Published in final edited form as:

Psychol Med. 2015 April ; 45(5): 977–983. doi:10.1017/S0033291714001986.

Attention-deficit/hyperactivity disorder and risk for drug use disorder: a population-based follow-up and co-relative study

J. Sundquist^{1,2,*}, H. Ohlsson¹, K. Sundquist^{1,2}, and K. S. Kendler^{3,4,5}

¹Center for Primary Health Care Research, Lund University, Malmö, Sweden

²Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, USA

³Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA

⁴Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA

⁵Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, VA, USA

Abstract

Background—Although the association between attention-deficit/hyperactivity disorder (ADHD) and drug use disorder (DUD) is well documented, it is unclear whether it is causal or results from familial confounding.

Method—In this study we included all 551164 individuals born in Sweden between 1991 and 1995 and used linked data from multiple nationwide registries to identify those with ADHD prior to age 15 years (1.71%). We used Cox proportional hazards models to investigate the future risk for DUD as a function of an ADHD registration and then compared the results from the entire population with the results from a co-relative design. Using the Swedish MultiGeneration Register, we identified all full-sibling, half-sibling and first-cousin pairs discordant for ADHD.

Results—In the population sample, ADHD had a substantially increased risk for future DUD with a hazard ratio (HR) of 3.34 after accounting for gender and parental education. Examining discordant cousin pairs, discordant half-siblings and discordant siblings, those with ADHD had HRs for DUD of 3.09, 2.10 and 2.38 respectively. Controlling for the number of ADHD registrations, ADHD patients with and without stimulant treatment were similarly associated with later DUD risk.

Conclusions—ADHD diagnosed before 15 years of age was strongly related to future risk for DUD. The magnitude of this association was modestly reduced in relative pairs discordant for ADHD, suggesting that the ADHD–DUD association is partly causal and partly a result of familial

confounding. We found no evidence to suggest that this association resulted from stimulant treatment.

Keywords

ADHD; Cox regression; drug use disorders; Swedish national cohort

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common psychiatric disorder of childhood with a worldwide pooled prevalence of 5.3% (Polanczyk et al. 2007; Looby, 2008). ADHD is associated with drug use and drug use disorder (DUD) in cross-sectional epidemiological studies (Kessler et al. 2006; Faraone & Wilens, 2007). In addition, most (Mannuzza et al. 1993; Milberger et al. 1997; Molina & Pelham, 2003; Elkins et al. 2007) but not all (Boyle et al. 1992; Biederman et al. 1997) longitudinal investigations (Szobot & Bukstein, 2008) have shown associations with alcohol use disorders (Edwards & Kendler, 2012) and smoking (Kollins et al. 2005). These results are consistent with a range of studies showing that behavioral disinhibition and/or impulsivity, common symptoms in ADHD, are important risk factors for future DUD (Iacono et al. 1999; Kollins et al. 2005; Elkins et al. 2007; Urcelay & Dalley, 2012).

From these data, it is plausible to conclude that ADHD is a direct cause of DUD. However, alternative interpretations are possible. In particular, both ADHD (Asherson & Gurling, 2012; Larsson et al. 2013) and DUD (Tsuang et al. 1996; Merikangas et al. 1998; Kendler et al. 2000) are strongly familial, with a large proportion of the familial aggregation resulting from genetic factors. Prior studies have suggested a genetic link between ADHD traits and risk for DUD (Young et al. 2000; Knopik et al. 2006; Hicks et al. 2012; Kendler & Myers, 2014) and alcohol use disorders (Young et al. 2000; Knopik et al. 2006; Edwards & Kendler, 2012).

Our initial objective in this study was to use, for the first time to our knowledge, a nationally representative sample to examine the prospective association between an ADHD diagnosis and a subsequent registration for DUD. We also examined the possible causal relationship between ADHD and DUD by using a co-relative design in cousins, half-siblings and full siblings. Such a design compares the risk for an outcome, here DUD, in relative pairs who are discordant for the risk factor, which in this study was a diagnosis of ADHD.

