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Frequent intoxication and alcohol tolerance in adolescence: Associations with psychiatric disorders in young adulthood

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None.

ABSTRACT

Aims To assess associations of intoxication frequency and number of drinks needed to become intoxicated in mid-adolescence with onset of psychiatric disorders in early adulthood.

Design Prospective cohort study. **Setting** Northern Finland. **Participants** People from the Northern Finland Birth Cohort 1986 who self-reported adolescent alcohol use: 6,548 subjects (69.4% of the original sample). Data on alcohol use were collected using questionnaires at ages 15 – 16 years. **Measurements** Outcomes were any non-organic psychosis, mood disorder, anxiety disorder, any substance use disorder (SUD) and all the studied psychiatric disorders in early adulthood gathered from nationwide health care, pension and insurance registers. Number of drinks needed to become intoxicated was categorized into three classes: (1) No alcohol use or intoxication, and (2) low and (3) high alcohol tolerance (more than 7/9 drinks for females/males) groups. Similarly, intoxication frequency was divided into three classes: (1) never, (2) 1 – 2 times and (3) 3 or more times during the past 30 days.

Information regarding gender, family type, other drug use, psychopathology using Youth Self-Report (YSR) total score, and parental psychiatric disorders were used as covariates.

Findings In the multivariable analyses, both low [OR 3.0, 95% CI 1.3 – 6.7, p -value=0.009] and high [OR 4.4, 95% CI 1.8 – 11.1, p -value=0.001] alcohol tolerance were associated with increased risk of SUD. More frequent intoxication was associated with increased frequency of SUD [OR 3.9, 95% CI 2.0 – 7.3, p -value<0.001] and mood disorder [OR 1.6, 95% CI 1.1 – 2.3, p -value=0.008]. The latter was attenuated after adjusting with concurrent psychopathology (YSR) and other drug use. **Conclusions** Both higher alcohol tolerance and

frequent intoxication in adolescence appear to be associated with increased risk of future substance use disorder.

Accepted Article

INTRODUCTION

Alcohol consumption, and especially heavy drinking, begins globally in adolescence in many countries (1). Heavy drinking, at least occasionally, may be culturally normative and it has been reported to associate with better well-being and a lower level of depression and anxiety than abstinence or excess drinking (2-5). Nonetheless, for those individuals who develop problems with substance use, some drinking patterns may confer risk. Indeed, drinking frequency in adolescence was related to alcohol use disorders (AUDs) and alcohol dependence rather than the amount of alcohol consumed per event or frequency of heavy episodic drinking (6). On the other hand, teenage frequent heavy episodic or binge drinking increasing problem drinking, AUDs, and alcohol dependence in young adulthood has been reported (7-12). However, the sample sizes have been fairly small in these studies (n = from 600 to 2000) (7,8,11,12). Thus, there is limited knowledge using prospective longitudinal large birth cohort studies about how drinking patterns in adolescence, e.g. frequency of intoxication or number of drinks needed for experience it, are related to later diagnoses in adulthood. In addition, although many studies have investigated the relationship between quantity of alcohol consumed in a single occasion and problematic alcohol use (6,8,11), research relating the number of drinks reported necessary to achieve intoxication and later-life mood disorder or substance use disorder (SUD) is scarce.

Adolescent problem drinking has been associated with teenage depression and anxiety disorders in cross-sectional studies (13,14). In turn, associations between adolescent alcohol abuse, frequent intoxication, frequent high density drinking and AUDs in late-adolescence and early adulthood has been obtained in longitudinal studies (7-12,15-18). Furthermore, AUD and major depression are often comorbid outcomes in young adulthood, and AUDs

have been shown to increase the risk of major depression and anxiety disorder in young adults (19-21).

Using data from the Northern Finland Birth Cohort 1986, we aimed to investigate the prospective association between self-reported frequency of intoxication and alcohol tolerance in mid-adolescence with register-based psychiatric diagnoses by the age of 29 – 30 years. Alcohol tolerance was determined by self-reported number of drinks required to experience intoxication. We assessed the predictive associations of self-reported number of drinks required to achieve intoxication and frequency of intoxication during the previous 30 days of mid-adolescence with psychiatric outcomes in early adulthood, controlling for other risk factors, including illicit drug use, psychiatric symptoms in adolescence, and parental psychiatric and SUD diagnoses.

