



Short Communication

ADHD, stimulant treatment in childhood and subsequent substance abuse in adulthood – A naturalistic long-term follow-up study

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HIGHLIGHTS

- This is the longest and most complete follow-up study of children with ADHD.
- 208 children with ADHD were followed until a mean age of 31 years.
- Childhood ADHD increased the risk for SUD in adulthood.
- Both girls and boys with ADHD were at increased risk.
- Early initiation of stimulant treatment in childhood reduced the risk of later SUD.

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ABSTRACT

The purpose of the study was to estimate the risk of substance use disorder (SUD) and alcohol abuse in adulthood among children and adolescents with attention-deficit hyperactivity disorder (ADHD) compared to the background population. Furthermore, to examine whether the age at initiation and duration of stimulant treatment in childhood predicts SUD and alcohol abuse in adulthood. 208 youths with ADHD (183 boys; 25 girls) were followed prospectively. Diagnoses of SUD and alcohol abuse were obtained from The Danish Psychiatric Central Register. The relative risk (RR) of SUD and alcohol abuse for cases with ADHD, compared to the background population was 7.7 (4.3–13.9) and 5.2 (2.9–9.4), respectively. Female gender, conduct disorder in childhood and older age at initiation of stimulant treatment increased the risk of later SUD and alcohol abuse. Our results warrant increased focus on the possibly increased risk of substance abuse in females with ADHD compared to males with ADHD.

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1. Introduction

It is well documented that children with attention-deficit hyperactivity disorder (ADHD) are at increased risk of developing substance use disorder (SUD) and use of nicotine in adolescence and adulthood (Charach, Yeung, Climans, & Lillie, 2011). Five to fifty percent of adolescents and adults with SUD are estimated to have ADHD (Arias et al., 2008; Wilens, 2004; Wilens, 2007). Dopamine is thought to be the neurotransmitter

mainly involved in the pathophysiology of ADHD, and methylphenidate also has the dopamine transporter as its main target (Dichter, Damiano, & Allen, 2012). Imaging studies suggest that brain circuits modulated by dopamine are involved in the development of addiction (Volkow, Wang, Fowler, & Tomasi, 2012). There has been a substantial increase in the prescription rates of methylphenidate and other medications for patients with ADHD over the last decade worldwide (Bruckner et al., 2012; Castle, Aubert, Verbrugge, Khalid, & Epstein, 2007; Dalsgaard, Nielsen, & Simonsen, 2013; Zuvekas, Vitiello, & Norquist, 2006). There is a concern regarding the possible associations between ADHD and treatment with methylphenidate and the risk of developing SUD and the direction of such possible associations. Some studies have found that stimulant treatment was not associated with developing SUD (Barkley, Fischer, Smallish, & Fletcher, 2003; Burke, Loeber, & Lahey, 2001; Milberger, Biederman, Faraone, Chen, & Jones, 1997; Molina et al., 2007; Paternite, Loney, Salisbury, & Whaley, 1999). Other studies have found that pharmacological treatment of children with ADHD actually

Abbreviations: ADHD, Attention-deficit/hyperactivity disorder; CD, Conduct disorder; DCRS, Danish Civil Registration System; DPCR, Danish Psychiatric Central Register; DSM, Diagnostic and Statistical Manual of Mental Disorders; HR, Hazard ratio; ICD, International Classification of Diseases; ODD, Oppositional defiant disorder; RR, Relative risk; SUD, Substance use disorder.

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decreased the risk of later SUD (Biederman, Wilens, Mick, Spencer, & Faraone, 1999; Katusic et al., 2005; Wilens, Faraone, Biederman, & Gunawardene, 2003; Wilens et al., 2008). However, previous follow-up studies examining the effect of pharmacological treatment have been limited by short periods of follow-up and high rates of attrition. The objectives of the present study were to assess the long-term risk of developing SUD and abuse of alcohol in children with ADHD compared to controls and to examine whether duration of stimulant treatment in childhood predicted later SUD and alcohol abuse in adulthood.

2. Methods

2.1. Study population

In a historical prospective follow-up design, a clinical sample of 208 children and adolescents with ADHD was identified (183 boys, 25 girls). All included subjects with ADHD were treated with methylphenidate or dexamphetamine in childhood. Using validated diagnostic checklists according to DSM-IV (A.American Psychiatric Association, 1994) and ICD-10 (World Health Organization, 1993), diagnostic criteria for ADHD, oppositional defiant disorder (ODD), conduct disorder (CD) and other comorbid disorder case records were reassessed diagnostically. For the predictor analyses, cases were divided into three categories according to duration of stimulant treatment: Less than two years, two to five years, and more than five years of treatment. A control group from the general Danish population ($N = 2.15$ mill) was identified by The Danish Civil Registration System (Pedersen, Gøtzsche, Møller, & Mortensen, 2006). Detailed descriptions of the study have previously been published (Dalsgaard, Hansen, Mortensen, Damm, & Thomsen, 2001; Dalsgaard, Mortensen, Frydenberg, & Thomsen, 2002, 2013).

