and cannabis abuse (p <.0001) than males with ADHD when compared to individuals of the same gender without ADHD.

The Effect of Comorbid Conditions on Risk of SUD

Both females and males with ADHD who had not been diagnosed with any of the ten different comorbid psychiatric disorders had increased risks of alcohol (HRs 2.6 and 1.81, in females and males) and cannabis (HRs 7.15 and 4.20) and other illicit substances abuse (HRs 4.79 and 4.10) compared to female and male controls without any of these psychiatric disorders (see Table 2).

(Insert Table 2 about here)

Some of the ten comorbid disorders increased the risk of SUD further in individuals with ADHD. In females, comorbid bipolar disorder further increased the risk of alcohol, cannabis, and other illicit substance abuse (all p<.005). Having comorbid ODD/CD or schizophrenia resulted in a higher risk of all three types of SUD, in both females and males (p<0.005). Comorbid depression also added significantly to the risk of cannabis abuse in females and males with ADHD, compared to pure ADHD (p<.05). Interestingly, males with ADHD and ASD had a significantly lower risk of all three types of SUD than males with the pure ADHD (p<.005). In fact, males with ADHD and ASD only had an increased risk of cannabis abuse when compared to individuals without these psychiatric disorders, not an increased risk of alcohol or other illicit substance abuse.

Gender Differences in Effects of Comorbid Disorders

In individuals with the more pure ADHD (without any of the comorbidities), females had significantly higher risk of alcohol abuse (p=.01) and cannabis abuse (p=.01) than males. In those with ADHD and ODD/CD, females also had significantly higher risk of cannabis abuse (p=.017). In none of the comorbid conditions did males with ADHD have significantly higher risk of SUD than females with ADHD.

Use, Abuse, and Dependence

In the fully adjusted analyses individuals with ADHD had a 1.5- to 2.6-fold increased risk of use, abuse, and dependence of substances, compared to individuals without ADHD. We found no gender differences in these estimated risks when adjusted for the effect of comorbidities (see Table 3).

(Insert Table 3 about here)

DISCUSSION

This nationwide, prospective, population-based cohort study found that, compared to individuals without mental disorders, children and adolescents with ADHD (n=20,333) had 1.57- to 2.72-fold increased risks of different types of SUDs. Importantly, we found very few gender differences in the association between ADHD and SUD compared to individuals of the same gender without ADHD and when adjusting

estimates for effects of potential confounders, including other psychiatric disorders. Although females with ADHD in the crude and partially adjusted models did have significantly higher risk of SUD than males with ADHD, this was mainly explained by differences in comorbidities, as no statistically significant gender differences were found in the fully adjusted analyses. However, some gender differences were found in sub-analyses of groups of individuals with and without different comorbid disorders. Among individuals without comorbidities, with the more pure ADHD, females had higher risk of alcohol and cannabis abuse, compared to males, and among those with ADHD and comorbid ODD/CD, females also had higher risk of cannabis abuse than males. In none of our analyses did males with ADHD have higher risk of SUD than females with ADHD.

Risk of SUD in ADHD

The finding of an increased risk of SUD in ADHD is not surprising but consistent with many previous follow-up studies[5-9,12,13] and two meta-analyses.[14,15] The largest meta-analysis of 27 studies included more than 4,000 individuals with ADHD and almost 7,000 controls and estimated that individuals with ADHD had a 1.7-fold increased risk of alcohol abuse, 2.8-fold increased risk of cannabis abuse, and a 2.6-fold increased risk of other illicit drugs. Our findings among almost 20,000 individuals with ADHD and 700,000 controls are very much in line with these estimates (alcohol abuse: HR 1.6-1.7; cannabis abuse: HR 2.2-2.7; other Illicit drugs: HR 2.1-2.4). Comparing the results from the three adjustment models, accounting for family history of psychiatric disorders (in mothers, fathers, siblings, and half-siblings) only had small effects on the associations between ADHD and SUD, with slightly lower HRs (Model 2 compared to Model 1). However, adjusting for the effect of comorbid disorders in the individual with ADHD had much stronger effects, and HRs were significantly lowered (Model 3).

