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Associations of adolescent alcohol use and self-reported alcohol tolerance with risk of self-harm and suicide in early adulthood: a birth-cohort study

Jonna Levola, M.D., Ph.D. [1,2], Alexander Denisoff [3], Antti Mustonen, M.D., Ph.D. [4,5,6], Anni-Emilia Alakokkare, M.Sc. [4], Jouko Miettunen, Professor M.Sc., Ph.D. [4], Jørgen G. Bramness, Professor, M.D., Ph.D. [7,8,9], Solja Niemelä, Associate professor (tenure-track), M.D., Ph.D. [3,10]

[1] Department of Psychiatry, University of Helsinki, Helsinki, Finland

[2] Psychiatry, Hyvinkää Area, Hospital District of Helsinki and Uusimaa, Finland

[3] Department of Psychiatry, University of Turku, Turku, Finland

[4] Centre for Life Course Research, University of Oulu, Oulu, Finland

[5] Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland

[6] Department of Psychiatry, Seinäjoki Central Hospital, Finland

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[7] Norwegian Institute of Public Health, Oslo, Norway

[8] The Arctic University of Norway, Tromsø, Norway

[9] Norwegian National Advisory Unit on Concurrent Substance Abuse and Mental Health Disorders, Innlandet Hospital Trust, Hamar, Norway

[10] Addiction Psychiatry Unit, Department of Psychiatry, Turku University Hospital, Turku, Finland

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Abstract

Objective

We aimed to assess the predictive associations of age at first drink (AFD), age at first intoxication (AFI), frequency of intoxication, and self-reported alcohol tolerance at age 15-16 to self-harm requiring medical attention or suicide death by age 33.

Method

In an ongoing follow-up study, the Northern Finland Birth Cohort 1986, a total of 7,735 individuals were included at age 15-16. Information on alcohol and other substance use was assessed via questionnaires. Information on self-harm or suicide was collected from national registers until the participants were 33 years of age. Baseline psychiatric symptomatology measured with the Youth Self-Report questionnaire and socio-demographic background variables were controlled for in multivariable analyses using Cox regression analyses.

Results

Male gender and psychiatric symptoms at age 15-16 were consistently associated with greater risk of self-harm and suicide death. When baseline psychiatric symptomatology and other background variables were adjusted for, younger AFI (Hazard Ratio, HR, 2.28. 95% CI 1.16-4.47) and high inherent alcohol tolerance (HR 3.76, 95% CI 1.55-9.08) were associated with self-harm. Furthermore, frequent alcohol intoxication (HR 5.39, 95% CI 1.44-20.23) and high inherent alcohol tolerance (HR 6.20, 95% CI 1.18-32.45) were associated with suicide death by age 33.

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Conclusions

High alcohol tolerance, age of onset and frequency of alcohol intoxication in adolescence, appear to be significant predictors of self-harm and suicide in early adulthood. Self-reported alcohol tolerance in adolescence is a novel empirical approach to assess adolescent alcohol use associating with subsequent harms.

Keywords: self-harm, suicide, alcohol, adolescence, birth-cohort study

Introduction

Suicide is among the leading causes of death among young adults (World Health Organization., 2019) and acute use of alcohol is a potent risk factor for suicidal behaviors (Borges et al., 2017 Conner & Bagge, 2019). A significant portion of the excess mortality associated with alcohol use among young adults is attributable to suicide (Laramée et al., 2015; The World Health Organization, 2018).

Self-harm encompassing non-suicidal self-injury (NSSI) and suicide attempts is highly prevalent among adolescents (e.g., Duarte et al., 2020; Moran et al., 2012). Self-harm requiring medical attention is a serious concern, as it has previously been shown to be a strong predictor for risk of death by suicide (Erlangsen & Nordentoft, 2019).Heavy alcohol use and binge drinking (drinking large amounts in a short timeframe) significantly increase the risk of suicidal behavior among adolescents and young adults (e.g., Anderson, 1999; Moran et al., 2012; Rossow & Norström, 2014; Windle, 2004).

While it is unclear how alcohol use during adolescence is related to the risk of self-harm later in life, the association with suicide in adulthood has been more extensively studied. Both age at first drink (AFD) and age at first intoxication (AFI) have been associated with adversities later in life (Mustonen et al., 2021; Newton-Howes, Cook, Martin, Foulds, & Boden, 2019) including an excess mortality risk for AFI (Hu, Eaton, Anthony, Wu, & Cottler, 2017; Levola, Rose et al., 2020).

Both total volume of alcohol consumption and binge drinking are well-known risk factor for mortality due to suicide (Stockwell et al., 2016; The World Health Organization, 2018). High frequency binge drinking (drinking to achieve intoxication) in adolescence has also been

associated with an increased risk for accidental and suicide deaths in early adulthood (Levola et al., 2020).

