

Is attention deficit/hyperactivity disorder among men associated with initiation or escalation of substance use at 15-month follow-up? A longitudinal study involving young Swiss men

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ABSTRACT

Background and Aims Young adults with attention deficit/hyperactivity disorder (ADHD) show higher substance use disorder (SUD) prevalence relative to non-ADHD controls; few longitudinal studies have examined the course of substance use with reference to conduct disorder (CD). We compared initiation and escalation of substance use at 15-month follow-up in men screened positive or negative for ADHD (ADHD⁺ versus ADHD⁻), controlling for CD presence in early adolescence. **Design** Participants were recruited during August 2010 and November 2011 from the census of all young men who have to pass mandatory army conscription from three of six Swiss Army recruitment centres. A two-wave data collection was performed via questionnaires at baseline and 15-month follow-up as a part of the longitudinal Cohort Study on Substance Use Risk Factors. **Setting** Recruitment centres in Lausanne, Windisch and Mels, responsible for 21 cantons in German- and French-speaking areas of Switzerland. **Participants** Consecutive sample of 5103 male Swiss Army conscripts who provided informed consent and responded to questionnaires at baseline and 15-month follow-up. Their mean age was 20.0 (standard deviation = 1.21) years at baseline. **Measurements** ADHD and CD were assessed using the adult ADHD Self-Report Scale and the MINI International Neuropsychiatric Interview Plus, respectively, at baseline, and substance use was measured via self-administered substance use questionnaires at baseline and follow-up. **Findings** Compared with the ADHD⁻ group, the ADHD⁺ group ($n = 215$, 4.2%) showed heavier baseline substance use and increased likelihood of alcohol ($\chi^2 = 53.96$; $P < 0.001$), tobacco ($\chi^2 = 21.73$; $P < 0.001$) and cannabis use disorders ($\chi^2 = 48.43$; $P < 0.001$). The extent of alcohol, tobacco and cannabis use in the two groups remained stable from baseline to follow-up (no escalation). The ADHD⁺ group was more likely to initiate substance use compared with the ADHD⁻ group (higher initiation rates), particularly with amphetamines [odds ratio (OR) = 3.81; 95% confidence interval (CI) = 2.20–6.60; $P < 0.001$] and non-medical use of ADHD medication (OR = 4.45; 95% CI = 2.06–9.60; $P < 0.001$). CD was associated with initiation of substance use but did not mediate the associations between ADHD and substance use, revealing that the impact of ADHD on substance use was independent of CD. **Conclusions** For men in their early 20s, attention deficit/hyperactivity disorder is a risk factor for continued heavier but not escalating use of alcohol, tobacco and cannabis when already consuming these substances, compared with young men with no ADHD. It is also a risk factor for initiating the use of cannabis, stimulants, hallucinogens and sedatives, independent of conduct disorder in early adolescence.

Keywords ADHD, conduct disorder, longitudinal study, substance use, substance use disorders, young men.

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INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD), which involves inattention, hyperactivity and impulsivity [1], is a common childhood disorder with an estimated world-wide prevalence rate of 3.4% in children and adolescents [2]. In approximately half to two-thirds of cases, symptoms and impairment associated with the disorder persist into adulthood [3,4]. Having a childhood history of ADHD and persistent ADHD are both associated with higher prevalence and a more severe and chronic course of substance use disorders (SUDs) in adolescence and adulthood [4–8], indicating that ADHD contributes to an earlier SUD onset [9] and a longer SUD duration [9,10].

Several longitudinal studies have examined the course of SUD diagnoses such as substance abuse or dependence. Two meta-analyses demonstrated that subjects with childhood ADHD were more likely to develop alcohol, nicotine, cannabis, cocaine and other illicit drug abuse or dependence in late adolescence or early adulthood [5,8]. Biederman *et al.* [11] also reported a more rapid progression from substance abuse to dependence among 140 ADHD male adolescents within 4 years when compared to 120 normal control subjects. Recent studies continued to confirm that individuals with persistent ADHD are more likely to develop SUD between late adolescence and early adulthood compared to those without ADHD, suggesting that once individuals with ADHD have developed SUD in adolescence, SUD prevalence remains stable until early adulthood [12–16]. Moreover, as long as individuals with ADHD did not develop SUD prior to early adulthood, they did not appear to be at a higher risk of doing so later in life [15,17].

Although there are studies on SUD, little is known about the course of substance use in early adulthood, particularly with respect to whether there is a change in substance use (e.g. escalation of cannabis use) and/or initiation of substance use (e.g. starting cannabis use) in those individuals with an ADHD. To our knowledge, only two prospective studies have examined the escalation or initiation of use of separate substances. Molina & Pelham [18] observed an association between ADHD persistence and higher rates of daily cigarette smoking, repetitive drunkenness and alcohol-related problems in 142 adolescents diagnosed with childhood ADHD compared to 100 controls. Individuals with persistent ADHD were three times more likely to have used inhalants, hallucinogens and cocaine and engaged in non-medical use of prescription stimulants. Sibley *et al.* [19] showed that 113 individuals who were diagnosed with ADHD in early childhood and initiated cigarette and cannabis use in early adolescence were four to five times more likely to progress to heavy use of these substances by the age of 18 years relative to 65 individuals without ADHD. These results provide

some evidence for the assumption that individuals with ADHD show an initiation and/or escalation in the use of certain substances between late adolescence and early adulthood compared to those without ADHD.