Effects of Comorbidities on SUD Risk

We also found that even individuals with a more pure ADHD, who did not have any of the ten examined comorbid disorders, were at significantly increased risk of SUD. This contrasts findings from a meta-analysis of 15 studies including 1,000 participants (ADHD and controls), which found that individuals with ADHD without comorbid ODD/CD were not at increased risk of SUD.[16] However, compared to the meta-analysis, our study was better powered to assess the effects of comorbid ODD/CD and estimated the fully adjusted risk of SUD in individuals without such comorbidity. In our study, ODD/CD was the only comorbid disorder to further add to the increased risk of all three types of SUD, in both females and males with ADHD,

which, consistent with previous studies, suggests that ODD/CD is indeed a very important predictor of SUD in individuals with ADHD,[41] as it predicts many other adverse outcomes in ADHD.[17,19,42,43] Only a few of the other comorbid conditions increased the risk of SUD further, including schizophrenia, bipolar disorder, and personality disorders, all well-known for their increased risk of SUD.[44-47] Our finding of comorbid ASD actually reducing the risk of SUD in males with ADHD is consistent with a previous study.[6] Individuals with ADHD and ASD may be in closer contact with clinicians, treatment facilities, and other professionals and hence signs of risky behavior may be identified earlier. Children with ADHD and comorbid ASD may also be less likely to interact with peers with SUD than those with ADHD and other comorbidities.

Gender Differences in Association Between ADHD and SUD

Few previous studies have examined gender differences in the association between ADHD and SUD. We found that among individuals with ADHD without comorbidities and among those with ADHD and comorbid ODD/CD, females had higher risk of some SUDs, compared to the corresponding males with ADHD. However, in our overall analyses, we found no gender differences, and males with ADHD did not have a significantly increased risk of SUD compared to females with ADHD in any of our analyses. Neither did we find gender differences in the risk of the severity of SUD, as females and males with ADHD had a 1.5- to 2.6-fold increased risk of use, abuse, and dependence of alcohol, cannabis, and other illicit substances.

Females and males with ADHD can have different patterns of comorbid conditions,[48] and although females with ADHD are often perceived as less impaired than males with ADHD,[49] females have been found to be at higher risk of some adverse outcomes, with higher risk of developing schizophrenia,[18] admission to an in-patient psychiatric department in adulthood,[17] and also increased mortality, compared to males with ADHD.[19] In addition, females tend to be diagnosed with ADHD at an older age than males,[50] and among children diagnosed with ADHD, females are less likely to receive pharmacological treatment, compared to males with ADHD.[51] Stimulant treatment of ADHD may also reduce the risk of developing SUD,[7,52] and earlier onset of treatment seems to be a protective factor.[6,7]

We studied a nationwide population-based cohort including all children born in Denmark between 1990 and 2003, with almost complete follow-up data for up to 22 years. Thus, bias in selection of study population and non-differentiated attrition during follow-up are unlikely explanations of our findings. The extensive Danish registers provide detailed information about birth characteristics, SES, familial history of psychiatric disorders and psychiatric disorders of the child itself, which enabled adjustment for these possible

confounders and also follow-up of exposure and outcomes over the course of time, by applying time-dependent variables in a time to event model. However, our study also has limitations. Diagnoses in the registers are clinical diagnoses, not the result of systematic, well-described uniform assessments. The validity of the clinical ADHD diagnoses in the registers all obtained from public hospital departments has previously been shown to be high,[53,54] and diagnostic and treatment practices in Denmark are conservative compared to many other countries.[55-57] We only included children diagnosed with ADHD at a hospital department, and these individuals may have more impairing ADHD than those diagnosed by child and adolescent psychiatrists in private practices, and our results may not be generalizable to those. Prevalence of comorbid disorders were lower than in some other studies, and this may be due to underreporting of comorbidities in the registers. This may have biased our results, as comorbidities of moderate to severe severity may more likely have been diagnosed as compared to less severe or less impairing comorbid conditions. In addition, we were not able to include use of nicotine in individuals with ADHD, and the estimated risk of SUD may have been underestimated due to this. The selection of cohorts for our study means that the risk of SUD after the age of 23 was not estimated.