Tolerance to the effects of alcohol is a complex phenomenon (Pietrzykowski & Treistman, 2008). In repeated alcohol use, alcohol tolerance is related to e.g., neurobiological changes and the liver's metabolic capacity, and is acquired after alcohol exposure over time (Fillmore, Marczinski, & Bowman, 2005; Martin & Moss, 1993). The subjective response to alcohol, here termed inherent tolerance, is an intrinsic and at least partially inherited characteristic of an individual and appears to more of a trait feature. Inherent tolerance is related to the number of drinks needed to feel alcohol's effects (Schuckit et al., 2008), a higher number of drinks need being related to several alcohol-related problems, including alcohol use disorder (AUD) (Schuckit, 1994).

Studying subjective responses to alcohol through inherent tolerance (i.e., number of drinks needed to achieve intoxication) could potentially capture a different phenomenon distinct from binge drinking. In other studies from the Finnish birth-cohort utilized in the present study, high inherent tolerance was associated with increased all-cause mortality (Levola et al., 2020) as well as higher incidence substance use disorder (SUD) (Sarala et al., 2020).

The current study aimed to study the predictive association of AFD, AFI, frequency of alcohol intoxication and inherent alcohol tolerance at age 15-16 with subsequent self-harm and/or suicide by the age of 33 in the Northern Finland Birth Cohort Study 1986 (NFBC1986). Data from the NFBC clinical study were linked with nationwide health care registers regarding visits to health service providers due to self-harm and register data on suicide deaths.

Method

The 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 1 July 1985 and 30 June 1986, from the two northernmost provinces in Finland with a highly ethnically homogenous Caucasian population (University of Oulu: Northern Finland Birth Cohort 1986. University of Oulu. Available from: urn.fi/urn:nbn:fi:att:f5c10eef-3d25-4bd0-beb8-f2d59df95b8e.). In the present study, secondary data linked from national registers was utilized.

During 2001-2002, a multidisciplinary follow-up was conducted when the NFBC1986 adolescents were 15–16 years of age. All participants received a postal questionnaire and subsequently were invited to a clinical study. During the clinical study, participants completed self-report questionnaires including questions on alcohol and illicit substance use. Those with self-harm-related diagnoses before age 16 years were excluded (n<5). The final sample included 7,735 (49.8% male) of the 9,340 individuals alive at the time of the survey (response rate 82.2%).

The 15-16-year follow-up study was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District in Finland (May 17th 2006). Informed consent for participation in the follow-up was obtained from all participants and their parents, as was permission for subsequent register linkage.

Measures

Self-harm and suicide

Information on severe instances of self-harm requiring medical attention and suicide deaths was obtained from different registers until the end of 2018, i.e., when the participants were 33 years old.

Information on self-harm was extracted from the Care Register for Health Care of the National Institute for Health and Welfare, which contains information on both inpatient care and specialized outpatient care, from the year 2001 when the clinical study was conducted, up to the end of 2018. Additionally, information for primary care visits was available from 2011 up to the end of 2018.

Self-harm was identified according to coding of the International Classification of Disease, 10th revision (ICD-10) (The World Health Organization, 2016): X60-X84 (Intentional self-harm), Z91.5 (Personal history of self-harm), Y87.0 (Sequelae of intentional self-harm) and Z72.8 (Other problems related to lifestyle, Self-damaging behavior) and the International Classification of Primary Care 2 (ICPC-2) for primary care visits (World Organization of Family Doctors, 2016): P77 (Suicide/suicide attempt). If participants had several instances of self-harm, the first instance was considered. The lack or presence of suicidal intent during the instances of self-harm was not an inclusion criterion as it was not always deductible from the registers. This definition of self-harm could encompass both NSSI and suicide attempts, as in Moran et al. (2012), and required that the self-inflicted injuries were severe enough to require medical attention.

Information on times and causes of death were obtained from the Population Register Data and Registry for Causes of Death which cover all deaths in Finland. The deaths were categorized

based on cause of death according to the ICD-10 (The World Health Organization, 2016), and categorized into deaths due to suicide for the ICD-10 codes X60-X84 (Intentional self-harm). An autopsy is routinely carried out in all unclear cases in Finland. In the cases of accidents where suicidal intent was unclear (n=3), the deaths were not included as suicides.

A number of psychosocial and psychiatric risk factors that are known to be associated with self-harm or suicide were considered as covariates (e.g., Greydanus & Shek, 2009).

Alcohol use and inherent tolerance in adolescence

The data on alcohol use in adolescence was collected using questionnaires during the clinical study. The participants were asked at what age did they first drink the following alcoholic beverages: beer, wine, spirits. The response options were never; age 11 or under; 12; 13; 14; 15 or 16. Based on these answers, a variable designating the age when any alcoholic beverage was consumed for the first time, was formed. The participants were also asked at what age they had first been intoxicated (same response options). Alcohol intoxication was determined according to self-report i.e., no set cut-off for the amount of alcohol was used. The participants were also asked how many times in the previous 30 days they had been intoxicated. In order to determine the level of alcohol tolerance, the participants were asked how many drinks they needed to feel intoxicated. A visual depiction of a standard Finnish drink (12 g pure ethanol) was given.