METHODS

Participants

Northern Finland Birth Cohort (NFBC) 1986 is an ongoing follow-up study of 99% of all births, comprising all live-born children (n=9,432) with an expected date of birth between 1st of July 1985 and 30th of June 1986, from the two northernmost provinces in Finland (22). In all, 7,344 (48.8% boys) participated in the study in 2001 – 2002, when the study members were aged 15 – 16 years. The data collection on alcohol use was done in two parts: First, a postal questionnaire was sent to the participants. After that, the participants were invited to attend a field study, where they filled-in another questionnaire including questions on their alcohol use. Participants who signed the informed consent form and answered the questions on alcohol use under study were included in the study. We excluded those with mental retardation (ICD-10 diagnose F70) and those who were deceased on follow-up. Those who

moved abroad after participating in the study at age 15 – 16 years were included (n=106, 1.1% of the original participants). The final sample included 6548 (49% boys) (Fig. 1).

Information on psychiatric diagnoses was collected cumulatively from the four nationwide registers from the participant age 15-16 years until the end of 2016, i.e. by the participant's age of 29 – 30 years. If the same diagnosis occurred twice or more in the same patient during the collection, only the first event was included. Additionally, psychiatric diagnoses at ages 29 – 30 years were not available for 200 participants who answered to both questionnaires in adolescence. The study was approved by the Ethics committee of the Northern Ostrobothnia Hospital District in Finland (17 May 2006).

insert figure 1 here

Attrition analyses concerning data collection at age 15-16 years have been presented elsewhere (23). There, fewer males (64% v. 71%; χ^2 test, $p<0.001$), participants living in urban areas (66% v. 71%, $p<0.001$) and adolescents with parental psychiatric disorder (58% v. 69%, $p<0.001$) participated. Concerning psychiatric diagnoses, fewer of the diagnosed (65.1%) than undiagnosed (74.2%) subjects retained ($p<0.001$). The Youth Self Report (YSR) (24) total score mean of the excluded was 28.3 (SD 17.6). For information on attrition concerning missing data in the multivariate analyses, see Table 4. Data was not missing completely at random.

Exposures

Self-reported high alcohol tolerance was assessed with the question: 'How many drinks do you need to get drunk?' with options: I have never drunk alcohol, I have never been drunk, 1 – 2, 3, 4, 5, 6, 7 – 8 and 9 drinks or more. One drink was considered as 33 cl of beer, cider or long drink, 12 cl of wine or 4 cl of spirits. Options were pooled into three predictive

variables: 1) No alcohol use or intoxication; 2) low tolerance group, i.e. below the specified cut-off; and 3) high tolerance group, i.e. the exact specified cut-off number and above it concerning the self-reported number of drinks needed to become intoxicated. In many studies, heavy drinking has been determined as over 4 – 6 drinks for women and 5 – 7 drinks for men (25,26). In our data, those limits would have put 32.6% of females and 28.4% of males to the high tolerance group. Therefore, we set the cut-off to 7 drinks for females, classifying 10.1% of the participants in the high-tolerance group, and 9 drinks for males, 12.8% respectively.

Intoxication frequency was assessed with the question: ‘How many times have you been drunk during the past 30 days?’ Response options were: Never, 1 – 2, 3 – 5, 6 – 9, 10 – 19, 20 – 39 or 40 times or more, and this was categorized as a three-class variable: 1) never, 2) 1 – 2 times, and 3) 3 or more. Thus, 10.2% of females and 9.2% of males were included in the group of frequent intoxication (three or more times during the last 30 days).

Outcomes

Cumulative information on diagnosed psychiatric disorders until age 29-30 years were obtained from linkage to four nationwide registers: The Register of Primary Health Care Visits 2011 – 2015 and the Care Register for Health Care 2001 – 2015 of the National Institute for Health and Welfare, the medication reimbursement register of the Social Insurance Institution of Finland 2001 – 2015 and disability pensions of the Finnish Centre for Pensions 2001 – 2016. The Care Register contains information on patients discharged from inpatient care, and since 1998 also on specialized outpatient care. The Register of Primary Health Care Visits includes all outpatient primary health care delivered in Finland. For more information about the registers see (27) Supplement 1. Five outcomes of grouped psychiatric