In conclusion, ADHD was associated with an increased risk of alcohol, cannabis, and other illicit substance abuse in both females and males and with very few gender differences. Compared to individuals without psychiatric disorders, those with ADHD who have no comorbid psychiatric disorders were also at increased risk of abuse of alcohol, cannabis, and other illicit substances and some comorbid disorders further increased the risk. Females and males with ADHD had comparable risks of SUD, although females had higher risk of some SUDs. The study has important clinical implications as females with ADHD may be perceived as less impaired than males, but they are at equally increased risk of SUD.

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Table 1. Incidence Rates (IR), Crude and Adjusted Hazard Ratios (HR) for Alcohol Abuse, Cannabis Abuse and Abuse of Other Illicit Substances in Children With Attention-Deficit/Hyperactivity Disorder (ADHD; n=20,332), Compared to Individuals Without ADHD, in a Nationwide Cohort of all Children Born in Denmark 1990 to 2003 (n=729,560)

	Among Children With ADHD, IR	Among Children Without ADHD, IR	Crude Analyses, HR (95% CI)[a]	Model 1, HR (95% CI)[b]	Model 2, HR (95% CI)[c]	Model 3, HR (95% CI)[d]
Alcohol						
Females[e]	45.34	10.10	3.45 (2.89-4.11)	2.87 (2.40-3.43)	2.48 (2.07-2.97)	1.72 (1.42-2.08)
Males[f]	30.08	11.21	2.34 (2.08-2.63)	2.03 (1.80-2.29)	1.83 (1.62-2.06)	1.57 (1.37-1.79)
Gender difference	-	-	P < .0001	p=.002	p=.005	p=0.403
Cannabis						
Females	27.56	1.57	11.44 (9.16-14.29)	8.35 (6.65-10.50)	6.58 (5.22-8.29)	2.72 (2.12-3.47)
Males	28.59	2.24	5.60 (4.80-6.53)	4.32 (3.69-5.06)	3.61 (3.08-4.24)	2.24 (1.86-2.70)
Gender difference	-	-	p <.0001	p <.0001	p <.0001	p=0.186
Other illicit substances						
Females	23.54	1.40	9.75 (7.52-12.64)	6.89 (5.29-8.98)	5.40 (4.13-7.06)	2.05 (1.54-2.73)
Males	22.40	1.97	6.71 (5.72-7.88)	4.92 (4.17-5.80)	4.04 (3.42-4.78)	2.42 (1.98-2.96)
Gender difference	-	-	p=.016	p=.033	p=.067	p=0.305

Note: All estimates are significant with p-values <.05.
[a] Crude analyses, adjusted for calendar time.
[b] Model 1, adjusted for calendar time, maternal educational level, paternal income level, maternal and paternal age, Apgar score, birth weight and gestational age.
[c] Model 2, adjusted for the covariates in Model 1 and in addition the history of psychiatric disorders, in the mother, father, siblings and half-siblings
[d] Model 3, adjusted for the covariates in Model 2 and in addition for comorbid conduct disorder, oppositional defiant disorder, depression, anxiety disorder, autism spectrum disorder, tic disorder, mental retardation, bipolar disorder, schizophrenia spectrum disorder, schizophrenia, personality disorders and eating disorders.
[e] Compared to females without ADHD.
[f] Compared to males without ADHD.