In epidemiological and clinical samples, ADHD and conduct disorder (CD) were found to occur together in 30–50% of cases, most probably as a result of shared genetic and environmental influences between the two disorders rather than an aetiologically distinct subtype or a third, independent disorder [20]. However, few studies on ADHD adjusted for CD. Evidence as to whether children with ADHD and comorbid CD are at the highest risk of developing SUD is equivocal [21]. Two studies have shown a mediatory effect of CD, in that ADHD was no longer related significantly to SUD development if CD was controlled for. Moreover, ADHD was associated significantly with CD, which was related significantly to substance use outcomes [19,22]. However, most studies still demonstrated significant effects of ADHD on substance use outcomes after controlling for CD and showed additional significant effects of CD on substance use outcomes, independent of an ADHD diagnosis [11,13,16,18,23,24]. These findings suggest that ADHD and CD are likely to contribute independently to a higher risk of SUD development, and in some cases ADHD could be a risk factor for CD development. Therefore, it is important to control for CD, testing it as a mediator in prospective studies examining associations between ADHD and the course of substance use.

The aim of the present prospective study was to determine the initiation of substance use at 15-month follow-up among baseline non-users and to examine the course of substance use (escalation) at 15-month follow-up among baseline users in a large sample of Swiss men in their early 20s. Specifically, we expected increased frequencies of initiation of use of alcohol, tobacco, cannabis and other drugs, particularly of stimulants including all types of amphetamines, ADHD medication and cocaine, in baseline non-users screened positive for ADHD (ADHD⁺), relative to those screened negative for ADHD (ADHD⁻). Among baseline users, we hypothesized that alcohol, tobacco and cannabis use escalation could be observed in the ADHD⁺ group but not in the ADHD⁻ group. Finally, we expected that ADHD would be an independent predictor of substance use initiation and escalation, particularly for stimulants, even if CD was included as a mediator in the relationship between ADHD and substance use outcomes, and even if CD contributed to initiation and escalation independently.

METHOD

Participants and procedures

The current study analysed data from the longitudinal Cohort Study on Substance Use Risk Factors (C-SURF) [25],

which examined substance use patterns in young Swiss men. Participants were recruited from three of Switzerland's six army recruitment centres (Lausanne, Windisch and Mels). In Switzerland, army recruitment is mandatory for men nearing 19 years of age to determine their eligibility for military or civil service. Due to mandatory conscription there are no preselection criteria, e.g. affluence or education as in college student samples. The three recruitment centres cover 21 of 26 Swiss cantons, and we used them solely for participant recruitment. These centres were chosen for the following reasons: the centre in Lausanne is responsible for all French-speaking Swiss men, Windisch is the largest centre with the largest number of German-speaking Swiss conscripts and Mels is responsible for eastern Switzerland. Thus, men from the Italian-speaking region and from Zurich were excluded from the sample. In total, 15 066 Swiss men attended the three army recruitment centres within 1 year (between August 2010 and November 2011 at the latest). This is a quasi-census of all men called for conscription during this period in these three centres. Exceptions were those who did not show up after convocation and those who were severely disabled. Principally, all men were eligible for study participation, which was independent of their suitability for military service. Therefore, not only did the sample include recruits serving in the army but also civil servants and those judged not being able for any service. Participants were assured of strict confidentiality, and they were assessed outside the military environment. Therefore, those who provided written informed consent received the baseline questionnaire approximately 2 weeks later at their home addresses. Questionnaires could be completed via paper and pencil or online. Baseline data were collected between August 2010 and March 2012, as data collection lasted longer than enrolment during army conscription, and the young men received the follow-up questionnaire approximately 15 months after the completion of the baseline questionnaire.

Of the total sample (census), 1829 men could not be informed about the study during army recruitment procedures because of organizational reasons, leaving 13 237 potential participants. Of these, 7556 (50.1% of the eligible population) provided written informed consent to participate in the C-SURE. Despite extensive efforts to encourage all young men who provided informed consent for participation in the Army centres to complete the baseline questionnaire, only 5990 men (79.3%) did so at baseline, and of these 5464 participated at follow-up (91.2%). Reasons for silent refusal among consenters were that they lost interest in the study or that they believed that signing the consent form was mandatory, as it was asked during the army recruitment procedures. Two published reports showed that differences between respondents, non-respondents and non-consenters were small [26,27] and

showed different substance use trends, i.e. non-consenters/non-respondents were more often users of some substances, but less often users of other substances. Owing to missing data for at least one of the analysed variables, data for 361 men (ADHD⁺ group: 9; ADHD⁻ group: 352) were excluded from the analysis, leaving a total sample of 5103 young men. The study protocol (Protocol no. 15/07) was approved by the Lausanne University Medical School Clinical Research Ethics Committee.