Participants were first classified into three groups according to AFD and AFI, frequency of intoxication and self-reported alcohol tolerance. For AFD and AFI, these groups consisted of individuals who had had their first drink or had first been intoxicated at age 14 or younger, over the age of 14 years, and those who had not consumed alcohol or had never been intoxicated

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(reference groups). For frequency of intoxication, the groups were defined as infrequent (1-2 times), frequent (≥3 times), and no intoxication during the past 30 days (reference group). Finally, for self-reported inherent alcohol tolerance, based on the distribution of responses, groups were divided according to self-reported tolerance into low to intermediate tolerance (<9 drinks for males and <7 drinks for females) and high tolerance (≥9 drinks for males and ≥7 drinks for females) groups, with participants who had never been intoxicated considered the reference group. High tolerance was defined to correspond to the highest 10 percentile of drinks reported to achieve intoxication.

For the final multivariable analyses, the AFD and AFI groups were aggregated due to small subgroup sizes in order to allow for analyses; those who had had their first drink or had first been intoxicated at age ≤14 or >14 with the latter groups including those participants who had never by the age of 15-16 consumed alcohol or been intoxicated.

Parental education level and family structure

Parental education level was gathered from a parental postal questionnaire in 2001–2002. Parental education was categorized into ≥12 years corresponding to vocational or university studies and <12 years corresponding to primary school without a secondary degree. Information on structure of the family were collected by combining data from parents at birth and at 15-16 years follow-up. Family structure was classified as (a) two parents (both biological parents living with the participant from birth to age 15-16 years) and (b) other families.

Illicit substance use

Data on lifetime illicit substance use up to age 15-16 years were collected with several questions (no/yes) concerning e.g., cannabis use, non-medicinal prescription drug use, use of inhalants and other illicit drugs. These were combined as 'Illicit substance use (no/yes)'.

Baseline psychiatric symptomatology and parental psychiatric diagnoses

The participants' psychiatric diagnoses (F00-99) according to ICD-10 (The World Health Organization, 2016) were obtained from four national registers: outpatient registers for primary and specialized care (up to 2018), the Care Register for Health Care for inpatient care (up to 2018), disability pensions of the Finnish Centre for Pensions (up to 2006) and the medication reimbursement register of the Social Insurance Institution of Finland (up to 2005). SUD and other psychiatric diagnoses were considered separately. Parental psychiatric diagnoses were obtained from the same registers, except for the latter, up to the year 2001 when the participants were 15-16 years, and the clinical study was conducted.

Information on adolescent baseline psychiatric symptomology was collected using the Youth Self-Report (YSR) (Achenbach & Rescorla, 2001) during the clinical study when participants were aged 15-16 years. The YSR is a validated instrument, which measures symptoms of emotional or behavioral problems among 11-18-year-old adolescents. The YSR includes 118 statements in eight subscales, including 29 items from two subscales for externalizing problems (e.g., 'I am mean to others' and 'I get in many fights') and 30 items from three subscales for internalizing problems (e.g., 'I worry a lot' and 'I am unhappy, sad or depressed'). In this study, one item of the externalizing subscales concerning alcohol use was excluded form analyses.

Responses are scored on a three-point scale: not true (0), somewhat/sometimes true (1) or very true (2) reflecting how respondents have felt within the past 6 months. Item scores are added together to obtain a summary score for each subscale, externalizing and internalizing symptoms separately, as well as a total score sum score of externalizing and internalizing symptoms. YSR subscales were excluded if more than three answers were missing in the subscales. If there were three or fewer missing values in a subscale, they were replaced by the mean value of items in the particular subscale for that person (Miettunen et al., 2014).

Due to overlap between register-based psychiatric diagnoses and baseline YSR scores, we decided to use the latter to reflect also less severe, sub-diagnostic baseline psychiatric symptomatology as this data were available for most participants at age 15-16.

Statistical analyses

Cross-tabulation, χ^2 tests, Fischer's exact tests and Mann Whitney U -test (means and SD for continuous variables) for significance testing were used for studying the associations of potential confounders, self-harm and suicide. Effect sizes were computed using Cramer's V with >0.25 reflecting very strong, 0.16-0.25 strong, 0.11-0.15 moderate, 0.06-0.10 weak and 0-0.05 no or very weak associations (Cohen, 1992).