If the association between ADHD and DUD is not causal but instead results from confounding familial factors, we would expect to see the association decline systematically from that seen in the general population to that seen in cousins, half-siblings and full siblings. By contrast, if the association between ADHD and DUD is largely or entirely causal, the association would remain strong in discordant relative pairs, with no clear trend to be reduced in relative pairs sharing more genetic and family environmental risk factors.

Finally, we examined the degree to which the association between ADHD and subsequent DUD could be mediated through stimulant treatment.

Method

We included all individuals born in Sweden between 1991 and 1995 ($n=551\,164$) and linked them with multiple nationwide registries to identify those with ADHD prior to age 15 years (1.71%). Cox proportional hazards models were used to examine the future risk for DUD as a function of an ADHD registration. In a second step, we compared the results from the entire population with the results from a co-relative design.

We used linked data from multiple Swedish nationwide registries. Linking was achieved through the unique individual Swedish 10-digit personal ID number assigned at birth or immigration to all Swedish residents. This ID number was replaced by a serial number to preserve confidentiality.

The following sources were used to create our database: the Total Population Register, containing annual data on family and geographical status; the Multi-Generation Register, providing information on family relationships; the Swedish Hospital Discharge Register, containing all hospitalizations for all Swedish inhabitants from 1964 to 2010; the Swedish Prescribed Drug Register, containing all prescriptions in Sweden picked up by patients from July 2005 to 2010; the Out-patient Care Register, containing information from all out-patient clinics between 2001 and 2010; the Swedish Crime Register, which included complete national data on all convictions from 1973 to 2011; the Swedish Suspicion Register, which included complete national data on all individuals strongly suspected of crime from 1998 to 2011; the Swedish Mortality Register, containing causes of death; and the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA), containing annual information on socio-economic factors for all individuals from 16 years of age. We secured ethical approval for this study from the Regional Ethical Review Board of Lund University (No. 2008/409).

DUD was identified in the Swedish medical registries by ICD codes [ICD-10: mental and behavioral disorders due to psychoactive substance use (F10–F19), except those due to alcohol (F10) or tobacco (F17)]; in the Suspicion Register by codes 3070, 5010, 5011 and 5012, which reflect crimes related to DUD; and in the Crime Register by references to laws covering narcotics (law 1968:64, paragraph 1, point 6) and drug-related driving offences (law 1951:649, paragraph 4, subsection 2 and paragraph 4A, subsection 2). DUD was identified in individuals (excluding those suffering from cancer) in the Prescribed Drug Register who had retrieved (on average) more than four defined daily doses a day for 12 months from either of Hypnotics and Sedatives [Anatomical Therapeutic Chemical (ATC) Classification System N05C and N05BA] or Opioids (ATC: N02A).

The database began with all individuals born in Sweden between 1991 and 1995. We also required that the individual was living in Sweden during the entire period from 0 to 15 years of age. This database included 551 164 individuals. In the database, 2.8% of the individuals were registered for DUD. Our main exposure variable was childhood ADHD. ADHD was identified in the Hospital Discharge Register and the Out-patient Care Register by ICD codes (ICD-8: 308.3; ICD-9: 314; ICD-10: F90). ADHD was also identified in individuals in the Prescribed Drug Register who had picked up any prescription for stimulants (ATC

Classification System codes N06BA01, N06BA02, N06BA04 and N06BA09). The ADHD registration had to be recorded prior to age 15 years; 1.71% of all individuals were registered for ADHD.

There were relatively few missing data. For the population, in-patient and pharmacy registers, missingness was <2%, <1% and nearly 0% respectively. However, for out-patient diagnoses missingness was higher, at approximately 10%.

We used Cox proportional hazards models to investigate the future risk for DA as a function of ADHD registration. Robust standard errors were used to adjust the 95% confidence intervals (CIs) as we had several sibling pairs from the same parents. Follow-up time in number of years was measured from age 15 of the child until the year of first registration for DUD, death, emigration or end of follow-up (year 2011), whichever came first. The proportionality assumption was fulfilled in all models. As covariates in the models we also considered sex of the individual and parental education. To investigate whether use of stimulants confounded the association between ADHD and DUD, we included the use of stimulants in a final model. Of the individuals with ADHD, 77.6% were registered for stimulant use.