Measures

Assessment of socio-demographic characteristics and ADHD

All assessment instruments can be found on the C-SURE website [25]. ADHD and socio-demographic characteristics, i.e. age, marital status, highest educational level and current employment, were assessed at baseline.

Current ADHD was assessed using the adult ADHD Self-Report Scale (ASRS version 1.1), a short screening scale developed by the World Health Organization for use in general population screening [28]. The ASRS consists of six questions concerning the frequency of recent ADHD symptoms, based on the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [1]. In this study, each of the six questions asked how often a symptom had occurred over the preceding 12 months, with responses provided using a five-point scale ranging from 0 ('never') to 4 ('very often'). The total score ranged from 0 to 24. As proposed by Kessler *et al.* [29], a score of 14 was defined as the cut-off point for ADHD⁺ versus ADHD⁻. In a previous study that used this cut-off point, 64.9% of clinician-defined ADHD cases and 93.9% of clinician-defined non-ADHD cases were classified correctly in a sample of 218 participants [29].

CD in early adolescence was assessed retrospectively using the self-report version of the Mini International Neuropsychiatric Interview Plus, which measures six behaviours (e.g. destruction of property and frequent aggression towards people and animals) exhibited before the age of 15 years [30], as part of the antisocial personality disorder diagnostic criteria. In early adolescence, if two or more of the dichotomous items (no = 0; yes = 1) receive a response of 'yes', the individual is considered to have a CD.

Assessment of substance use

Substance use was measured at baseline and follow-up with a recall period of 12 months. Alcohol use was assessed by asking participants about whether they had consumed any type of alcohol in the preceding 12 months, the number of days per week that involved alcohol consumption and the number of standard drinks (i.e. 10–12 g pure alcohol) they consumed on a usual drinking day. High-risk binge drinking was defined as the consumption of six or

more standard drinks on one occasion at least monthly [31]. Alcohol abuse and dependence were assessed via a questionnaire [32] based on the diagnostic criteria of the DSM-5 diagnostic criteria and included items adapted originally from the Semi-Structured Assessment for the Genetics of Alcoholism [33,34].

For tobacco use, participants were asked about whether they had smoked in the preceding 12 months, the number of days per week that involved smoking and the number of cigarettes they smoked on a usual smoking day. Nicotine dependence was assessed using the Fagerström Test for Nicotine Dependence [35].

Regarding cannabis use, participants were asked about whether they had used cannabis in the preceding 12 months, the frequency of cannabis used and the number of hours spent under the influence of cannabis on days on which they used it. Cannabis use disorder was determined using the Cannabis Use Disorder Identification Test [36].

The use of illicit drugs in the preceding 12 months was measured, including drugs such as amphetamines and methamphetamines (known as speed), 3,4-methylenedioxy-methamphetamine (known as MDMA/ecstasy), hallucinogenic mushrooms, psilocybin, peyote and mescaline and other hallucinogens such as lysergic acid diethylamide (known as LSD), phencyclidine (known as PCP/angel dust), 2,5-dimethoxy-4-bromophenethylamine (known as 2C-B) and 2,5-dimethoxy-4-iodophenethylamine (known as 2C-I); heroin; and cocaine/crack/freebase.

Non-medical use of prescription drugs was determined by asking participants whether they had taken ADHD medication such as methylphenidate (e.g. Ritalin[®]) or amphetamine sulphate (e.g. Aderall[®]), or sedatives, such as hypnotics or tranquillizers, without a prescription or for any reason other than those for which the substance is prescribed by a physician, in the preceding 12 months.

Statistical analysis

χ^2 and independent-sample *t*-tests were performed using SPSS version 23 to compare socio-demographic characteristics and substance use outcomes at baseline between the ADHD⁺ and ADHD⁻ groups. For *t*-tests of continuous variables, when the variable was positively skewed, the values were square root-transformed to produce normality. Random-effect multiple regression analyses were

performed in Stata intercooled 14 to account for random centre clustering effects using the xtreg procedure for continuous outcomes on change between baseline and follow-up (i.e. standard drinks, cigarette use per week and days of cannabis use per year) among baseline users. Random-effect logistic regression analyses were performed using the Stata procedure xtlogit for dichotomous outcomes (i.e. any use of alcohol, tobacco, cannabis or illicit drugs and non-medical use of prescription drugs in the preceding 12 months) on initiating substance use among baseline non-users of the corresponding substance. All multiple regression analyses controlled for socio-demographic characteristics. Random-effect mediation analyses were performed using the baseline measure of CD as a mediator. Changes in the effects of substance use on ADHD without CD were compared with the direct paths that included CD as a mediator (*c'*; see Fig. 1). A change in the amount and significance of effects with and without the mediator was considered to indicate mediation. Paths from ADHD to CD (a) and from CD to substance use (b) were also analysed (see Fig. 1). A mediation analysis was chosen because ADHD and CD most probably share genetic and environmental influences and ADHD precedes CD chronologically [20]. We also tested the random-effect moderation of ADHD by CD, as suggested by an anonymous referee on an earlier version of the present paper.