Cox regression was used to analyze differences between survival rates for the groups categorized according to AFD, AFI, frequency of alcohol intoxication during the past 30 days and self-reported alcohol tolerance. Self-harm, suicide death, and both self-harm and suicide death were considered the outcomes. Times at emigration (n=314) and death due to other causes than suicide (n=47) were considered when defining survival times. The confounders were included in the

multivariable models when they were associated ($p<0.1$) with self-harm or suicide in this study. The subsequent confounders that were selected were: gender, family structure, parental education, parental psychiatric diagnoses before the participants' aged 16, having a history of illicit substance use before the participants' aged 16 and psychiatric symptomatology at age 15-16 according to YSR. Separate multivariate models were created to evaluate the predictive significance of AFD, AFI, frequency of alcohol intoxication during the past 30 days and self-reported alcohol tolerance on self-harm and/or suicide after adjusting for confounders. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

The Cox proportional hazards assumption was tested using hazard logarithms and scaled Schoenfeld residuals. No statistically significant variance of effect over time was observed regarding the alcohol related variables and endpoints of self-harm and/or suicide and the proportional hazards assumption held. The final multivariable analyses were also run using time-varying alcohol related variables, and no significant differences between the results compared to the original models were detected, except for a possible time interaction of family structure and suicide. However, statistical power was not sufficient for conducting a sensitivity analysis of this particular covariate.

A previous attrition analysis for the NFBC1986 clinical study (Miettunen et al., 2014) found that males were less likely to participate in the adolescent follow-up than females (67% v. 74%; χ^2 test, $p<0.001$). Also, adolescents with register-based psychiatric diagnoses at follow-up (65.1% v. 74.2%, $p<0.001$) as well as maternal (65% v. 72%, $p<0.001$) or paternal (71% v. 81%, $p<0.001$) history of psychiatric disorders were less likely to participate than others. This attrition was addressed using inverse probability weighting (Haukoos & Newgard, 2007). We compared crude odds ratios (logistic regression; 95% CIs) with those weighted by sex, parental psychiatric

disorder and urbanicity and found very little difference between the crude and weighted results (Supplement 1).

Statistical analyses were conducted with SPSS statistical software for Windows (IBM SPSS Statistics, version 28) and for hazard logarithms and Schoenfeld residuals R (R Foundation for Statistical Computing, version 4.2.0) packages survival and survminer.

Results

By the year 2018 i.e., age 33, 109 (1.4%) participants included in this study had at least one incident of self-harm requiring medical attention and 29 (0.4%) had died due to suicide (Table 1). Four participants (<0.01%) who had first had an incident of self-harm thereafter died by suicide. No statistically significant gender difference was observed for self-harm. However, males were significantly more likely to have die by suicide than females (0.6% vs. 0.1%; p<0.001). In bivariate analyses, all of the other studied confounders were associated with self-harm. In addition to male gender, parental psychiatric disorder was associated with suicide, as were the participants own psychiatric diagnoses, especially SUD, before age 15-16. The effect sizes for these associations were weak to moderate.

YSR externalizing symptoms were associated with both self-harm and suicide in bivariate analyses. YSR internalizing symptoms were associated with self-harm, but not suicide. YSR total score was associated with both self-harm and suicide.

Insert Table 1 here

All the alcohol related variables were associated with self-harm, and frequency of intoxication and self-reported alcohol tolerance were associated with suicide in bivariate analyses (Table 1), however, small subgroup sizes did not allow for comparisons between AFI and suicide. Unadjusted Cox regression models (Figures 1 and 2) show the differences between groups in self-harm and suicide according to the alcohol use variables. The largest unadjusted HRs were observed among the high inherent alcohol tolerance group compared to those without alcohol

use. The HR for self-harm was 6.76 (95% CI 3.23-14.13; p<0.001) and for suicide 9.74 (95% CI 2.02-46.87; p=0.005).

Insert Figure 1 here

Insert Figure 2 here

In the fully adjusted models, younger AFI (HR 2.28, 95% CI 1.16-4.47) and high inherent tolerance (HR 3.76, 95% CI 1.55-9.08) were associated with self-harm requiring medical attention (Table 2). The associations of AFD and frequency of intoxication and self-harm attenuated to statistically non-significant after confounding variables were adjusted for. However, when self-harm and suicide were combined, frequency of intoxication was significant with a HR of 1.83 for 1-2 instances of intoxication in the previous 30 days (95% CI 1.06- 3.16) and HR 2.84 for 3 or more (95% CI 1.46-5.54). The associations between frequency of intoxication and self-reported alcohol tolerance with suicide remained statistically significant in the adjusted models. An apparent dose-response relationship was observed for frequency of intoxication; 1-2 instances of intoxication in the previous 30 days HR 3.44 (95% CI 1.16-10.23) and 3 or more HR 5.39 (95% CI 1.44-20.23). As in the unadjusted analyses, the largest HRs were again observed among the high inherent alcohol tolerance group compared to those without alcohol use. In the fully adjusted models, the HR for self-harm requiring medical attention was 3.76 (95% CI 1.55-9.08; p=0.003) and for suicide 6.20 (95% CI 1.18-32.45; p=0.031).

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Insert Table 2 here

Discussion

In this large birth cohort study with follow-up from age 15-16 years until age 33 years, earlier age of first intoxication (AFI) and high inherent alcohol tolerance during adolescence were associated with increased risk of self-harm requiring medical attention. Further, more frequent alcohol intoxication and high inherent alcohol tolerance were associated with suicide by age 33.