disorder were formed. The first combined all the studied psychiatric disorders. For the other outcome groupings, the ICD-10 psychiatric diagnoses were divided into four classes: 1) any non-organic psychosis, 2) mood disorder, 3) anxiety disorder and 4) any diagnosis in the “mental and behavioural disorders due to psychoactive substance” category referred to as substance use disorder (SUD). Therefore, SUD includes diagnoses on either alcohol or other drugs or both (ICD details available on request). The reference group in all groupings consisted of those without any diagnosis. Those with psychosis diagnosis could have had a mood, anxiety or SUD diagnosis at some point during the follow-up. The mood disorder outcome excluded any psychosis and any SUD; therefore, those with mood disorder diagnosis may have had an anxiety diagnosis at some point during the follow-up. From the anxiety disorder outcome, any psychosis, SUD and mood disorders were omitted. The SUD outcome excludes any psychosis meaning that those having SUD could also have a mood or anxiety disorder diagnoses at some point of the follow-up period according to the register data.

Confounders

Data on lifetime illicit drug use at age 15 – 16 years was collected using a questionnaire during the field study. The participants were asked two questions: ‘Have you used marihuana or hashish?’ and ‘Have you used ecstasy, heroin, cocaine, amphetamine, LSD or other similar intoxicating drugs?’ These questions were combined as a two-class variable: Illicit drug use (no/yes). A person was categorized to the yes-group, if she/he had used drugs at least once.

During the field study at age 15 – 16 years, information was collected on adolescence psychiatric problems using YSR questionnaire (24) and pubertal maturation (ejaculation/menstruation) as a possible confounding factor.

Data on family structure was gathered by combining information collected from parents at birth and when the cohort member was aged 15 – 16. The classification of the family structure included families with (1) both parents living with the subject all the time and (2) all other families.

Assessed parental education level and alcohol use were gathered from the 15 – 16-year questionnaire administered to the families and answered by parents. Education level of both parents separately was divided into two groups: 1) schooling for 12 years and 2) schooling for less than 12 years. Maternal and paternal alcohol use was divided into three variables: 1) No alcohol use, 2) less than once a week and 3) once a week or more often.

Information on mother's and father's psychiatric diagnoses was based on parental diagnoses in the nationwide registers, which include: 1) Register of Health Care during the years 1972 – 2015. This register includes inpatient care and visits to specialized outpatient health care since 1998. 2) Disability pensions of the Finnish Centre for Pensions (1965 – 2016), and 3) The Register of Primary Health Care Visits (2011 – 2015).

Statistical methods

The data were analyzed using Cox regression analysis with hazard ratios (HR) and 95% confidence intervals (95% CI). The reference group was the abstinent adolescents who had never consumed alcohol. We defined the outcome as psychiatric diagnoses divided to five different classes: any psychiatric disorder, any psychosis, mood disorders, anxiety disorders and SUDs. The probability of surviving without psychiatric diagnosis in the study groups was determined with adjusted Cox regression survival analyses from age 15 – 16 to 29 – 30.

Multinomial logistic regression analyses were used to measure the strength of associations in SUD and mood disorders with odds ratios (OR) and their 95% confidence intervals (95% CI).

Non-drinking adolescents were used as a reference group. Four separate models were built with which the logistic regression analyses were performed. In model 1 number of drinks to become intoxicated, gender and family type were included as independent variables. Model 2 included number of drinks to become intoxicated, gender, family type, other drug use and YSR total score. In model 3 number of drinks to become intoxicated, gender, family type, parental psychiatric diagnoses were included as covariates. Model 4 (the final model) comprised all the studied covariates. Attrition analyses were performed for those participants not included in the Model 4 due to missing data. The models for testing the association between intoxication frequency and mood or SUD were the same except for the number of drinks needed to become intoxicated, which was switched with frequency of intoxication.

Interactions between alcohol tolerance or intoxication frequency and variables in Table 1 in relation to studied psychiatric disorders were detected with interaction test. We also examined for a dose–response between alcohol tolerance and intoxication frequency and psychiatric disorders with a trend test, using the number of drinks needed to become intoxicated and frequency of intoxication as continuous variables in the logistic regression analysis. A correlation between the two outcome variables, i.e. intoxication frequency and alcohol tolerance, was detected with linear regression and multicollinearity diagnostics. The statistical analyses were performed using SPSS statistical software (version 24).