RESULTS

Socio-demographic characteristics and ADHD symptom groups

Socio-demographic characteristics for the two groups have been summarized in Table 1, using a dichotomous classification: 'ADHD⁻' (ASRS score 0–13 for 4888 men: 95.8%) and 'ADHD⁺' (ASRS score 14–24 for 215 men: 4.2%). Participants' mean age at baseline was 20.0 [standard deviation (SD) = 1.21] years. ADHD⁺ and ADHD⁻ were not statistically different with reference to socio-demographics, but the ADHD⁺ group was significantly more likely to have been screened positive for CD compared with the ADHD⁻ group.

Baseline substance use

Using the dichotomous classification described above, participants who screened positive for ADHD showed

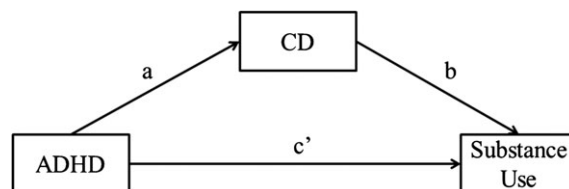


Figure 1 Mediation analysis with attention deficit/hyperactivity disorder (ADHD) as the predictor, substance use as the dependent variable and conduct disorder (CD) as the mediator. Paths a, b and *c'* (for explanation see statistical analysis)

Table 1 Baseline socio-demographic characteristics for the attention deficit/hyperactivity disorder (ADHD)-negative and ADHD-positive groups.

	ADHD-negative (ASRS < 14; n = 4888)		ADHD-positive (ASRS ≥ 14; n = 215)		<i>t</i> / χ^2	<i>P</i>
	Mean/% (n)	SD	Mean/% (n)	SD		
Age (years)	20.0	1.21	20.1	1.22	-1.36	0.178
Marital status					2.18	0.536
Married	0.6 (27)		0.5 (1)			
In a relationship	4.4 (215)		2.4 (5)			
Single	95.0 (4609)		97.2 (206)			
Divorced	0.0 (1)		0.0 (0)			
Education					6.01	0.111
Lower than high school	49.9 (2416)		47.2 (100)			
High school	23.7 (1150)		19.3 (41)			
High school + 2 years	24.9 (1206)		31.1 (66)			
College	1.5 (74)		2.4 (5)			
Employment					3.18	0.529
High school/college	74.9 (3621)		75.4 (159)			
Employed (incl. unskilled work or self-employed)	17.6 (852)		15.6 (33)			
Unemployed	5.0 (243)		5.2 (11)			
Welfare/disability pension	0.3 (13)		0.0 (0)			
Other (sabbatical, internship, military or civil service)	2.2 (108)		3.8 (8)			
Conduct disorder in early adolescence					23.64	< 0.001
Yes	18.8 (913)		32.5 (69)			
No	81.2 (3940)		67.5 (143)			

ASRS = adult ADHD Self-Report Scale; *n* varies from 5048 to 5103 because of missing data. SD = standard deviation.

significantly higher baseline substance use rates compared with those who were screened negative for ADHD (see Table 2). Alcohol use outcomes in the 12 months preceding baseline assessment indicated that the quantity of alcohol consumed daily, number of drinking days and weekly frequency of alcohol use were significantly higher in the ADHD⁺ group compared to those in the ADHD⁻ group. The prevalence of high-risk binge drinking and of alcohol use disorder were also considerably higher in the ADHD⁺ group relative to those of the ADHD⁻ group.

Compared to the ADHD⁻ group, the ADHD⁺ group relative to those of the ADHD⁻ group showed significantly higher smoking patterns on all measured variables, including nicotine dependence prevalence, which was more than two times higher.

There were significant between-group differences in cannabis use prevalence in the preceding 12 months. The annual frequency of cannabis use was non-significant, but the number of hours under the influence of cannabis per use day in the ADHD⁺ group was significantly higher than that of the ADHD⁻ group. The number of men who met the cannabis use disorder criteria was almost three times higher in the ADHD⁺ group than that in the ADHD⁻ group.

Further, the presence of ADHD was associated significantly with amphetamine, ecstasy, hallucinogen and

cocaine use as well as of non-prescribed use of ADHD medication and sedatives. There were no significant between-group differences in heroin use prevalence.

Change in substance use from baseline to follow-up

There were no significant effects of ADHD on changes in nicotine and cannabis use from baseline to follow-up (see Table 3), and significant change in alcohol use became non-significant when controlling for CD (see Table 4). However, the significant group effects shown in Table 2 indicate that overall numbers of standard drinks consumed weekly, cigarettes smoked weekly and days of cannabis use per year were significantly higher in the ADHD⁺ group compared to those of the ADHD⁻ group.

There was a significantly greater initiation of all illicit substances (including non-medical use of ADHD medicine and sedatives) in the ADHD⁺ group relative to those of the ADHD⁻ group; the prevalence rates for initiation of the licit substances alcohol and tobacco did not differ significantly between groups.