The finding that inherent tolerance was related to self-harm and suicide is novel. High inherent alcohol tolerance in adolescence is associated with subsequent AUD in early adulthood (Sarala et al., 2020; Schuckit, 1994), and AUD is clearly associated with an increased risk for self-harm and suicide. It is plausible that high inherent alcohol tolerance in adolescence is associated to these endpoints as an early proxy for the development of AUD and should thus be considered a warning sign not only for AUD, but also future suicide behaviors. In their recent editorial, Wellman and Morgenstern (2020) discuss whether adolescents who are at greater risk of developing alcohol-related problems in later life could be detected by asking how many drinks they need to get intoxicated.

In our study, inherent alcohol tolerance was assessed through self-report. Whether increased self-reported tolerance in fact was the result high inherent tolerance as the individuals' trait or rather a result of alcohol exposure and thus more of an acquired feature, could not be determined. Due to the participants' young age, it is plausible that this self-report at least in part reflected some individual intrinsic characteristic (i.e., a trait) as 15–16-year-old adolescents have rarely had prolonged exposure to alcohol. It is to be noted, that even if the youth do not meet the diagnostic criteria for AUD, many can have developed increased alcohol tolerance and can experience withdrawal symptoms (Caetano & Babor, 2006).

The associations between frequency of intoxication and self-reported alcohol tolerance with suicide were statistically significant after controlling for confounders. Further, a dose-response relationship was found for frequency of intoxication, where more frequent instances of intoxication during adolescence resulted in higher HRs. These findings are in line with previous research where heavy drinking where a pattern of binge drinking is included, is a risk factor for death due to unintentional and intentional injuries, including suicide (Stockwell et al., 2016; The World Health Organization, 2018). Both AFD and AFI have been found to be associated with adversities later in life (Mustonen et al., 2021; Newton-Howes, Cook, Martin, Foulds, & Boden, 2019). AFD was not associated with self-harm or suicide in this study, however, AFI was associated with both. AFI has previously been reported to be associated with an excess mortality risk also outside of this cohort (Hu, Eaton, Anthony, Wu, & Cottler, 2017).

After adjusting for confounders, males had a greater risk of self-harm and suicide, while previous studies have shown self-harm to be more common among females (e.g., Greydanus & Shek, 2009). This discrepancy could be explained by the fact that self-harm in this study was defined as self-harm requiring medical attention, and not e.g., by self-report. Thus, probably only the most severe forms of self-harm are included, and e.g., less severe patterns of self-cutting in may not be included.

The absolute number of males who had died by suicide was higher in this study compared to females, which is in concordance with previous literature; however previous literature has also demonstrated that the mortality hazard ratio due to alcohol and substance use is stronger for women compared to men (Kendler, Ohlsson, Sundquist, & Sundquist, 2016; Kendler, Ohlsson, Sundquist, & Sundquist, 2017). Thus, clinically, even though males are more likely to die by

suicide, the increased risk among females with alcohol and/or substance use should be rigorously addressed.

Even though suicide is a leading cause of death among young adults (World Health Organization., 2019), it remains a relatively rare incident. Accordingly, the number of suicides by age 33 in this cohort was relatively low. This is likely to cause power issues and increases the likelihood of type 2 error. Though this may result in underestimation of some associations resulting in difference the groups with self-harm and those who had died by suicide, in light of previous research, it is possible if not probable, that individuals who engage in self-harm and those who die by suicide do differ (e.g., Greydanus & Shek, 2009). This is reflected in this study e.g., in the gender differences between individuals with self-harm and those who had died by suicide.

This study has several strengths. The NFBC 1986 is one of the largest birth cohort studies with high genetic and ethnic homogeneity. The study utilized several nationwide registers, providing data on diagnoses with low attrition. Attrition concerning those not participating the study at age 15/16 years is not likely a significant source of bias based on the additional analyses using inverse probability weighting. The wide range of information included in this data made it possible to address many potential confounders and we included four different alcohol related predictors. However, the small number of suicides have likely caused power issues.

The information on substance use was collected using self-reports, which is subject to bias. Self-reports typically underestimate substance use (Searles, Helzer, & Walter, 2000) and may lead to underestimation of true associations. Information on lifetime alcohol use was collected using self-reports at one time-point and we were not able to account for differential follow-up due to AFD or AFI. We were unable to differentiate between participants who remained abstinent from

age 15/16 through age 33 from those who's true AFD/AFI is older than age 16. The list of alcohol types used to determine AFD did not include ciders or long drinks, which may bias the results especially for female adolescents, who tend to prefer these beverages (Lintonen, Ahtinen, & Konu, 2018). It should also be noted that the data regarding alcohol and substance use was collected over 20 years ago and may not fully reflect the current trends in alcohol and substance use seen among today's adolescents and their risk factors for self-harm and suicide.