In a second step we sought to compare the results from the entire population with the results from a co-relative design (Lawlor & Mishra, 2009). By means of the Swedish Multi-Generation Register, we identified all full-sibling, half-sibling and first-cousin pairs discordant for ADHD. Monozygotic (MZ) twin pairs discordant for ADHD exposure would have been of particular interest in these analyses as they provide complete control for genetic and familial–environmental confounding, where the family environment is defined as those environmental experiences that tend to make siblings or twins reared together similar for the trait in question. However, no MZ twin pairs met our definition of discordance. In a Cox proportional hazards model with a separate stratum for each relative pair, we investigated the future risk for DUD as a function of ADHD diagnosis. The co-relative design allowed us to contrast the rates of DUD in relatives with different exposure of ADHD. The stratum-specific regression provided regression coefficients for ADHD that were adjusted for the familial cluster, and therefore accounted for an array of unknown shared genetic and environmental factors.

We further conducted several sensitivity analyses to test the robustness of the results from our main analyses: in three separate models we investigated (1) the association between individuals with ADHD from the out-patient/in-patient register without stimulant use and DUD; (2) the association between individuals with ADHD from the out-patient/in-patient register and stimulant use, on the one hand, and DUD, on the other; (3) the association between individuals without ADHD from the out-patient/in-patient register but with stimulant use, on the one hand, and DUD, on the other. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., USA).

Results

The total number of individuals contained in the sample born in Sweden between 1991 and 1995 was 551164. In this sample, adolescents with childhood ADHD had a substantially increased risk for future DUD with a hazard ratio (HR) of 4.69 (Table 1). The HR decreased to 3.60 when including gender and to 3.34 when parental education was added as a covariate.

We next compared the results from the entire population with the results from a co-relative design analyzing all first-cousin, half-sibling and full-sibling pairs discordant for ADHD with the aim of accounting for family confounding. When we examined discordant cousin pairs, we found that ADHD predicted future DUD with an HR of 3.96 (Table 1). After including gender, the HR decreased to 3.11 and changed minimally (to 3.09) when parental education was also included. Examining discordant half-siblings, those with ADHD had an HR for DUD of 2.10. This increased risk only changed marginally after adding gender and parental education to the model. In discordant full siblings, the HR was 2.80, decreasing to 2.38 after accounting for gender.

As children and adolescents with ADHD are often treated with stimulant medication, an obvious question to ask was whether the association we observed between ADHD and future DUD was a result of stimulant exposure. The simplest way to address this question was to divide our ADHD cases into three groups: (i) ADHD only: those with an assigned ADHD diagnosis but no record of receiving stimulant medication; (ii) ADHD+stimulants: those with an assigned ADHD diagnosis with a record of also receiving stimulant medication; and (iii) stimulants only: those who were identified as ADHD cases solely through receiving stimulant medication. As shown in Table 2, the HR for DUD was substantially increased in all three groups, although somewhat more so for the ADHD+stimulant and stimulant only versus the ADHD only group. In a more formal statistical test, in the entire population, we added stimulant treatment as a covariate. The HR for DUD decreased modestly from 3.34 to 2.66 (95% CIs 2.32–3.06) and remained highly significant.

However, these analyses do not take into account the possibility that the ADHD+stimulant group might be more severely ill than the other ADHD groups. Our best available measure for symptomatic severity of ADHD was the number of independent medical registrations. These were considerably higher in the ADHD+stimulant group (mean±standard error=7.3±0.07) than in the ADHD only group (3.3±0.04) (and unavailable in the stimulant only group). As shown in Table 3, an expanded model 2 from Table 2 adding the number of registrations shows that risk for DUD is significantly predicted by the number of ADHD registrations and controlling for that, somewhat more strongly predicted by a diagnosis of ADHD only compared to ADHD+stimulants.