The analysis was not pre-registered and the results should be considered exploratory.

RESULTS

At age 15 – 16 years, 12.8% of males and 10.1% of females reported needing nine/seven drinks or more to become intoxicated. In addition, 9.2% of boys and 10.2% of girls reported being intoxicated three or more times during the last 30 days (data not shown). Moreover, of those meeting the criteria for high tolerance 31.8% reported being intoxicated three or more times during the past 30 days (Table 1). Other background variables associated with alcohol tolerance and intoxication frequency are shown in Table 1 and 2. No statistically significant interactions were detected between alcohol tolerance or intoxication frequency and variables in Table 1 and 2, including gender, in relation to subsequent psychiatric disorders. In addition, one parent or other family type and any parental psychiatric disorder were associated with any offspring psychiatric diagnosis (data not shown).

insert Table 1 here

insert Table 2 here

The prevalences of psychiatric disorders by age 29 – 30 years as a function of number of drinks needed to become intoxicated and intoxication frequency during the past 30 days at age 15 – 16 are illustrated in Figs. 2 and 3. One fifth (21%) of the high alcohol tolerance, 17% of the low alcohol tolerance, and 14% of the no alcohol use or intoxication group had some psychiatric disorder. Also, any psychiatric disorder was diagnosed for 23% among those with high intoxication frequency, 17% in with low intoxication frequency, and 15% in the no intoxication group.

insert figure 2 here

insert figure 3 here

High alcohol tolerance was statistically significantly associated with any psychiatric diagnosis compared to non-drinking reference (HR 1.5, 95% CI 1.3 – 1.9, $p<0.001$) as well as between low alcohol tolerance and reference groups (HR 1.2, 95% CI 1.1 – 1.4, $p<0.001$) (Table 3, Fig. 4a). Of the individual psychiatric disorders, only SUD associated with alcohol tolerance: high tolerance HR 6.8, 95% CI 3.4 – 13.2, $p<0.001$ and low tolerance HR 3.1, 95% CI 1.6 – 5.7, $p<0.001$ (Table 3, Fig. 4b). In addition, high intoxication frequency associated with any psychiatric diagnosis (HR 1.6, 95% CI 1.3 – 1.9, $p<0.001$) (Table 3, Fig. 5a). Of specific diagnosis groups, high intoxication frequency was associated with SUD (HR 5.5, 95% CI 3.4 – 8.9, $p<0.001$) and mood disorder (HR 1.7, 95% CI 1.2 – 2.3, $p<0.001$) (Table 3, Figs. 5b and c), with also use of 1 – 2 times during the past month associating with SUD (HR 1.9, 95% CI 1.2 – 3.0, $p=0.007$) (Table 3, Fig 5b).

insert Table 3 here

insert Figure 4 here

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Similar to the previous analyses, we found an association with high and low alcohol tolerance groups and SUD in multinomial logistic regression analyses (high tolerance OR 5.9, 95% CI 2.7 – 13.0, $p<0.001$ and low tolerance OR 3.1, 95% CI 1.5 – 6.4, $p=0.002$, Model 1) (Table 4) and it remained significant after adjusting with all the covariates (high tolerance OR 4.4, 95% CI 1.8 – 11.1, $p=0.001$ and low tolerance OR 3.0, 95% CI 1.3 – 6.7, $p=0.009$, Model 4). The association with high intoxication frequency and SUD was also found (OR 5.4, 95% CI 3.2 – 9.3, $p<0.001$, Model 1) (Table 4) and it too remained significant even after adjustments with all the covariates (OR 3.9, 95% CI 2.0 – 7.3, $p<0.001$, Model 4). Additionally, the association with high intoxication frequency and mood disorder was seen (OR 1.6, 95% CI 1.1 – 2.3, $p=0.008$, Model 1) (Table 4), even after adjustments with parental psychiatric illness (Model

3). However, this association disappeared after adjusting for all covariates (Model 4). No association between alcohol tolerance and any psychosis, mood disorders or anxiety disorders as well as between intoxication frequency and any psychosis or anxiety disorder was found (data not shown). Also, there were no significant differences between any alcohol tolerance or drinking frequency groups with the participants having both mood and SUD (data not shown). A significant multicollinearity ($\tau = 0.538, p < 0.001$) was detected between number of drinks needed to become intoxicated and drinking frequency.

insert Table 4 here

A dose-response effect was found between alcohol tolerance and any psychiatric diagnosis (HR 1.03, 95% CI 1.01 – 1.06, $p < 0.011$) and between alcohol tolerance and SUD (HR 1.3, 95% CI 1.2 – 1.4, $p < 0.001$). Similar findings were seen between intoxication frequency and any psychiatric diagnosis (HR 1.2, 95 % CI 1.1 – 1.4, $p < 0.001$), mood disorder (HR 1.3, 95% CI 1.1 – 1.4, $p < 0.001$), and SUD (HR 1.9, 95% CI 1.6 – 2.3, $p < 0.001$).