When including CD as mediator, the effects of ADHD remained unchanged except that changes in alcohol use and initiation of ecstasy became non-significant (see Table 4). Thus, the effects of ADHD were mainly

Table 2 Substance use in the attention deficit/hyperactivity disorder (ADHD)-negative and ADHD-positive groups in the 12 months preceding baseline assessment.

	ADHD-negative (ASRS < 14; n = 4888)		ADHD-positive (ASRS ≥ 14; n = 215)		<i>t</i> / χ^2	<i>P</i>
	Mean/% (n/N)	SD	Mean/% (n/N)	SD		
Alcohol						
Abstinence	7.6 (373/4888)		7.4 (16/215)		0.00	1.000
Drinking days per week ^a	1.7	1.37	2.0	1.70	-2.70	0.008
Standard drinks per drinking day ^a	4.3	3.76	5.1	4.23	-2.72	0.007
Standard drinks per week ^{a,b}	7.7	12.01	11.0	17.25	-3.23	0.001
High-risk binge drinking	45.1 (2198/4873)		54.2 (116/214)		6.48	0.011
Any alcohol use disorder	9.5 (466/4883)		25.4 (54/213)		53.96	<0.001
Tobacco						
Smoking	45.2 (2207/4886)		57.7 (124/215)		12.48	<0.001
Smoking days per week ^a	4.2	2.97	4.9	2.81	-2.59	0.011
Cigarettes per smoking day ^a	8.4	7.22	11.1	8.61	-3.22	0.002
Cigarettes per week ^{a,b}	49.4	54.75	69.1	66.10	-3.46	0.001
Nicotine dependence	9.9 (483/4888)		20.0 (43/215)		21.73	<0.001
Cannabis						
Cannabis use	29.3 (1432/4888)		49.3 (106/215)		38.20	<0.001
Days of cannabis use per year ^{a,b}	89.1	124.42	111.4	136.86	-1.94	0.052
Hours under the influence of cannabis per using day ^a	2.5	1.67	3.0	2.22	-2.24	0.027
Cannabis use disorder	8.0 (392/4888)		21.9 (47/215)		48.43	<0.001
Illicit drug use						
Amphetamines/meth-amphetamines	3.1 (151/4880)		6.5 (14/214)		6.71	0.010
Ecstasy/MDMA	3.4 (167/4882)		8.4 (18/214)		13.20	<0.001
Hallucinogens	3.7 (179/4881)		9.3 (20/214)		16.13	<0.001
Heroin	0.4 (18/4882)		0.9 (2/214)		0.54	0.461
Cocaine/crack/freebase	2.9 (141/4882)		9.3 (20/214)		25.87	<0.001
Non-medical use of prescription drugs						
ADHD medication (methylphenidate, amphetamine sulphate)	1.7 (83/4878)		5.6 (12/213)		15.15	<0.001
Sedatives (tranquillizers, hypnotics)	4.1 (201/4878)		12.2 (26/213)		29.45	<0.001

ASRS = adult ADHD Self-Report Scale; MDMA = 3,4-methylenedioxy-methamphetamine. ^aMen who did not use this substance were excluded from this analysis, resulting in samples of *n* = 4653 for alcohol, *n* = 2186 for tobacco and *n* = 1537 for cannabis. ^bDue to variables' positive skewness, values were transformed into square roots and tested via *t*-test. The untransformed mean and standard deviation (SD) are presented for ease of interpretation of the results.

independent of the effects of CD, which had significant effects on all substance use variables with the exception of changes in cigarette use and initiation of drinking alcohol (see Table 4).

We tested additionally for an ADHD by CD moderation. Moderation effects were largely non-significant (*P* > 0.1), with two exceptions: for changes in alcohol use the main effects of ADHD [*b* = -0.30; 95% confidence interval (CI) = -2.30, 1.71; *P* = 0.770) and CD (*b* = -0.72; 95% CI = -1.59, 0.15; *P* = 0.103) were non-significant. Only the interaction effect of ADHD and CD was significant (*b* = -4.23; 95% CI = -7.82, -0.65; *P* = 0.021), showing a reduction in alcohol use between baseline and follow-up in men with both ADHD and CD. The second significant moderation was found for the initiation of amphetamine/methamphetamine use: the negative interaction effect (*b* = -1.31; 95% CI = -

2.56, -0.07; *P* = 0.039) together with the positive main effects for ADHD (*b* = 1.69; 95% CI = 1.05, 2.34; *P* < 0.001) and CD (*b* = 1.13; 95% CI = 0.73, 1.52; *P* < 0.001) indicates a similarly higher incidence of amphetamine/methamphetamine use among ADHD⁺-only men compared with men being screened positively for both ADHD and CD; that is, the incidence is similarly high independent of the presence of CD. The incidence was also higher for men with CD only but without ADHD. The effects of the moderation analysis of ADHD and CD for amphetamine/methamphetamine use are illustrated in Fig. 2.

DISCUSSION

This longitudinal study compared substance use patterns in 215 men who were screened positive for ADHD with

Table 3 Change in and initiation of substance use in the attention deficit/hyperactivity disorder (ADHD)-negative and ADHD-positive groups from baseline to follow-up.