This study could not differentiate between environmental and genetic factors related to parental psychiatric disorders. Finally, we were not able to adjust for potential confounding due to childhood or familial adversity.

Despite these limitations, this study was able to robustly examine novel questions regarding early life alcohol exposure and subsequent self-harm and suicide deaths. Our findings suggest that AFI, self-reported alcohol tolerance and frequency of intoxication during adolescence should be included when implementing screening strategies aimed at identifying adolescents with high-risk alcohol use. Systematic implementation of screening and brief interventions, together with regulatory policies and multifaceted developmental interventions need be implemented in order to reduce the harm consequent on adolescent alcohol use. Ongoing research on treatment strategies for adolescent AUD is also needed.

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Table 1. *Association of background variables and substance use during adolescence with subsequent self-harm requiring medical attention and suicide death.*

	All n=7,735	Self-harm[1] n=109			Suicide death n=29		
	n	n (%)	p	Effect size[2]	n (%)	p	Effect size[2]
Gender	7,735	109 (1.4)	0.094	0.019	29 (0.4)	***<0.001***	0.045
Male	3,855	63 (1.6)			25 (0.6)		
Female	3,880	46 (1.2)			4 (0.1)		
Family type	6,575	91 (1.4)	***<0.001***	0.069	25 (0.4)	0.114	0.019
Two parents	5,078	48 (0.9)			16 (0.3)		
One parent or other	1,497	43 (2.9)			9 (0.6)		
Parental education	6,691	88 (1.3)	***0.014***	0.030	26 (0.4)	0.757	0.004
≥12 years	2,512	22 (0.9)			9 (0.4)		
<12 years	4,179	66 (1.6)			17 (0.4)		
Parental psychiatric disorder[3]	7,735	109 (1.4)	***<0.001***	0.072	29 (0.4)	***0.021***	0.026
No	4,809	36 (0.7)			12 (0.2)		
Yes	2,926	73 (2.5)			17 (0.6)		
Age at first drink	6,615						
No alcohol use	1,418	6 (0.4)	***0.003***	0.042	1 (0.1)	**	0.030
>14 years	537	4 (0.7)			17 (0.4)		
≤14 years	4,660	70 (1.5)			4 (0.7)		
Age at first intoxication	6,549						
No alcohol use / intoxication	2,158	10 (0.5)	***<0.001***	0.065	3 (0.1)	0.152	0.024
>14 years	3,308	63 (1.9)			14 (0.4)		
≤14 years	1,083	6 (0.6)			5 (0.5)		
Frequency of alcohol intoxication[4]	6,446	77 (1.2)	***<0.001***	0.065	21 (0.3)	***0.008***	0.039
0 times	3,851	30 (0.8)			6 (0.2)		
1-2 times	1,963	27 (1.4)			10 (0.5)		
≥3 times	632	20 (3.2)			5 (0.8)		
Alcohol tolerance[5]	6,599	80 (1.2)	***<0.001***	0.071	22 (0.3)	***0.003***	0.042
No alcohol use / intoxication	2,112	10 (0.5)			2 (0.1)		
<9 (males) / <7 (females)	3,724	46 (1.2)			13 (0.3)		
≥9 (males) / ≥7 (females)	763	24 (3.1)			7 (0.9)		
History of illicit substance use[3]	6,611	79 (1.2)	***<0.001***	0.069	22 (0.3)	0.533*	0.007
No	5,699	51 (0.9)			18 (0.3)		
Yes	912	28 (3.1)			4 (0.4)		
Any psychiatric disorder	7,735	109 (1.4)	***<0.001***	0.176	29 (0.4)	***0.001***	0.038
No	5,787	12 (0.2)			14 (0.2)		
Yes	1,948	97 (5)			15 (0.8)		
Substance use disorder (SUD)	7,735	109 (1.4)	***<0.001***	0.369	29 (0.4)	***<0.001***	0.074
No psychiatric diagnosis	5,787	12 (0.2)			14 (0.2)		
Psychiatric diagnosis, other than SUD	1,699	35 (2.1)			8 (0.5)		
SUD	249	62 (24.9)			7 (2.8)		

		All	Self-harm		Suicide	
	n	mean (SD)	mean (SD)	p	mean (SD)	p
YSR[6], total score	6,909	27.23 816.43)	40.10 (21.93)	***<0.001***	27.23 (16.43)	***0.009***
Internalizing, mean (SD)	6,957	9.23 (6.94)	12.95 (9.86)	***0.001***	10.65 (7.97)	0.457
Externalizing, mean (SD)	6,988	10.05 (6.53)	15.56 (8.77)	***<0.001***	14.45 (7.18)	***0.001***

[1] Self-harm requiring medical attention [2] Cramer's V; very strong >0.15, strong, >0.10 moderate, >0.05 weak and >0 no or very weak associations [3] Before the participants' aged 16 [4] In the last 30 days [5] Number of drinks needed in

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order to feel intoxicated [6] Youth Self-Report *Fisher's exact test **Chi squared test or Fisher's exact test couldn't be counted

Statistical significance at $p<0.05$.