Discussion

This national cohort study is the largest study to date to analyze whether childhood ADHD predicts subsequent DUD and the first, to our knowledge, to use a co-relative design to attempt to disentangle the potential causal nature of this association. We found in the entire

population that an ADHD diagnosis robustly predicted future risk for DUD registration, with an HR of 4.69 that decreased to 3.34 when controlling for gender and parental education. In our co-relative design, we found a modest decrease in the association between ADHD and DUD from the general population to cousins and half-siblings discordant for ADHD. However, the association was slightly more pronounced in full siblings than in half-siblings. This finding is inconsistent with expectation but might result from sampling errors as the HRs in half-siblings were not known precisely.

These results are most consistent with the hypothesis that the association between ADHD and DUD is partly causal and partly a result of familial etiological factors that impact on both disorders. If the association was entirely due to familial confounding, we would expect the ADHD–DUD association to be somewhat weaker in full siblings than in half-siblings because full siblings are twice as genetically related as half-siblings and much more likely to share familial–environmental factors. However, the opposite was seen.

We suggest three plausible explanations for the causal features of the ADHD–DUD relationship. First, the effect could be mediated through stimulant treatment. However, in accord with prior studies on this issue (Faraone & Wilens, 2007), our results are not consistent with this hypothesis. We found a substantial elevation of DUD risk in ADHD cases with no stimulant treatment. When we controlled for stimulant treatment in the entire population, the association between ADHD and DUD remained highly significant. Furthermore, both clinical experience and one high-quality epidemiological survey (Angold et al. 2000) confirm that ADHD subjects treated with stimulants are more severely ill than those not treated. Our analyses, using the number of independent registrations for ADHD as an index of severity, support these earlier findings. Indeed, when we controlled for the number of registrations, DUD was slightly more strongly predicted by a diagnosis of ADHD alone than ADHD +stimulants. These results argue strongly that the observed association between ADHD and DUD in our data is not mediated through exposure to stimulant medication.

A second possible causal pathway from ADHD to DUD is through attempts at self-medication. We do not have data to directly address this hypothesis. However, Wilens et al. (2007) specifically examined this hypothesis as part of a longitudinal study of ADHD cases and controls and found no evidence that the two groups differed in their motivation for psychoactive substance use. The third, and probably most likely, explanation for the causal elements of the ADHD–DUD relationship is that certain ADHD traits directly or indirectly predispose to future DUD. Direct effects might include traits such as behavioral disinhibition and/or impulsivity, which are common symptoms in ADHD, and have repeatedly been shown to be important risk factors for DUD (Iacono et al. 1999; Kollins et al. 2005; Elkins et al. 2007; Urcelay & Dalley, 2012). In a prospective study, Elkins et al. (2007) noted that dimensional measures of ADHD predicted future drug use and drug problems. However, further analyses indicated that the predictive effect was entirely a result of symptoms of hyperactivity/impulsivity and not inattention (Elkins et al. 2007). Similar findings have been seen in other cohorts (Kellam et al. 1980; Chang et al. 2012). Indirect effects of ADHD that might predispose to DUD would include leaving school early, poor socialization and high levels of peer deviance (Marshall et al. 2003; Wolke et al. 2009).

The evidence that the ADHD–DUD association is not entirely causal but results in part from familial confounding is also consistent with several prior studies that suggest the existence of an ‘externalizing spectrum of disorders’. This spectrum has been detected both in studies examining only phenotypic measures (Krueger, 1999; Krueger et al. 2005; Markon & Krueger, 2005) and in genetically informative studies that find evidence for a set of common genetic risk factors that impact on a range of externalizing disorders and traits including, in several studies, ADHD and DUD (Hicks et al. 2004; Kendler & Myers, 2014). For example, in adult twin males in Virginia, Kendler & Myers (2014) defined a genetic externalizing spectrum. Path estimates from the genetic common factor were estimated at +0.67 for DUD and +0.30 for ADHD as reported in childhood/adolescence.