DISCUSSION

In this large birth cohort study with a register-based follow-up into adulthood, adolescents who reported a higher alcohol tolerance, i.e. higher number of drinks to become intoxicated, as well as frequent intoxication at ages 15 – 16, were found to be at increased risk of SUDs in early adulthood. Frequent intoxication at ages 15 – 16 years was associated also with increased risk of subsequent mood disorder, and this was evident independently of parental mood disorders. However, this association attenuated when YSR total score and other drug use in teenage or all confounding factors were considered.

Previous research testing the association of heavy drinking (defined as consuming three or more drinks in a row at least once a month) with major depressive disorder and anxiety in adolescent and adults has yielded contradictory results (3,7,15,28,29). In our work, frequency of intoxication appeared to have a prospective association with any mood disorder, but not with any psychosis or anxiety disorder. The association attenuated after adjusting for other drug use and psychopathology symptoms at age 15 – 16. This suggests that heavy drinking in adolescence is an independent risk factor for later mood disorder, but simultaneous use of other drugs or concurrent mental health problems modulate the development of mood disorder in young adulthood. The factors predisposing adolescents to frequent intoxication and subsequent mood disorder could be directly due to alcohol's neurotoxic effects on developing brain (30) or could act indirectly via multiple harmful social consequences related to heavy alcohol use (31,32).

Adolescent binge drinking and high-density alcohol use (more than six drinks on one occasion) have been reported unrelated to major depression disorder in young adulthood (28). Consistent with this previous research, we found no association between alcohol tolerance and any psychosis, mood disorders or anxiety disorders. High alcohol tolerance has been documented to associate with heavier drinking (i.e. an almost doubling of the number of drinks needed to feel alcohol's effects) and increased alcohol dependency (33,34). Our results of high alcohol tolerance associating with SUDs are in accordance with these previous findings. Alcohol tolerance is one of the symptoms linked with alcohol dependence (34,35), which further explains the connection with SUD. Also, heavy episodic drinking (defined as consuming three or more drinks in a row at least once a month) in adolescence has been reported to associate with increased AUD and alcohol dependence in early adulthood (8,11). Our result of high intoxication frequency associating with SUDs agrees with these previous

studies. Repeated heavy exposure to alcohol and other drugs over time sensitizes brain's neural systems of alcohol reward and increases the craving of drugs (36,37) predisposing to later SUD. The factors predisposing teenagers to recurrent alcohol use at mid-adolescence may be more social and familial and less genetic (38-40).

The results are consistent with causal inferences by time-dependency as the alcohol tolerance and intoxication frequency data was collected before the study members sought treatment for mood disorder or SUD. Also, there was a dose-dependent increase in risk for SUD with the risk being highest among most alcohol tolerant and frequently drinking participants. In addition, the risk of mood disorder in the most frequently intoxicated group increased dose-dependently.

Strengths and limitations

The current study has major strengths: We could use prospective data from a large population-based birth cohort with relatively small attrition at adolescence and minimal attrition concerning the long follow-up from using comprehensive register data. However, attrition at the 15 - 16-years questionnaires may have had an impact on the results of the multivariate analyses. There are also other limitations: We had to rely on participants subjective and self-report measure on alcohol use since no data on blood alcohol level were available. However, in this study, the high alcohol tolerance group included the highest 10% of the people needing the largest amount of drinks to become intoxicated. Also, register data covered only those individuals who have been diagnosed with a psychiatric illness in national health care and omits those who have not sought help for their problems. However, data in this work describes more severe disorders and actual diagnoses. Furthermore, the self-reported number of drinks to become intoxicated was assessed on only one occasion and no

data on continuation of alcohol use was available. Moreover, due to multicollinearity we could not reliably unravel with logistic regression analysis whether number of drinks needed to become intoxicated is a primary feature or a consequence of frequent intoxication and subsequent drink training.