Table 2. Fully Adjusted Hazard Ratios for Alcohol Abuse, Cannabis Abuse and Abuse of Other Illicit Substances for Children With Attention-Deficit/Hyperactivity Disorder (ADHD) and Comorbid Psychiatric Conditions Compared to Individuals With no Psychiatric Disorders

	Alcohol Abuse HR (95% CI)	Cannabis Abuse HR(95% CI)	Other Substances HR(95% CI)
ADHD			
Females	2.61 (2.05-3.33)	7.15 (5.07-10.09)	4.79 (3.16-7.26)
Males	1.81 (1.54-2.14)	4.20 (3.36-5.24)	4.10 (3.24-5.21)
Gender difference	p=.01	p=.01	p=.52
ADHD + Anxiety			
Females	2.05 (1.15-3.64)	8.47 (4.54-15.80)	2.55 (0.98-6.66)
Males	2.24 (1.50-3.34)	4.57 (2.73-7.64)	4.93 (2.89-8.40)
Gender difference	p=.807	p=.133	p=.240
ADHD + Autism			
Females	1.06 (0.39-2.87)	2.95 (0.72-12.09)	---
Males	1.14 (0.77-1.68)*	2.33 (1.38-3.95)*	1.38 (0.69-2.75)*
Gender difference	p=.897	p=.761	p=.000
ADHD + Bipolar disorder			
Females	17.07 (6.16-47.28)*	45.71 (14.24-146.73)*	25.88 (6.01-111.50)*
Males	5.34 (1.97-14.46)*	---	7.30 (1.79-29.70)
Gender difference	p=.110	p=.000	p=.221
ADHD + Conduct Disorder			
Females	2.83 (1.78-4.48)	14.51 (8.98-23.45)*	11.84 (6.98-21.01)*
Males	2.41 (1.92-3.02)*	7.48 (5.17-9.79)*	9.19 (7.06-11.96)*
Gender difference	p=.54	p=.017	p=.400
ADHD + Depression			
Females	3.01 (1.85-4.91)	15.18 (9.29-24,81)*	4.85 (2.40-9.81)
Males	3.22 (2.00-5.25)*	10.35 (6.38-16.78)*	4.69 (2.48-8,87)
Gender difference	p=.846	p=.273	p=.943
ADHD + Eating disorder			
Females	3.57 (1.70-7.50)	3.89 (1.17-12.88)	9.64 (3.85-24,10)
Males	1.00 (0.14-7.20)	8.26 (2.02-33.84)	8.49 (2.04-35.28)
Gender difference	p=0.237	p=0.424	p=0.887
ADHD + Mental retardation			
Females	2.21 (1.22-4.01)	3.52 (1.39-8.91)	5.82 (2.72-12.45)
Males	1.44 (0.95-2.18)	2.30 (1.28-4.11)*	3.33 (1.98-5.57)
Gender difference	p=.248	p=.446	p=.231
ADHD + Personality disorders			
Females	2.56 (1.48-4.42)	11.44 (6.70-19.51)	12.16 (6.90-21.45)*
Males	3.12 (1.74-5.60)	10.93 (6.40-18.67)*	9.70 (5.38-1.49)*
Gender difference	p=.626	p=.906	p=.586
ADHD + Schizophrenia			
Females	6.27 (3.34-11.77)*	12.71 (5.71-28.28)	12.94 (5.75-29.14)*
Males	3.69 (2.00-6.78)*	16,27 (8.96-29,53)*	15.92 (8.43-30.05)*
Gender difference	p=.236	p=.627	p=.694
ADHD + Tic disorder			
Females	3.07 (1.24-7.59)	7.31 (2.24-23,86)	6.09 (1.76-21.06)
Males	1.39 (0.86-2.26)	2.29 (1.11-4.72)	3.23 (1.68-6.21)
Gender difference	p=.132	p=.101	p=.374

Note: The analyses for each comorbid condition are adjusted for the effect of other psychiatric comorbid conditions.
*Significantly different from ADHD alone (p<.05)

Table 3. Estimated Crude and Adjusted Hazard Ratios for Use, Abuse, and Dependence of Alcohol and Illicit Substances in Children With Attention-Deficit/Hyperactivity Disorder (ADHD; n=20,332) in a Nationwide Cohort of all Children Born in Denmark 1990 to 2003 (n=717,501)