2.2. Substance use disorder and alcohol abuse during adolescence and adulthood

Data from The Danish Psychiatric Central Register, DPCR (Munk-Jørgensen & Mortensen, 1997) gave complete follow-up information on all cases and controls regarding any inpatient and day-patient psychiatric admissions during which an ICD-8 (World Health Organization, 1967) or ICD-10 diagnosis of abuse of alcohol, alcohol dependence (291, 303 or F 10.x) or substance use disorder (304 or F 11.x–19.x) was given. The substance use disorders were not mutually exclusive. DPCR is a nationwide register containing data on all admissions to Danish psychiatric in-patient facilities since April 1969 and outpatient consultations at psychiatric departments since 1995 covering the total Danish population. For 1969–1993 the register contains ICD-8 diagnoses and from 1994 ICD-10 diagnoses. According to data from the Causes of Deaths Register (Juel & Helweg-Larsen, 1999), two cases died in the follow-up period, both were male. Both cases were included in the analyses.

Table 1
Psychiatric hospitalization in adulthood due to substance use disorder and alcohol abuse during follow-up until a mean age of 31 years. Observed, expected number of events, relative risk, and risk ratio, by gender and with exact 95% confidence intervals (Exact 95% CI). Children with ADHD ($N = 208$) compared to the general Danish population ($N \approx 2.15$ mill).

Diagnosis	Observed number of events	Expected number of events	Relative risk (Exact 95% CI)	Risk ratio (Exact 95% CI)
<i>Alcohol use disorder</i>				
All probands ($N = 208$)	11	2.11	5.2 (2.9–9.4)	
Female probands ($N = 25$)	2	0.09	21.5 (5.4–85.8)	
Male probands ($N = 183$)	9	2.02	4.5 (2.5–8.1)	
Gender difference, females versus males				4.8 (1.1–21.7)
<i>Substance use disorder</i>				
All probands ($N = 208$)	11	2.11	7.7 (4.3–13.9)	
Female probands ($N = 25$)	3	0.08	38.7 (12.5–119.9)	
Male probands ($N = 183$)	8	1.36	5.9 (3.3–10.7)	
Gender difference, females versus males				6.6 (1.8–23.5)

2.3. Statistical analysis

The expected number of events was generated on the basis of rates of psychiatric admissions in the general Danish population, standardized for gender, age and calendar year. The relative risk (RR) of SUD or alcohol abuse in adulthood for cases compared to the general population was calculated as risk ratios, i.e. the observed to the expected number of events, and exact 95% confidence intervals (95% CI) were calculated. The gender differences in relative risks were calculated as relative risk ratios, i.e. dividing the relative risk of females by the relative risk of males. Hazard ratios by Cox regression were calculated in the predictor analyses giving crude and adjusted hazard ratios with 95% confidence intervals. Data were censored on date of the first psychiatric admission after the age of 15, date of death or the 15th of June 2000, whichever came first. The statistical package SPSS 19.0.0 (I.B.M.Corp, 2010) was used in the survival analyses.

3. Results

Cases with ADHD ($N = 208$) were at a mean age of 31 years (standard deviation 6.6) at the time of follow-up. Fifteen of the cases with ADHD were given a diagnosis of substance use disorder or alcohol abuse in adulthood (7.2%). Eleven cases were diagnosed with SUD and eleven with alcohol abuse. Seven cases were given diagnoses of both alcohol abuse and SUD. Substance use disorders involved the use of opioids, cannabis and illicit use of non-prescribed drugs such as benzodiazepines. The relative risks of SUD and alcohol abuse in cases with ADHD compared to the general Danish population are given in Table 1, for males and females.

Alcohol abuse was four times more frequent in male cases than in the male general population and in females 21 times more frequent. The relative risk of substance use disorder was almost six times higher in male and 38 times higher in female ADHD cases compared to the general population. For both disorders, females had significantly higher risks than male cases. Compared to the general population rates, female cases had almost five times the risk of males for alcohol abuse, and six times the risk of males for substance use disorder. Two male cases died during follow-up. One had five psychiatric admissions in adulthood under diagnoses of antisocial personality disorder, ASPD and abuse of alcohol before he died 25 years old from suicide. The other had become a chronic addict of opioids and died 27 years old from an overdose of morphine.

3.1. Childhood predictors of substance abuse in adulthood

The results of the predictor analyses are shown in Table 2.

The age of the child at time of initiation of stimulant treatment was associated with later substance abuse. For every year older at initiation of stimulants, the risk of SUD in adulthood increased by a factor of 1.46.

Table 2

Long-term childhood predictors of substance use disorders. Crude and adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) by Cox regression.

	Crude HR (95% CI)	Adjusted HR (95% CI)
Cumulative duration of stimulant treatment, years	0.99 (0.81–1.21)	1.07 (0.86–1.33)
Age at initiation of stimulant treatment, per year	1.47 (1.14–1.91)	1.46 (1.09–1.93)
Conduct disorder in childhood	4.77 (1.73–13.21)	3.69 (1.32–10.29)

The duration of stimulant treatment in childhood did not predict later SUD in adulthood. Comorbid conduct disorder in childhood was also associated with later substance abuse, increasing the risk of SUD in adulthood by almost four times.