CONCLUSIONS

Both higher alcohol tolerance and frequent intoxication in adolescence elevate the risk for future SUD. Prognosis of adolescent alcohol use may vary according to alcohol use habits, but also with concurrent psychopathology and use of other substances and needs further exploring. To our knowledge, this is the first longitudinal study of the association between adolescent self-reported alcohol tolerance and early adulthood psychiatric disorders extending previous research on prognosis of adolescent alcohol use.

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Table 1 Background variables, self-reported number of drinks needed to become intoxicated at age 15-16 years.

Self-reported number of drinks needed to become intoxicated										
	Total n	n=6548		No alcohol / intoxication n=2095		Low alcohol tolerance ¹ n=3705		High alcohol tolerance ¹ n=748		p- value*
Adolescent variables at age 15-16		n	%	n	%	n	%	n	%	
Gender	6548									
Male		3207	49.0	1109	52.9	1689	45.6	409	54.7	<0.001
Female		3341	51.0	986	47.1	2016	54.4	339	45.3	
Intoxication frequency (last 30 days)	6376									
Never		3813	59.8	2012	100	1641	45.3	160	21.5	<0.001
1-2 times		1944	30.5	0	0	1597	44.1	347	46.7	
3 times or more		619	9.7	0	0	383	10.6	236	31.8	
Other drug use	6527									
No		6153	94.3	2089	99.9	3445	93.3	619	83.1	<0.001
Yes		374	5.7	2	0.1	246	6.7	126	16.9	
Ejaculation/menstruation	5855									
No		473	8.1	266	14.2	173	5.2	34	5.3	<0.001
Yes		5382	91.9	1613	85.8	3163	94.8	606	94.7	
Family type	5586									
One parent or other		1168	20.9	215	11.7	763	24.2	190	31.5	<0.001
Two parents		4418	79.1	1615	88.3	2389	75.8	414	68.5	
Parental education level	5680									
At least nine years		3494	61.5	1071	57.7	2002	62.3	421	64.8	<0.001
12 years or more		2186	38.5	784	42.3	1210	37.7	192	31.3	
Mother's alcohol use	5552									
Never / Not anymore		1258	22.7	819	45.0	377	12.0	62	10.4	<0.001
Rarely than once a week		3323	59.9	791	43.4	2111	67.4	421	70.6	
Once a week or more often		971	17.5	212	11.6	646	20.6	113	18.0	
Father's alcohol use	5214									
Never / Not anymore		1029	19.7	741	42.4	241	8.3	47	8.4	<0.001
Rarely than once a week		2373	45.5	606	34.7	1488	51.2	279	50.0	
Once a week or more often		1812	34.8	401	22.9	1179	40.5	232	41.6	
Mother's psychiatric illness	6500									
No		5291	81.4	1734	83.2	2974	80.9	583	78.9	0.019
Yes		1209	18.6	351	16.8	702	19.1	156	21.1	
Father's psychiatric illness	6333									
No		5158	81.4	1697	83.5	2912	81.3	549	76.3	<0.001
Yes		1175	18.6	335	16.5	669	18.7	171	23.8	
	Total n	No alcohol / intoxication		Low alcohol tolerance ¹		High alcohol tolerance ¹		p-value		
		n	Mean ± SD	n	Mean ± SD	n	Mean ± SD			
YSR total score ²	5795	1885	22.2 ± 13.7	3277	28.3 ± 16.1	633	31.3 ± 16.6	<0.001		

* Chi square test.

¹ Participants in low alcohol tolerance group needed 6/8 drinks or less for females/males and in high alcohol tolerance group 7/9 drinks or more for females/males to become intoxicated.

² Information for Youth Self Report (YSR) are reported as continuous variables.

Table 2 Background variables and intoxication frequency at age 15-16 years.