	Crude Analyses, HR (95% CI)[a]	Model 1, HR (95% CI)[b]	Model 2, HR (95% CI)[c]	Model 3, HR (95% CI)[d]
Use				
Females [e]	3.44 (2.87-4.11)	2.89 (2.40-3.47)	2.50 (2.08-3.01)	1.76 (1.45-2.13)
Males[f]	2.22 (1.96-2.52)	1.93 (1.70-2.19)	1.74 (1.53-1.98)	1.46 (1.27-1.69)
Gender difference	0.000	0.000	0.001	0.111
Abuse				
Females	7.87 (6.14-10.08)	5.85 (4.55-7.53)	4.83 (3.74-6.23)	1.98 (1.51-2.59)
Males	5.62 (4.80-6.57)	4.38 (3.73-5.14)	3.78 (3.21-4.44)	2.29 (1.88-2.77)
Gender difference	0.024	0.055	0.106	0.349
Dependence				
Females	11.20 (9.03-13.87)	8.12 (6.51-10.11)	6.29 (5.03-7.86)	2.40 (1.90-3.04)
Males	6.42 (5.59-7.37)	4.80 (4.16-5.53)	3.97 (3.43-4.58)	2.61 (2.21-3.09)
Gender difference	0.000	0.000	0.001	0.540

Note: All estimates are significant with p-values <.05.
[a] Crude analyses, adjusted for calendar time.
[b] Model 1, adjusted for calendar time, maternal educational level, paternal income level, maternal and paternal age, Apgar score, birth weight and gestational age.
[c] Model 2, adjusted for the covariates in Model 1 and in addition the history of psychiatric disorders, in the mother, father, siblings and half-siblings.
[d] Model 3, adjusted for the covariates in Model 2 and in addition for comorbid conduct disorder, oppositional defiant disorder, depression, anxiety disorder, autism spectrum disorder, tic disorder, mental retardation, bipolar disorder, schizophrenia spectrum disorder, schizophrenia, personality disorders and eating disorders.
[e] Compared to females without ADHD.
[f] Compared to males without ADHD.

Table S1: Classification of Comorbid Psychiatric Disorders of the Child According to *International Classification of Diseases, Eighth Revision (ICD-8)* and *Tenth Revision (ICD-10)*

	ICD-8	*ICD-10*
Anxiety disorder	300.09, 300.19, 300.29	F40-F42, F93
Autism spectrum disorder	299.00, 299.01, 299.02, 299.03	F84 (excl. F84.2-F84.4)
Bipolar disorder	296.19, 296.39, 298.19	F30-F31
Depression	296.09, 296.29, 298.09, 300.49	F32, F33, F92.0
Eating disorders	305.60, 306.50, 306.58, 306.59	F50
Mental retardation	311, 312, 313, 314, 315	F70-F79
Oppositional defiant disorder/conduct disorder	308.03, 308.04, 308.05, 308.06	F90.1, F91
Personality disorders	301.x9 (excl. 301.19), 301.80, 301.81, 301.82, 301.84	F60
Schizophrenia spectrum disorder	295.x9, 296.89, 297.x9, 298.29-298.99, 299.04, 299.05, 299.09, 301.83	F20-F29
Tic disorder	306.29	F95

Table S2: Incidence Rates (IR) of Substance Abuse in Different Groups of the Total Cohort