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Table 2*. Association of alcohol use variables and self-harm and/or suicide death, fully adjusted models.*

	Self-harm[1]				Suicide death				Self-harm[1]/suicide death			
	HR	95% CI upper	95% CI lower	p-value	HR	95% CI upper	95% CI lower	p-value	HR	95% CI upper	95% CI lower	p-value
Age at first drink (n=5,355)												
Female gender	0.51	0.29	0.92	***0.024***	0.06	0.01	0.27	***<0.001***	0.35	0.21	0.59	***<0.001***
Family without both parents	2.87	1.64	5.02	***<0.001***	2.07	0.83	5.19	0.119	2.81	1.74	4.54	***<0.001***
Parental education <12 years	0.70	0.38	1.27	0.242	1.25	0.52	2.97	0.619	0.87	0.53	1.43	0.590
Parental psychiatric disorder[2]	1.67	0.89	3.14	0.111	1.35	0.44	4.15	0.600	1.51	0.86	2.64	0.152
History of illicit substance use[2]	1.41	0.74	2.69	0.299	1.06	0.33	3.42	0.923	1.27	0.72	2.26	0.409
YSR[2]-total score	1.04	1.02	1.05	***<0.001***	1.04	1.01	1.07	***0.005***	1.04	1.02	1.05	***<0.001***
Age at first drink[4]												
≤14 years	1.46	0.67	3.20	0.338	1.27	0.41	3.91	0.678	1.53	0.79	2.96	0.213
Age at first intoxication (n=5,307)												
Female gender	0.50	0.28	0.89	***0.018***	0.06	0.01	0.26	***<0.001***	0.34	0.21	0.57	***<0.001***
Family without both parents	2.72	1.56	4.76	***<0.001***	1.99	0.80	4.99	0.140	2.69	1.66	4.34	***<0.001***
Parental education <12 years	0.71	0.39	1.29	0.256	1.26	0.53	3.00	0.602	0.88	0.54	1.44	0.622
Parental psychiatric disorder[2]	1.65	0.88	3.09	0.121	1.34	0.44	4.11	0.610	1.49	0.85	2.61	0.164
History of illicit substance use[2]	1.23	0.64	2.35	0.533	0.96	0.29	3.11	0.941	1.13	0.63	2.00	0.684
YSR[2]-total score	1.03	1.02	1.05	***<0.001***	1.04	1.01	1.06	***0.007***	1.03	1.02	1.05	***<0.001***
Age at first intoxication[5]												
≤14 years	2.28	1.16	4.47	***0.017***	1.69	0.65	4.38	0.278	2.16	1.24	3.78	***0.007***
Frequency of alcohol intoxication[6] (n=5,229)												
Female gender	0.53	0.29	0.95	***0.032***	0.06	0.01	0.29	***<0.001***	0.37	0.22	0.62	***<0.001***
Family without both parents	2.75	1.57	4.84	***<0.001***	1.93	0.77	4.87	0.163	2.70	1.66	4.39	***<0.001***
Parental education <12 years	0.71	0.39	1.30	0.271	1.13	0.46	2.77	0.794	0.86	0.52	1.41	0.543
Parental psychiatric disorder[2]	1.60	0.84	3.06	0.155	1.46	0.47	4.50	0.511	1.49	0.84	2.64	0.174
History of illicit substance use[2]	1.14	0.57	2.25	0.712	0.72	0.21	2.42	0.595	0.97	0.53	1.78	0.926
YSR[2]-total score	1.04	1.02	1.05	***<0.001***	1.03	1.01	1.06	***0.013***	1.03	1.02	1.05	***<0.001***

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Frequency of alcohol intoxication[6]												
	1-2	1.45	0.77	2.71	0.247	3.44	1.16	10.23	***0.026***	1.83	1.06	3.16	***0.030***
	≥3	2.10	0.97	4.55	0.061	5.39	1.44	20.23	***0.012***	2.84	1.46	5.54	***0.002***
Alcohol tolerance[7] (n=5,335)												
Female gender		0.54	0.30	0.97	***0.039***	0.06	0.01	0.28	***<0.001***	0.38	0.23	0.63	***<0.001***
Family without both parents		2.68	1.53	4.70	***0.001***	1.80	0.73	4.49	0.205	2.60	1.61	4.20	***<0.001***
Parental education <12 years		0.72	0.40	1.32	0.288	1.29	0.54	3.08	0.560	0.91	0.55	1.48	0.695
Parental psychiatric disorder[2]		1.71	0.91	3.20	0.094	1.35	0.44	4.13	0.599	1.53	0.87	2.67	0.137
History of illicit substance use[2]		1.08	0.56	2.10	0.813	0.81	0.25	2.61	0.726	0.97	0.54	1.75	0.930
YSR[2]-total score		1.04	1.02	1.05	***<0.001***	1.03	1.01	1.06	***0.011***	1.03	1.02	1.05	***<0.001***
Alcohol tolerance[8]												
	<9 (males) / <7 (females)	1.33	0.59	3.00	0.485	3.45	0.76	15.59	0.108	1.64	0.80	3.34	0.174
	≥9 (males) / ≥7 (females)	3.76	1.55	9.08	***0.003***	6.20	1.18	32.45	***0.031***	4.36	2.01	9.49	***<0.001***