Strengths and limitations

The current study has several important strengths. It is the largest and most comprehensive study to date to prospectively examine the association between ADHD in childhood and adolescence and subsequent development of DUD. The use of nationwide out-patient and in-patient diagnoses allowed a more complete ascertainment of ADHD than in previous studies, enabling more generalizable results. The power of the co-relative design originates from our ability to match in relative pairs discordant for ADHD for varying levels of sharing of genetic risk and environmental exposures.

These strengths should be interpreted in the context of potential methodological limitations. First, we detected subjects with DUD from medical, legal and pharmacy records and ADHD from medical and pharmacy records. This method has an important advantage in not requiring cooperation or precise respondent recall and reporting. However, it does produce a proportion of false-negative and false-positive diagnoses. We cannot precisely estimate these biases as no large epidemiological study of DUD has been carried out in Sweden. However, such a survey was conducted in another Scandinavian country, Norway, which has similar rates of drug use and abuse as in this study (Kraus et al. 2003; Hibell et al. 2007). The lifetime prevalence rate of DSM-III-R (APA, 1987) drug abuse and dependence in Norway was estimated at 3.4% (Kringlen et al. 2001), relatively close to the 2.7% DUD we detected in all of Sweden. The similarity between our data and those from Norway may reflect the completeness in our data.

Second, although full siblings share much of their rearing environment, they are not fully matched for genetic risk factors. It is possible that the HR for DUD in MZ twins discordant for ADHD could approach unity, suggesting full confounding. However, if a large decline in HR was seen between full siblings and MZ twins, it would predict a similar decline between half-siblings and full siblings, which was not observed. Furthermore, the co-relative design cannot prove causality, it can only produce data consistent with such a hypothesis. The pattern that we observed in full siblings could result from some environmental event unique to one sibling, such as head trauma or meningitis/encephalitis leading to impulsivity, that predisposes to both ADHD and DUD.

Third, our decision to include as ADHD cases those with only stimulant medication might be questioned. However, these medications are prescribed exclusively at a diagnosis of ADHD and only specialists in, for example, child psychiatry are allowed to prescribe

stimulants. We were able to support the validity of this decision with additional findings. Of the cases treated with stimulants, 29% were later diagnosed with ADHD after their 15th birthday. The tetrachoric correlation within sibling pairs between ADHD in one sibling who was treated with stimulants and stimulant treatment without a recorded ADHD diagnosis was substantial for a familial trait and highly significant ($+0.26, p<0.0001$) (Table 4). In addition, we have very limited data on what sort of treatment, either pharmacological or psychosocial, was delivered and as such we cannot comment on the long-term impact of treatment.

Fourth, unlike with structural models, the co-relative design when applied as it was in this study to multiple relative classes does not produce a single estimate of the proportion of the association under examination that is causal. Instead, a more global sense must be obtained from reviewing results from the general population and all the relative classes. Furthermore, this design also does not produce specific estimates of the degree to which observed confounding results from genetic *versus* shared environmental factors.

Fifth, compared with the detailed study guidelines from the National Institute for Health and Care Excellence (NICE; <http://pathways.nice.org.uk>), this study has very crude matching and our findings need to be interpreted with caution.

Conclusions

In a large national Swedish cohort, we found that ADHD diagnosed before age 15 was strongly related to future risk for DUD. The magnitude of this association was modestly reduced in relative pairs discordant for ADHD. These results are most consistent with the hypothesis that the ADHD–DUD association is partly causal and partly a result of shared familial risk factors. Consistent with the prior literature, we found that the causal relationship between ADHD and DUD could not plausibly be the result of stimulant treatment. The findings are important for all clinicians encountering patients diagnosed with ADHD and for drug use prevention.

Acknowledgments

This study was supported by grant R01DA030005 from the National Institute on Drug Abuse and an Agreement on Medical Training and Research (Avtal om Lakarutbildning och Forskning) project grant, Lund, Sweden, the Swedish Research Council for Health, Working Life and Welfare (Reg. no. 2013-1836) and the Swedish Research Council (2012-2378).