Outcomes at follow-up ^a	ADHD-negative (ASRS < 14)		ADHD-positive (ASRS ≥ 14)		OR	95% CI	P
	Mean/% (n/N)	SD	Mean/% (n/N)	SD			
Change in substance use ^b							
Standard drinks per week	0.6	11.66	-1.0	14.96	-	-3.41 to 0.09 ^d	0.039
Cigarettes per week	2.2	28.63	0.5	35.04	-	-5.74 to 2.27 ^d	0.396
Days of cannabis use per year	-1.4	55.60	-4.9	90.69	-	-11.50 to 4.49 ^d	0.390
Initiation of substance use ^c							
Licit substances							
Drinking alcohol	34.6 (129/373)		43.8 (7/16)		2.10	0.69 to 6.37	0.189
Smoking cigarettes	14.0 (376/2678)		14.3 (13/91)		1.07	0.59 to 1.96	0.816
Illicit substances							
Cannabis use	11.8 (409/3456)		19.3 (21/109)		1.85	1.12 to 3.06	0.016
Amphetamines/methamphetamines	2.4 (112/4718)		8.0 (16/200)		3.81	2.20 to 6.60	<0.001
Ecstasy/MDMA	3.4 (158/4707)		6.1 (12/196)		2.01	1.09 to 3.69	0.025
Hallucinogens	3.0 (139/4697)		6.2 (12/194)		2.24	1.22 to 4.12	0.010
Heroin	0.6 (28/4845)		1.9 (4/212)		3.62	1.25 to 10.47	0.018
Cocaine/crack/freebase	2.4 (112/4731)		6.7 (13/194)		3.25	1.79 to 5.90	<0.001
Non-medical use of prescription drugs							
ADHD medication (methylphenidate, amphetamine sulphate)	1.0 (46/4791)		4.0 (8/200)		4.45	2.06 to 9.60	<0.001
Sedatives (tranquilizers, hypnotics)	3.3 (156/4666)		11.8 (22/187)		2.43	1.32 to 4.48	0.004

ASRS = adult ADHD Self-Report Scale; MDMA = 3,4-methylenedioxy-methamphetamine. ^aCovariates included age, marital status, education and employment. ^bMean and standard deviation (SD) for the total sample, including men who used the corresponding substance at baseline. ^cMen who used the corresponding substance at baseline were excluded from these analyses. ^d95% confidence interval (CI) for B. OR = odds ratio.

Table 4 Mediation analysis of attention deficit/hyperactivity disorder (ADHD), conduct disorder and substance use from baseline to follow-up.

Outcomes at follow-up ^a	ADHD to substance use (c') ^d			ADHD to CD (a) ^d			CD to substance use (b) ^d		
	b	95% CI	P	b	95% CI	P	b	95% CI	P
Change in substance use ^b									
Standard drinks per week	-1.62	-3.29, 0.04	0.056	0.80	0.49, 1.11	<0.001	-0.96	-1.80 to 0.12	0.025
Cigarettes per week	-1.57	-5.58, 2.45	0.445	0.82	0.51, 1.12	<0.001	-1.22	-3.26 to 0.82	0.242
Days of cannabis use per year	-2.69	-10.70, 5.32	0.511	0.81	0.51, 1.12	<0.001	-5.91	-9.97 to 1.86	0.004
Initiation with substance use ^c									
Licit substances									
Drinking alcohol	0.74	-0.36, 1.85	0.188	0.15	-1.22, 1.52	0.830	-0.03	-0.68 to 0.61	0.924
Smoking cigarettes	0.03	-0.57, 0.64	0.911	0.62	0.07, 1.17	0.027	0.41	0.11 to 0.71	0.008
Illicit substances									
Cannabis use	0.59	0.08, 1.09	0.022	0.44	-0.08, 0.95	0.097	0.52	0.26 to 0.79	<0.001
Amphetamines/methamphetamines	1.23	0.67, 1.78	<0.001	0.70	0.37, 1.02	<0.001	0.97	0.60 to 1.35	<0.001
Ecstasy/MDMA	0.55	-0.07, 1.16	0.083	0.74	0.41, 1.07	<0.001	1.17	0.84 to 1.49	<0.001
Hallucinogens	0.63	0.01, 1.26	0.046	0.81	0.49, 1.14	<0.001	1.12	0.77 to 1.46	<0.001
Heroin	1.12	0.04, 2.20	0.040	0.77	0.46, 1.07	<0.001	1.02	0.30 to 1.75	0.006
Cocaine/crack/freebase	1.05	0.45, 1.66	0.001	0.70	0.37, 1.03	<0.001	1.07	0.69 to 1.44	<0.001
Non-medical use of prescription drugs									
ADHD medication (methylphenidate, amphetamine sulphate)	1.41	0.64, 2.19	<0.001	0.70	0.38, 1.37	<0.001	0.63	0.04 to 1.22	0.040
Sedatives (tranquillizers, hypnotics)	0.83	0.21, 1.44	0.008	0.67	0.33, 1.01	<0.001	0.55	0.17 to 0.93	0.004

CD = conduct disorder; MDMA = 3,4-methylenedioxy-methamphetamine. ^aCovariates included age, marital status, education and employment. ^bMean and standard deviation (SD) for the total sample including men who used the corresponding substance at baseline. ^cMen who used the corresponding substance at baseline were excluded from these analyses. ^dInterpretation of the paths a, b and c', see statistical analysis and Fig. 1. CI = confidence interval.