[1] Self-harm requiring medical attention [2] Before the participants' aged 16 [3] Youth Self-Report [4] Age at first drink >14 years or never drank alcohol used as reference [5] Age at first intoxication >14 years or never been intoxicated used as reference [6] In the past 30 days [7] Number of drinks needed in order to feel intoxicated [8] Never drank alcohol or never been intoxication used as reference

Statistical significance at $p<0.05$.

Figure 1. Alcohol use and self-harm requiring medical attention according to Cox regression analyses (unadjusted).

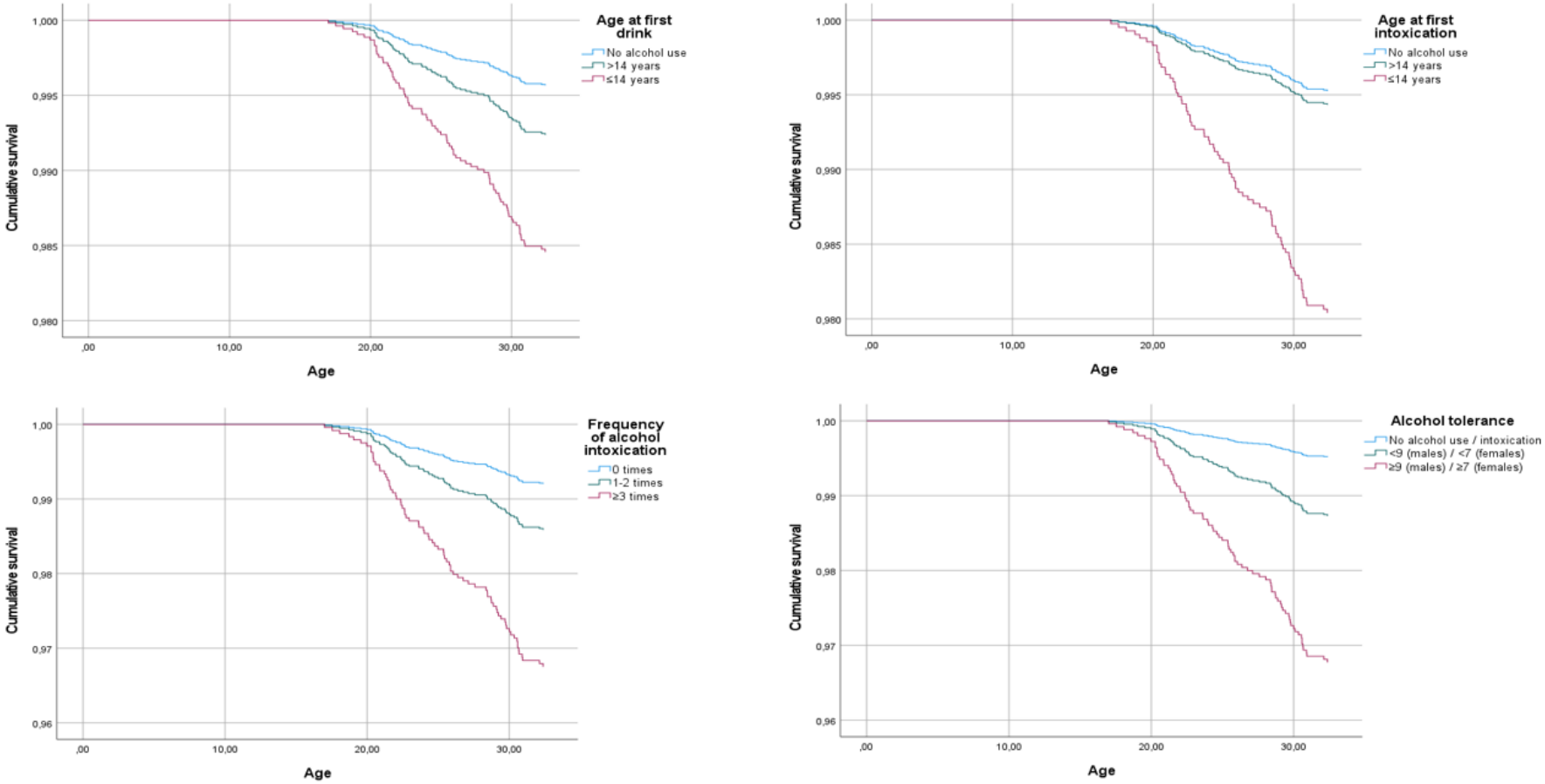

Figure 2. Alcohol use and suicide death according to Cox regression analyses (unadjusted).