References

- Angold A, Erkanli A, Egger HL, Costello EJ. Stimulant treatment for children: a community perspective. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2000; 39:975–984. discussion 984–994. [PubMed: 10939226]
- APA. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. American Psychiatric Association; Washington, DC: 1987.
- Asherson P, Gurling H. Quantitative and molecular genetics of ADHD. *Current Topics in Behavioral Neurosciences*. 2012; 9:239–272. [PubMed: 21989848]
- Biederman J, Wilens T, Mick E, Faraone SV, Weber W, Curtis S, Thornell A, Pfister K, Jetton JG, Soriano J. Is ADHD a risk factor for psychoactive substance use disorders? Findings from a four-

year prospective follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36:21–29. [PubMed: 9000777]

Boyle MH, Offord DR, Racine YA, Szatmari P, Fleming JE, Links PS. Predicting substance use in late adolescence: results from the Ontario Child Health Study follow-up. *American Journal of Psychiatry*. 1992; 149:761–767. [PubMed: 1590492]

Chang Z, Lichtenstein P, Larsson H. The effects of childhood ADHD symptoms on early-onset substance use: a Swedish twin study. *Journal of Abnormal Child Psychology*. 2012; 40:425–435. [PubMed: 21947618]

Edwards AC, Kendler KS. Twin study of the relationship between adolescent attention-deficit/hyperactivity disorder and adult alcohol dependence. *Journal of Studies on Alcohol and Drugs*. 2012; 73:185–194. [PubMed: 22333326]

Elkins IJ, McGue M, Iacono WG. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. *Archives of General Psychiatry*. 2007; 64:1145–1152. [PubMed: 17909126]

Faraone SV, Wilens TE. Effect of stimulant medications for attention-deficit/hyperactivity disorder on later substance use and the potential for stimulant misuse, abuse, and diversion. *Journal of Clinical Psychiatry*. 2007; 68(Suppl. 11):15–22. [PubMed: 18307377]

Hibell B.; Guttormsson, U.; Ahlström, S.; Balakireva, O.; Bjarnason, T.; Kokkevi, A. The 2007 ESPAD Report: Substance Use Among Students in 35 European Countries. The Swedish Council for Information on Alcohol and Other Drugs (CAN); Sweden: 2007.

Hicks BM, Iacono WG, McGue M. Index of the transmissible common liability to addiction: heritability and prospective associations with substance abuse and related outcomes. *Drug and Alcohol Dependence*. 2012; 123(Suppl. 1):S18–S23. [PubMed: 22245078]

Hicks BM, Krueger RF, Iacono WG, McGue M, Patrick CJ. Family transmission and heritability of externalizing disorders: a twin-family study. *Archives of General Psychiatry*. 2004; 61:922–928. [PubMed: 15351771]

Iacono WG, Carlson SR, Taylor J, Elkins IJ, McGue M. Behavioral disinhibition and the development of substance-use disorders: findings from the Minnesota Twin Family Study. *Development and Psychopathology*. 1999; 11:869–900. [PubMed: 10624730]

Kellam SG, Ensinger ME, Simon MB. Mental health in first grade and teenage drug, alcohol, and cigarette use. *Drug and Alcohol Dependence*. 1980; 5:273–304. [PubMed: 7371495]

Kendler KS, Karkowski LM, Neale MC, Prescott CA. Illicit psychoactive substance use, heavy use, abuse, and dependence in a US population-based sample of male twins. *Archives of General Psychiatry*. 2000; 57:261–269. [PubMed: 10711912]

Kendler KS, Myers J. The boundaries of the internalizing and externalizing genetic spectra in men and women. *Psychological Medicine*. 2014; 44:647–655. [PubMed: 23574685]

Kessler RC, Adler L, Barkley R, Biederman J, Conners CK, Demler O, Faraone SV, Greenhill LL, Howes MJ, Secnik K, Spencer T, Ustun TB, Walters EE, Zaslavsky AM. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *American Journal of Psychiatry*. 2006; 163:716–723. [PubMed: 16585449]