Variable	IR per 10,000 person years		
	Alcohol	Cannabis	Other illicit substances
Gender			
Male	11.95	1.98	1.75
Female	10.66	3.27	2.76
Calendar time			
1995-2004	0.82	0.03	0.06
2005-2009	13.43	1.72	1.97
2010-2012	21.25	7.27	5.44
Birth weight (g)			
<1,500	12.02	2.93	3.19
1,500-2,499	14.46	3.43	3.30
2,500-2,999	13.37	3.93	3.34
3,000-3,999	11.26	2.54	2.23
≥4,000	9.91	2.19	1.66
Gestational age at birth (weeks)			
<33	11.81	2.82	2.67
33-36.9	11.59	2.62	2.66
37-41.9	11.26	2.63	2.23
42-50	11.25	2.60	2.02
Apgar score (5 minutes after birth)			
1-9	10.88	3.10	2.60
10	11.37	2.62	2.25
Paternal age at birth (years)			
<20	23.54	10.97	10.00
20-24	18.30	5.58	5.15

25-29	11.83	2.72	2.45
30-34	10.01	2.03	1.84
35-39	9.23	2.14	1.38
40-44	10.90	2.60	1.77
≥45	13.48	2.51	2.03
Maternal age at birth (years)			
<20	25.63	9.25	9.62
20-24	16.63	4.76	4.13
25-29	11.06	2.33	2.15
30-34	9.02	1.94	1.45
35-39	9.04	1.74	1.19
40-44	7.71	1.48	1.05
≥45	0.00	0.00	0.00
Paternal level of income (quintiles)			
1st (lowest)	18.24	5.40	4.94
2nd	13.06	2.71	2.50
3rd	10.05	2.01	1.44
4th	7.27	1.64	1.13
5th	5.97	0.83	0.72
Maternal level of education			
No high school diploma	18.45	5.36	5.00
High school diploma	9.70	1.98	1.61
Some college education	7.54	1.31	0.84
Degree from 4-year college or more	6.19	0.57	0.44
Maternal history of psychiatric illness			
None	10.42	2.20	1.90
Any psychiatric disorder	23.50	8.67	7.22
ADHD	39.73	13.13	11.79
Maternal history of SUD			
None	10.72	2.39	2.03
SUD	35.26	11.38	11.86
Paternal history of psychiatric illness			
None	10.50	2.28	1.95
Any psychiatric disorder	26.53	9.27	7.94
ADHD	37.95	17.74	23.02
Paternal history of SUD			
None	10.42	2.25	1.88
SUD	28.96	10.36	9.76
Siblings' history of psychiatric illness			
None	10.62	2.33	2.00
Any psychiatric disorder	30.91	10.80	8.97
ADHD	25.85	10.85	9.88
Siblings' history of SUD			
None	10.88	2.50	2.13
SUD	56.20	17.55	16.67
Half-siblings' history of psychiatric illness			
None	10.67	2.31	1.98
Any psychiatric disorder	30.24	11.47	10.14
ADHD	32.21	16.24	13.62
Half-siblings' history of SUD			
None	10.92	2.37	2.00
SUD	35.81	11.28	12.33

Note: ADHD = attention-deficit/hyperactivity disorder; SUD = substance use disorder.

Table S3: Distribution of Variables Within the Study Cohort, Stratified on Gender and Attention-Deficit/Hyperactivity Disorder (ADHD) Status