Self-reported intoxication frequency (last 30 days)										
	Total <i>n</i>	<i>n</i> =6548		<i>0 times</i>		<i>1-2 times</i>		<i>3 times or more</i>		<i>p-value*</i>
Adolescent variables at age 15-16		n	%	n	%	n	%	n	%	
Gender	6376									
Male		3088	48.4	1877	49.2	926	47.6	285	46.0	0.238
Female		3288	51.6	1936	50.8	1018	52.4	334	54.0	
Number of drinks needed for intoxication	6376									
No alcohol / intoxication		2012	31.6	2012	52.8	0	0.0	0	0.0	<0.001
Low alcohol tolerance ¹		3621	56.8	1641	43.0	1597	82.2	383	61.9	
High alcohol tolerance ¹		743	11.7	160	4.2	347	17.8	236	38.1	
Other drug use	6360									
No		5991	94.2	3751	98.6	1765	91.1	475	76.9	<0.001
Yes		369	5.8	53	1.4	173	8.9	143	23.1	
Ejaculation/menstruation	5719									
No		460	8.0	366	10.6	79	4.5	15	2.9	<0.001
Yes		5259	92.0	3082	89.4	1670	95.5	507	97.1	
Family type	5454									
One parent or other		1142	20.9	570	17.3	403	24.4	169	33.3	<0.001
Two parents		4312	79.1	2728	82.7	1246	75.6	338	66.7	
Parental education level	5543									
At least nine years		3407	61.5	2000	59.8	1070	63.5	337	65.4	0.006
12 years or more		2136	38.5	1344	40.2	614	36.5	178	34.6	
Mother's alcohol use	5417									
Never / Not anymore		1209	22.3	992	30.3	167	10.1	50	10.1	<0.001
Rarely than once a week		3244	59.9	1793	54.8	1107	67.1	344	69.6	
Once a week or more often		964	17.8	489	14.9	375	22.7	100	20.2	
Father's alcohol use	5095									
Never / Not anymore		988	19.4	854	27.5	107	7.0	27	5.7	<0.001
Rarely than once a week		2320	45.5	1318	42.5	752	49.2	250	53.8	
Once a week or more often		1787	35.1	929	30.0	670	43.8	188	40.4	
Mother's psychiatric illness	6328									
No		5154	81.4	3117	82.2	1552	80.7	485	79.1	0.125
Yes		1174	18.6	676	17.8	370	19.3	128	20.9	
Father's psychiatric illness	6165									
No		5015	81.3	3024	81.9	1521	80.9	470	79.3	0.244
Yes		1150	18.7	667	18.1	360	19.1	123	20.7	
	<i>Total n</i>	<i>0 times</i>		<i>1-2 times</i>		<i>3 times or more</i>		<i>p-value</i>		
		n	Mean ± SD	n	Mean ± SD	n	Mean ± SD			
YSR total score¹	5659	3411	24.6 ± 14.8	1730	29.0 ± 15.9	518	33.5 ± 17.8	<0.001		

*Chi square test.

¹ Information for Youth Self Report (YSR) are reported as continuous variables.

Table 3. Results of Cox regression analyses for alcohol tolerance and frequency of intoxication¹

Alcohol tolerance	event s	N		total	H R	Low alcohol tolerance ²	p- valu e	HR	High alcohol tolerance ²	p- value
		censore d				95%CI			95%CI	
Any psychiatric disorder	1009	5081	6090	1.2	(1.1 - 1.4)	0.006	1.5	(1.3 - 1.9)	<0.001	
Any psychosis	114	6221	6335	0.9	(0.6 - 1.3)	0.524	1.4	(0.8 - 2.4)	0.227	
Mood disorder	367	5939	6306	1.1	(0.9 - 1.4)	0.343	1.4	(0.997 - 1.9)	0.052	
Anxiety disorder	276	6058	6334	1.3	(0.97 - 1.7)	0.087	1.2	(0.8 - 1.8)	0.476	
Substance use disorder	106	6232	6338	3.1	(1.6 - 5.7)	<0.001	6.8	(3.4 - 13.2)	<0.001	

Frequency of intoxication ³	event s	N		total	H R	1-2 times	p- valu e	HR	3 times or more	p- value
		censore d				95%CI			95%CI	
Any psychiatric disorder	985	4949	5934	1.1	(0.997 - 1.3)	0.054	1.6	(1.3 - 1.9)	<0.001	
Any psychosis	112	6058	6170	1.1	(0.8 - 1.7)	0.523	1.5	(0.8 - 2.6)	0.165	
Mood disorder	362	5781	6143	1.1	(0.9 - 1.4)	0.462	1.7	(1.2 - 2.3)	<0.001	
Anxiety disorder	264	5904	6168	0.97	(0.7 - 1.3)	0.824	1.2	(0.8 - 1.7)	0.453	
Substance use disorder	103	6069	6172	1.9	(1.2 - 3.0)	0.007	5.5	(3.4 - 8.9)	<0.001	

¹ Unadjusted analyses

² Participants in low alcohol tolerance group needed 6/8 drinks or less for females/males and in high alcohol tolerance group 7/9 drinks or more for females/males to become intoxicated.