Knopik VS, Heath AC, Jacob T, Slutske WS, Bucholz KK, Madden PA, Waldron M, Martin NG. Maternal alcohol use disorder and offspring ADHD: disentangling genetic and environmental effects using a children-of-twins design. *Psychological Medicine*. 2006; 36:1461–1471. [PubMed: 16734942]

Kollins SH, McClernon FJ, Fuemmeler BF. Association between smoking and attention-deficit/hyperactivity disorder symptoms in a population-based sample of young adults. *Archives of General Psychiatry*. 2005; 62:1142–1147. [PubMed: 16203959]

Kraus L, Augustin R, Frischer M, Kummeler P, Uhl A, Wiessing L. Estimating prevalence of problem drug use at national level in countries of the European Union and Norway. *Addiction*. 2003; 98:471–485. [PubMed: 12653817]

Kringlen E, Torgersen S, Cramer V. A Norwegian psychiatric epidemiological study. *American Journal of Psychiatry*. 2001; 158:1091–1098. [PubMed: 11431231]

Krueger RF. The structure of common mental disorders. *Archives of General Psychiatry*. 1999; 56:921–926. [PubMed: 10530634]

- Krueger RF, Markon KE, Patrick CJ, Iacono WG. Externalizing psychopathology in adulthood: a dimensional-spectrum conceptualization and its implications for DSM-V. *Journal of Abnormal Psychology*. 2005; 114:537–550. [PubMed: 16351376]
- Larsson H, Chang Z, D'Onofrio BM, Lichtenstein P. The heritability of clinically diagnosed attention deficit hyperactivity disorder across the lifespan. *Psychological Medicine*. 2013 Published online: 10 October 2013. 10.1017/S0033291713002493
- Lawlor, DA.; Mishra, GD. *Family Matters: Designing, Analysing and Understanding Family-based Studies in Life Course Epidemiology*. Oxford University Press; Oxford: 2009.
- Looby A. Childhood attention deficit hyperactivity disorder and the development of substance use disorders: valid concern or exaggeration? *Addictive Behaviors*. 2008; 33:451–463. [PubMed: 18037571]
- Mannuzza S, Klein RG, Bessler A, Malloy P, LaPadula M. Adult outcome of hyperactive boys. Educational achievement, occupational rank, and psychiatric status. *Archives of General Psychiatry*. 1993; 50:565–576. [PubMed: 8317950]
- Markon KE, Krueger RF. Categorical and continuous models of liability to externalizing disorders: a direct comparison in NESARC. *Archives of General Psychiatry*. 2005; 62:1352–1359. [PubMed: 16330723]
- Marshal MP, Molina BS, Pelham WE Jr. Childhood ADHD and adolescent substance use: an examination of deviant peer group affiliation as a risk factor. *Psychology of Addictive Behaviors*. 2003; 17:293–302. [PubMed: 14640825]
- Merikangas KR, Stolar M, Stevens DE, Goulet J, Preisig MA, Fenton B, Zhang H, O'Malley SS, Rounsaville BJ. Familial transmission of substance use disorders. *Archives of General Psychiatry*. 1998; 55:973–979. [PubMed: 9819065]
- Milberger S, Biederman J, Faraone SV, Wilens T, Chu MP. Associations between ADHD and psychoactive substance use disorders. Findings from a longitudinal study of high-risk siblings of ADHD children. *American Journal on Addictions*. 1997; 6:318–329. [PubMed: 9398930]
- Molina BS, Pelham WE Jr. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. *Journal of Abnormal Psychology*. 2003; 112:497–507. [PubMed: 12943028]
- Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *American Journal of Psychiatry*. 2007; 164:942–948. [PubMed: 17541055]
- Szobot CM, Bukstein O. Attention deficit hyperactivity disorder and substance use disorders. *Child and Adolescent Psychiatric Clinics of North America*. 2008; 17:309–323. viii. [PubMed: 18295148]
- Tsuang MT, Lyons MJ, Eisen SA, Goldberg J, True W, Lin N, Meyer JM, Toomey R, Faraone SV, Eaves L. Genetic influences on DSM-III-R drug abuse and dependence: a study of 3,372 twin pairs. *American Journal of Medical Genetics*. 1996; 67:473–477. [PubMed: 8886164]
- Urcelay GP, Dalley JW. Linking ADHD, impulsivity, and drug abuse: a neuropsychological perspective. *Current Topics in Behavioral Neurosciences*. 2012; 9:173–197. [PubMed: 21365439]
- Wilens TE, Adamson J, Sgambati S, Whitley J, Santry A, Monuteaux MC, Biederman J. Do individuals with ADHD self-medicate with cigarettes and substances of abuse? Results from a controlled family study of ADHD. *American Journal on Addictions*. 2007; 16(Suppl. 1):14–21. quiz 22–23. [PubMed: 17453603]
- Wolke D, Waylen A, Samara M, Steer C, Goodman R, Ford T, Lamberts K. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *British Journal of Psychiatry*. 2009; 195:249–256. [PubMed: 19721116]
- Young SE, Stallings MC, Corley RP, Krauter KS, Hewitt JK. Genetic and environmental influences on behavioral disinhibition. *American Journal of Medical Genetics*. 2000; 96:684–695. [PubMed: 11054778]