	Females		Males	
	Without ADHD, n (%)	With ADHD n (%)	Without ADHD n (%)	With ADHD n (%)
Birth weight (g)				
<1,500	1,675 (0.48)	56 (1.09)	1,539 (0.43)	147 (1.02)
1,500-2,499	10,839 (3.12)	244 (4.77)	9,672 (2.71)	690 (4.79)
2,500-2,999	40,948 (11.80)	775 (15.15)	30,402 (8.52)	1,692 (11.75)
3,000-3,999	238,044 (68.59)	3,387 (66.22)	228,663 (64.05)	8,894 (61.76)
≥4,000	55,532 (16.00)	653 (12.77)	86,718 (24.29)	2,978 (20.68)
Gestational age at birth (weeks)				
<33	2,559 (0.74)	68 (1.33)	3,014 (0.85)	235 (1.64)
33-36.9	11,612 (3.35)	244 (4.78)	13,931 (3.91)	843 (5.87)
37-41.9	301,784 (87.16)	4,382 (85.80)	306,304 (86.98)	12,074 (84.13)
42-50	30,267 (8.74)	413 (8.09)	33,009 (9.27)	1,200 (8.36)
Apgar score (5 minutes after birth)				
1-9	22,825 (6.59)	405 (7.95)	28,666 (8.05)	1,390 (9.68)
10	323,293 (93.41)	4,687 (92.05)	327,397 (91.95)	12,970 (90.32)
Paternal age at birth (years)				
<20	1,674 (0.48)	72 (1.40)	1,595 (0.44)	157 (1.08)
20-24	25,967 (7.44)	744 (14.46)	26,281 (7.32)	1,946 (13.42)
25-29	107,228 (30.74)	1,739 (33.81)	109,808 (30.60)	4,690 (32.34)
30-34	124,526 (35.70)	1,468 (28.54)	128,873 (35.91)	4,515 (31.14)
35-39	62,625 (17.95)	762 (14.81)	64,742 (18.04)	2,165 (14.93)
40-44	19,399 (5.56)	239 (4.65)	20,049 (5.59)	731 (5.04)
≥45	7,438 (2.13)	120 (2.33)	7,541 (2.10)	297 (5.05)
Maternal age at birth (years)				
<20	5,325 (1.53)	237 (4.61)	5,357 (1.49)	574 (3.96)
20-24	50,682 (14.53)	1,282 (24.92)	51,209 (14.27)	3,339 (23.03)
25-29	139,265 (39.92)	1,946 (37.83)	143,602 (40.01)	5,552 (38.29)
30-34	111,023 (31.82)	1,212 (23.56)	114,652 (31.95)	3,648 (26.16)
35-39	37,774 (10.83)	399 (7.76)	39,233 (10.93)	1,211 (8.35)
40-44	4,696 (1.35)	66 (1.28)	4,744 (1.32)	176 (1.21)
≥45	92 (0.03)	2 (0.04)	92 (0.03)	1 (0.01)
Paternal income (quintiles)				
1st (lowest)	69,166 (19.84)	1,690 (32.87)	70,108 (19.54)	4,314 (29.76)
2nd	69,768 (20.01)	1,158 (22.52)	71,177 (19,84)	3,394 (23.42)

3rd	69,898 (20.05)	938 (19.25)	71,985 (20.07)	2,739 (18.90)
4th	69,807 (20.02)	768 (14.94)	72,586 (20.24)	2,314 (15.97)
5th	70,039 (20.09)	587 (11.42)	72,858 (20.31)	1,733 (11.96)
Maternal level of education				
No high school diploma	81,549 (23.45)	2,254 (44.20)	82,740 (23.13)	5,832 (40.47)
High school diploma	164,447 (47.29)	2098 (14.14)	168,849 (47.20)	6,187 (42.94)
Some college education	82,653 (23.77)	651 (12.76)	86,346 (24.14)	2,096 (14.55)
Degree, +3-year college	19,062 (5.48)	97 (1.90)	19,810 (5.54)	295 (2.05)
Maternal history of psychiatric illness				
None	316,270 (90.66)	3,968 (77.14)	326,539 (90.99)	11,700 (80.68)
Any psychiatric disorder	31,820 (9.12)	981 (19.07)	31,556 (8.79)	2,408 (16.61)
ADHD	767 (0.22)	195 (3.79)	794 (0.22)	393 (2.71)
Maternal history of SUD				
None	335,706 (96.33)	4,659 (90.57)	345,512 (96.27)	13,392 (92.35)
SUD	13,151 (3.77)	485 (9.43)	13,377 (3.73)	1,109 (7.65)
Paternal history of psychiatric illness				
None	325,585 (93.33)	4,296 (83.51)	335,383 (93.45)	12,499 (86.19)
Any psychiatric disorder	22,354 (6.41)	711 (13.82)	22,672 (6.32)	1,702 (11.74)
ADHD	918 (0.26)	137 (2.66)	834 (0.23)	300 (2.07)
Paternal history of SUD				
None	326,654 (93.64)	4,428 (86.08)	336,894 (93.87)	12,700 (87.58)
SUD	22,203 (6.36)	716 (13.92)	21,995 (6.13)	1,801 (12.42)
Siblings' history of psychiatric illness				
None	322,508 (92.45)	4,208 (78.30)	332,523 (92.65)	11,819 (81.50)
Any psychiatric disorder	18,708 (5.36)	474 (9.21)	19,178 (15.34)	1,155 (7.96)
ADHD	7,641 (2.19)	642 (12.48)	7,188 (2.00)	1,527 (10.53)
Siblings' history of SUD				
None	340,794 (97.69)	4,952 (96.27)	350,595 (97.69)	14,022 (96.70)
SUD	8,063 (2.31)	192 (3.73)	8,294 (2.31)	479 (3.30)
Half-siblings' history of psychiatric illness				
None	329,358 (94.41)	4,330 (84.18)	339,494 (94.60)	12,625 (87.06)
Any psychiatric disorder	14,285 (4.09)	468 (9.10)	14,321 (3.99)	1,057 (7.29)
ADHD	5,214 (1.49)	346 (6.73)	5,074 (1.41)	819 (5.65)
Half-siblings' history of SUD				
None	339,439 (97.30)	4,836 (94.01)	349,448 (97.37)	13,752 (94.83)
SUD	9,418 (2.70)	308 (5.99)	9,441 (2.63)	749 (5.17)
Conduct disorder in proband				
None	348,326 (99.85)	4,470 (86.90)	357,479 (99.61)	11,833 (81.60)