³ In last 30 days

studied covariates.

**Intoxication
frequency (last 30
days)**

Yes	1.6	(0.8 - 3.1)	0.161			1.8	(0.9 – 3.5)	0.098	
YSR									
Total score	1.02	(1.01 - 1.04)	<0.001			1.02	(1.01 – 1.04)	0.004	
Mother's psychiatric illness									
Yes				1.9	(1.1 - 3.0)	0.012	1.6	(0.9 – 2.7)	0.098
Father's psychiatric illness									
Yes				2.4	(1.5 - 3.9)	<0.001	2.5	(1.5 – 4.1)	<0.001

	Mood disorder											
	Model 1 ⁹			Model 2 ¹⁰			Model 3 ¹¹			Model 4 ^{12, 15}		
	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value	OR	95%CI	p-value
Intoxication frequency (last 30 days)												
1 or 2 times	1.03	(0.8 - 1.3)	0.827	0.9	(0.7 - 1.2)	0.562	1.1	(0.8 - 1.4)	0.460	1.0	(0.8 - 1.4)	0.932
3 times or more often	1.6	(1.1 - 2.3)	0.008	1.1	(0.7 - 1.6)	0.704	1.7	(1.2 - 2.5)	0.003	1.2	(0.8 - 1.8)	0.480
Gender												
Male	0.4	(0.3 - 0.5)	<0.001	0.5	(0.4 - 0.6)	<0.001	0.4	(0.3 - 0.5)	<0.001	0.5	(0.4 - 0.6)	<0.001
Family type												
One parent or other	1.7	(1.3 - 2.2)	<0.001	1.7	(1.3 - 2.3)	<0.001	1.4	(1.05 - 1.8)	0.023	1.4	(1.1 - 1.9)	0.011
Other drug use												
Yes				1.6	(1.1 - 2.5)	0.024				1.6	(1.1 - 2.6)	0.029
YSR												
Total score				1.02	(1.01 - 1.03)	<0.001				1.02	(1.01 - 1.03)	<0.001
Mother's psychiatric illness												
Yes							1.9	(1.4 - 2.5)	<0.001	1.9	(1.5 - 2.6)	<0.001
Father's psychiatric illness												
Yes							1.5	(1.1 - 1.9)	0.007	1.4	(1.02 - 1.8)	0.038

¹ N=5406, ² N=4948, ³ N=5205, ⁴ N=4767, ⁵ N=5280, ⁶ N=4840, ⁷ N=5082, ⁸ N=4662, ⁹ N=5257, ¹⁰ N=4818, ¹¹ N=5059, ¹² N=4640

Missing values were more common with

¹³ male participants, parents not living together, paternal psychiatric disorders, and higher alcohol tolerance at age 15-16 years.

¹⁴ male participants, parents not living together, parental psychiatric disorders, and more frequent intoxication at age 15-16 years.

¹⁵ male participants, parents not living together, maternal psychiatric disorders, and more frequent intoxication at age 15-16 years.

Fig 1 Flowchart of the study.

Fig 2 Prevalence of any psychiatric disorder by the age of 29 – 30 years as a function of number of drinks needed to become intoxicated. Participants in low alcohol tolerance group needed 6/8 drinks or less for females/males and in high alcohol tolerance group 7/9 drinks or more for females/males to become intoxicated.

Fig 3 Prevalence of any psychiatric disorder by the age of 29 – 30 years as a function of intoxication frequency during the past 30 days.

Fig 4 Morbidity free survival by alcohol tolerance and age from a) any psychiatric disorder and b) substance use disorder. Participants in low alcohol tolerance group needed 6/8 drinks or less for females/males and in high alcohol tolerance group 7/9 drinks or more for females/males to become intoxicated.

Fig 5 Morbidity free survival by intoxication frequency and age from a) any psychiatric disorder, b) substance use disorder and c) mood disorder