Table 1
Results from the Cox proportional hazards model in the entire population and using a co-relative design for childhood ADHD and future drug use disorder (DUD)

	Model 1	Model 2^a	Model 3^b
Population sample	4.69 (4.39–5.00)	3.60 (3.38–3.84)	3.34 (3.13–3.56)
Cousins (<i>n</i> = 10194 pairs)	3.96 (3.51–4.48)	3.11 (2.75–3.52)	3.09 (2.73–3.50)
Half-siblings (<i>n</i> = 610 pairs)	2.10 (1.52–2.92)	2.02 (1.41–2.87)	2.06 (1.42–2.99)
Siblings (<i>n</i> = 3410 pairs)	2.80 (2.35–3.34)	2.38 (1.98–2.85)	

ADHD, Attention-deficit/hyperactivity disorder.

Values given as hazard ratio (95% confidence interval).

^a Adjusted for gender.

^b Adjusted for gender and parental education.

Table 2
Results from the Cox proportional hazards model for the association between subtypes of childhood ADHD and future DUD

Population sample	Model 1	Model 2 ^a
ADHD only (no stimulants)	3.50 (3.04–4.02)	2.75 (2.39–3.16)
ADHD and stimulants	5.16 (4.71–5.66)	3.94 (3.59–4.32)
Stimulants only	4.57 (4.10–5.10)	3.49 (3.12–3.89)

ADHD, Attention-deficit/hyperactivity disorder; DUD, drug use disorder.

Values given as hazard ratio (95% confidence interval).

^a Adjusted for gender.

Table 3
Results from the Cox proportional hazards model for cases of ADHD only and ADHD +stimulants controlling for the number of ADHD registrations and gender in the prediction of future DUD

	HR (95% CI)
ADHD only (no stimulants)	1.69 (1.44–1.99)
No. of registrations	1.11 (1.10–1.12)
ADHD+stimulants	1.44 (1.20–1.73)
No. of registrations	1.10 (1.09–1.12)

ADHD, Attention-deficit/hyperactivity disorder; DUD, drug use disorder; HR, hazard ratio, CI, confidence interval.

Table 4
Tetrachoric correlations among 127610 sibling pairs born in Sweden 1991–1995

	ADHD only (no stimulants)	ADHD+ stimulants	Stimulants only
ADHD only (no stimulants)	0.34 (0.04)	0.23 (0.04)	0.12 (0.05)
ADHD+stimulants		0.47 (0.02)	0.26 (0.04)
Stimulants only			0.46 (0.03)

ADHD, Attention-deficit/hyperactivity disorder.

Standard error given in parentheses.