Conduct disorder	531 (0.15)	674 (13.10)	1,410 (0.39)	2,668 (18.40)
Anxiety in proband				
None	343,953 (98.59)	4,443 (86.37)	355,210 (98.97)	13,362 (92.15)
Anxiety	4,904 (1.41)	701 (13.63)	3,679 (1.03)	1,139 (7.85)
Depression in proband				
None	343,781 (98.54)	4,556 (88.57)	356,796 (99.42)	14,030 (96.75)
Depression	5,076 (1.46)	588 (11.43)	2,093 (0.58)	471 (3.25)
Mental retardation in proband				
None	347,004 (99.47)	4,600 (89.42)	355,982 (99.19)	13,085 (90.24)
Mental retardation	1,853 (0.53)	544 (10.58)	2,907 (0.81)	1,416 (9.76)
Autism spectrum disorder in proband				
None	347,059 (99.48)	4,541 (88.28)	352,969 (98.35)	11,705 (80.72)
Autism spectrum disorder	1,798 (0.52)	603 (11.72)	5,920 (1.65)	2,796 (19.28)
Tic disorder in proband				
None	348,237 (99.82)	4,931 (95.86)	356,732 (99.40)	13,187 (90.94)
Tic	620 (0.18)	213 (4.14)	2,157 (0.60)	1,314 (9.06)
Bipolar disorder in proband				
None	348,631 (99.94)	5,108 (99.30)	358,769 (99.97)	14,459 (99.71)
Bipolar disorder	226 (0.06)	36 (0.70)	120 (0.03)	42 (0.29)
Schizophrenia in proband				
None	347,453 (99.60)	4,929 (95.82)	357,779 (99.69)	14,212 (98.01)
Schizophrenia	1,404 (0.40)	215 (4.18)	1,110 (0.31)	289 (1.99)
Personality disorder in proband				
None	346,526 (99.33)	4,672 (90.82)	358,270 (99.83)	14,284 (98.50)
Personality disorder	2,331 (0.67)	472 (9.18)	619 (0.17)	217 (1.50)
Eating disorder in proband				
None	345,305 (98.98)	4,945 (96.13)	358.312 (99.84)	14,434 (99.54)
Eating disorder	3,552 (1.02)	199 (3.87)	577 (0.16)	67 (0.46)

Note: SUD = substance use disorder.