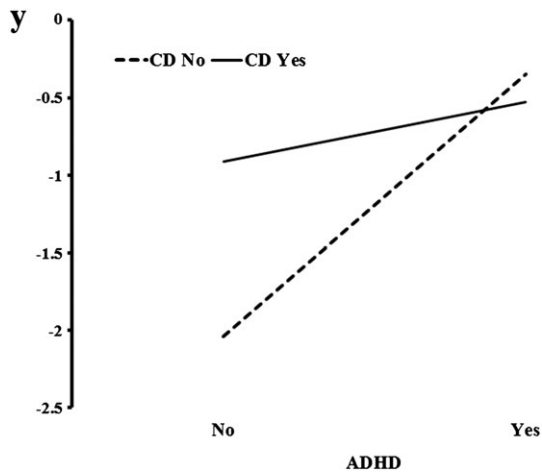


Figure 2 Result of the random effect moderation analysis of attention deficit/hyperactivity disorder (ADHD) by conduct disorder (CD) on initiation of amphetamine/methamphetamine use. Result of the regression analysis (y) includes the intercept ($a = -2.04$)

those of 4888 men who were screened negative for ADHD in a large sample of young Swiss men. Sizeable group differences in substance use and SUD were observed at baseline. The ADHD⁺ group showed considerably higher prevalence rates of alcohol, nicotine and cannabis use disorders and patterns of heavier use than those in the ADHD⁻ group. In addition, the 12-month prevalence rates of illicit drug use, except heroin, and of non-medical use of prescription drugs were considerably higher in the ADHD⁺ group compared to those of the ADHD⁻ group. Many studies examining SUD prevalence rates and other substance use outcomes in individuals with ADHD in early adulthood suggested that ADHD was related to a greater likelihood of use and abuse of a wide range of potentially addictive substances [5,8]. This study confirmed this association in a large sample of Swiss men in early adulthood, enhancing the validity of earlier studies.

An important finding was that when adjusting for CD the changes in alcohol, tobacco and cannabis use remained stable in both groups from baseline to follow-up, indicating that the ADHD⁺ group continued to use these substances more heavily compared to the ADHD⁻ group; the ADHD⁺ group neither increased (no escalation) nor decreased their use relative to that of the ADHD⁻ group. Similarly, Breyer *et al.* [12] and Levy *et al.* [15] did not observe any change in SUD prevalence rates over time. However, they examined only substance dependence as an outcome and did not consider use patterns.

The stable alcohol, tobacco and cannabis use patterns in early adulthood in the present study may be related to the age of participants. Commonly, age of onset for alcohol, tobacco and cannabis use starts at an earlier age. For example, Lambert *et al.* [14] reported the onset of alcohol use at 13.8 years, of tobacco at 12.3 years and of cannabis at 14.9 years. In individuals with childhood ADHD, Sibley

et al. [19] reported higher risk of alcohol, tobacco and cannabis use escalation by the age of 18 years once abuse had been initiated. The mean age of our sample was 20 years; therefore, the sample of the present study is 'too old' to show an increase in already initiated substance use such as alcohol, tobacco and the most prevalent drug, cannabis. However, the ADHD⁺ group continued to use alcohol, tobacco and cannabis more heavily and frequently relative to the ADHD⁻ group.

Men in the ADHD⁺ group who did not already use the corresponding substance at baseline were more likely to initiate use of cannabis and some illicit drugs (e.g. amphetamine/methamphetamine, hallucinogens and cocaine) and to engage in non-medical use of prescription drugs (i.e. ADHD medication and sedatives) between baseline and follow-up compared to the ADHD⁻ group. This was not observed for alcohol, tobacco and ecstasy/MDMA. Owing to our large sample size, we were able to report that young men with ADHD were more likely to initiate the use of certain drugs than those without ADHD. Similarly, Levy *et al.* [15] observed a greater likelihood of new-onset drug dependence in early adulthood in individuals with childhood ADHD. However, their small sample size and focus on the disorder rather than the substance use prevented them from evaluating differences between specific drug use. Higher rates of beginning to use stimulant drugs, such as amphetamine/methamphetamine and cocaine, and non-prescribed use of ADHD medication in particular, support the hypothesis that men with ADHD seek the stimulating effects of certain drugs (e.g. elevated concentration), possibly using them as a form of self-medication [37]. However, in this study, the ADHD⁺ group was also more likely to initiate the use of sedatives, cannabis and even heroin, perhaps because they sought a reduction in hyperactivity, which may remain at 20 years of age and is more likely to decline in their mid-to-late 20s [38,39]. Using substances of reasons for self-medication could lower the threshold for initiation of the use of other substances that may not have desired effects on ADHD symptoms. This is more likely to occur in those men with ADHD, as they initiate substance use more often. Men with ADHD could also be more likely to experience comorbid psychiatric disorders such as depression or personality disorders, elevating the risk of using addictive substances [40].