4. Discussion

4.1. Prevalence and relative risk of substance abuse

SUD was seven times more likely and alcohol abuse five times more likely in cases with ADHD than in controls. The estimated relative risks and the prevalence rates are consistent with the majority of previous studies, all with shorter follow-up. A study of a clinical sample including 85 boys with ADHD who had no conduct problems in childhood found that 19% of probands and 7% of controls had an SUD at age 24, and an increased risk of non-alcohol SUD (Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998). Another study found that 102 cases with ADHD had twice the risk of controls for nicotine, alcohol or substance dependence by age 22 (Biederman et al., 2006). Few of the previous studies found no increased risk of later SUD or alcohol abuse compared to controls (Biederman et al., 1997; Molina & Pelham, 2003; Weiss, 1985).

We found girls with ADHD to be at higher risk of both alcohol and substance use disorder than boys with ADHD. No previous study has reported on the adult addiction outcome of girls with ADHD. One follow-up study of females with ADHD into adolescence found a similar increased risk of SUD compared to males with ADHD (Disney, Elkins, McGue, & Iacono, 1999); another found a lower risk of SUD in females compared to males (Katusic et al., 2005).

4.2. Modifying effect of stimulant treatment on later substance abuse

Stimulant treatment in childhood did not increase or decrease the risk of later substance abuse in adulthood. A meta-analysis from 2003 of six studies concluded that stimulant treatment protected against later SUD with a two-fold increased risk in untreated subjects (Wilens et al., 2003). Three follow-up studies on the topic were published since the meta-analysis, two of which found a protective effect. In 140 children with ADHD, prior stimulant treatment reduced the risk of any SUD (HR = 0.27) and cigarette smoking (HR = 0.28), but not alcohol abuse at age 16 (Wilens et al., 2008). Duration of stimulant treatment or age at initiation of treatment was not associated with later SUD. At the follow-up at age 22, there was a protective effect on any SUD (HR = 0.5) (Biederman et al., 2006). However, the main effect in both studies may have been driven by the high prevalence of use of nicotine, which was included in the definition of any SUD. In a survey, adolescents with ADHD with good adherence to their pharmacological ADHD treatment reported lower prevalence of SUD and use of nicotine and alcohol than a matched control group of adolescents without symptoms of ADHD (Madsen & Dalsgaard, 2013).

The present study found that early initiation of stimulant treatment was associated with a reduced risk of later SUD and alcohol abuse. Few studies have examined this issue, one found similar results (Mannuzza et al., 2008).

Our finding that comorbid conduct disorder in children with ADHD is a strong predictor of later SUD is consistent with a number of previous studies (Barkley et al., 2003; Burke et al., 2001; Hechtman & Weiss, 1986; Hechtman, Weiss, Perlman, & Amsel, 1984; Katusic et al., 2005; Loney, Whaley-Klahn, Kosier, & Conboy, 1983; Molina & Pelham, 2003). Only one study of ADHD found that the risk of later SUD was carried forward entirely by conduct disorder (Biederman et al., 1997).

4.3. Strengths and limitations

The strengths of the present study include the long follow-up of females and males without attrition. Limitations include a selected population of cases with high severity of ADHD. The follow-up was naturalistic, not a randomized trial and the results on the effect of treatment should be interpreted with caution. The small sample size especially of females limits the power of the study. Substance abuse may be underreported in the register (Hansen et al., 2000). Still, this holds true for both cases and controls and thus this does not affect the estimated relative risks. Finally, the low number of probands with a substance use disorder in adulthood makes the confidence intervals for the estimated relative risks broad. Despite these limitations, the results from this study offers valuable new insights into the associations between ADHD stimulant treatment in childhood and later SUD and alcohol abuse in adulthood.

5. Conclusion

Both boys and girls with ADHD are at increased risk of substance abuse in adulthood. Age at initiation of stimulant in children with ADHD is associated with the risk of substance abuse in adulthood, with early initiation resulting in a reduced risk. Duration of stimulant treatment in childhood was not associated with later SUD or alcohol abuse. Our results on the predictive value of gender may warrant increased focus on the possibly increased risk of substance abuse in females with ADHD compared to males with ADHD.

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Contributors

Søren Dalsgaard, Preben Bo Mortensen, Morten Frydenberg and Per Hove Thomsen conceptualized and designed the study. Søren Dalsgaard and Preben Bo Mortensen obtained the funding for the study. Søren Dalsgaard and Morten Frydenberg conducted the data analyses and interpretation. Søren Dalsgaard wrote the first draft of the manuscript and all authors approved the final manuscript.

Conflict of interests

Dr's. Mortensen and Frydenberg have no conflict of interests. Dr. Thomsen has received speaker's honoraria from Novartis, Janssen and Medice. Dr. Dalsgaard is a consultant for The Danish Health and Medicines Authority.

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