These results did not change extensively when CD in early adolescence was included as a mediator in the analysis, revealing two important findings. First, CD elevated the risk of initiation of use of all substances except alcohol, independently of ADHD, as reported in numerous other studies [11,13,16,18,23,24]. Therefore, CD alone carries a risk of substance use and the interplay between ADHD and CD exert additive effects, rendering young men even more prone to substance use initiation [21]. Secondly, CD

exerted only a mediational effect on the association between ADHD and initiation of ecstasy use but not on those between ADHD and initiation of cannabis, stimulants, hallucinogens or sedative use. These findings suggest that ADHD carries a unique risk for substance use initiation, which is independent of the presence of CD in early adolescence, particularly for substances discussed within the context of self-medication [21]. To date, only two prospective studies have revealed a mediational effect of CD. However, Brook *et al.* [22] examined SUD but did not explore substance use initiation, and Sibley *et al.* [19] examined alcohol, tobacco and cannabis use but did not include other substances such as stimulants, including non-prescription use of ADHD medication, the potential use of which as a form of self-medication is high in men with ADHD.

This study has important clinical implications, suggesting that the use of an easily applicable screening instrument for ADHD, the ASRS, could help to identify a group of young men at particular risk of persistently high levels of alcohol, tobacco and cannabis use and initiating use of various drugs, including stimulants and sedatives. CD contributes independently to elevated risk of initiation of use of any substance except alcohol. This finding may be of specific interest within the context of (secondary) prevention programmes, allowing a specific focus on high-risk men in early adulthood.

Our results should be interpreted in the context of some limitations. First, the findings are valid only for men and may not be generalizable to women. However, in a meta-analysis, Lee *et al.* [5] did not observe sex differences in increased risk of developing SUD in individuals with ADHD. Secondly, ADHD was assessed using the ASRS screening instrument rather than structured diagnostic interviews; therefore, the diagnosis of ADHD could not be confirmed via extensive clinical examination. Similarly, the assessment of CD and substance use was based on self-administered questionnaires. We cannot exclude the possibility that some men may have under- or over-reported their ADHD and CD symptoms or substance use. However, the assessment instruments have been validated [29,31,35,36,41]; in particular, the reliability and validity of using self-report screening instruments to assess ADHD [42], including ADHD in the context of SUD [43] in adults, have been demonstrated in previous studies. Nevertheless, we could not rule out the possibility that some men with problematic substance use could have been more likely to answer the ASRS items in the affirmative, particularly as van de Glind *et al.* [43] showed that the sensitivity of the ASRS was high ($r=0.88$) but specificity was lower ($r=0.66$). However, this issue was minimized, as only men screened positive for ADHD who did not use the corresponding substance at baseline were included in initiation analyses. Thirdly, self-medication was not assessed;

therefore, intention to use substances in this manner was unknown and should be examined. Fourthly, surprisingly, we could not find significant differences in education or employment, but many studies have indicated that individuals with ADHD exhibit impairment in these domains [44]. In Switzerland, the education system supports pupils with low performance as much as possible to ensure that they are able to leave school with the best possible education. In addition, men with ADHD may have held secure employment, as for several years the Swiss unemployment rate has been approximately 3.2% [45]. Fifthly, the ADHD prevalence rate was 4.2% in this Swiss sample, which is at the lower end of the world-wide mean ADHD prevalence rates, and 5.3% in individuals aged 18 years or younger [46], suggesting that the prevalence of ADHD could have been under-represented. One reason could be that the men who had been treated for ADHD via medication and/or behavioural interventions may have lowered the prevalence rate in the present sample. Sixthly, although the total sample was large and the two groups were matched closely on important socio-demographic variables (e.g. same cantons, age, gender), the sample size of the ADHD⁺ group was reduced considerably by a few analyses of subgroups (e.g. initiation of alcohol use). Finally, while the between-group differences were large at baseline some effects were small for substance use initiation, possibly because the follow-up period was short at only 15 months. Future studies need to analyse the course of substance use over a longer period.

CONCLUSIONS

For men in their early 20s, ADHD is a risk factor for continued heavier but not escalating alcohol, tobacco and cannabis use when already consuming these substances. It is also a risk factor for initiating the use of cannabis, stimulants (i.e. amphetamines, cocaine and non-medical use ADHD medication), hallucinogens and sedatives (i.e. non-medical use of tranquilizers, hypnotics and heroin) when not consuming these substances. CD contributes independently to the risk of initiating the use of any substance, except for alcohol, and it did not mediate the association between ADHD and substance use. Young men with ADHD appeared to be prone to using specific drugs, possibly as a means of self-medication. A follow-up period of longer than 15 months would determine whether or not this initiation pattern could be confirmed. From a public health perspective, the identification of ADHD in early adulthood may be relevant for early interventions designed to lower the risk of drug use.

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Declaration of interests

None.

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