

Frequent alcohol intoxication and high alcohol tolerance during adolescence as predictors of mortality: a birth cohort study

Jonna Levola, M.D., Ph.D.^a, Marian Sarala, Ph.D.^b, Antti Mustonen, M.D., Ph.D.^c, Richard J. Rose, Professor Emeritus^d, Jouko Miettunen, Professor^{c,e}, Anni-Emilia Niemelä, M.Sc.^f, Solja Niemelä, Associate Professor (tenure-track)^{f,g}

^aPsychiatry, Hyvinkää Area, Hospital District of Helsinki and Uusimaa, Finland

^bResearch Unit of Clinical Neuroscience, University of Oulu, Oulu, Finland

^cCenter for Life Course Health Research, University of Oulu, Oulu, Finland

^dDepartment of Psychological & Brain Sciences, Indiana University, Bloomington, IN, USA

^eMedical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland

^fDepartment of Psychiatry, University of Turku, Turku, Finland

^gAddiction Psychiatry Unit, Department of Psychiatry, Turku University Hospital, Turku, Finland

Corresponding author

Jonna Levola

Psychiatry, Hyvinkää Area, Hospital District of Helsinki and Uusimaa, Finland

Sibeliuksenkatu 4C

04400 Järvenpää

jonna.levola@hus.fi

Tel. +358401832730; Fax. +35892716 3132

marian.sarala@student.oulu.fi; antti.mustonen@oulu.fi; rose@indiana.edu; jouko.miettunen@oulu.fi;

anni-emilia.niemela@oulu.fi; solnie@utu.fi

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Abbreviations

95% CI	95% confidence interval
AUD	Alcohol use disorder
HR	Hazard ratio
ICD-10	The International Classification of Disease, 10 th revision
NFBC1986	The Northern Finland Birth Cohort Study 1986
SUD	Substance use disorder

Abstract

Purpose

Long-term prospective studies evaluating the health burden that is consequent to adolescent drinking are needed. The aim of this study was to examine the predictive associations between self-reported alcohol tolerance and frequent intoxication at age 15–16 years and the risk of death by age 33.

Methods

A sample (n=6,615; 49.3% males) of the Northern Finland Birth Cohort Study 1986 (NFBC1986) was studied. Self-reported alcohol tolerance (drinks needed to feel intoxicated) and frequency of alcohol intoxication at age 15-16 were analyzed along with background variables and data regarding subsequent psychiatric diagnoses. Categories were formed for both predictive variables from self-reported tolerance and frequency of intoxication in mid-adolescence. Cox regression was used to calculate hazard ratios (HRs) with 95% confidence interval (95% CI) for death by age 30.

Results

By the age of 33, of all 6,615 participants, 53 (0.8%) were deceased. The HR for death by age 33 was 3.08 (95% CI 1.17-8.07) among adolescents with high alcohol tolerance compared to adolescents without alcohol use or intoxication. Frequency of alcohol intoxication was also associated with mortality; HR 2.05 (95% CI 1.01-4.16) for those who had been intoxicated 1-2 times and HR 3.02 (95% CI 1.21-7.54) ≥ 3 times in the past 30 days compared to adolescents without intoxication.

Conclusions

High self-reported alcohol tolerance and frequent alcohol intoxication during mid-adolescence significantly predicted death by age 33. These behaviors carry long term repercussions with respect to premature loss of life. Substantial efforts should be made to diminish this mortality risk.

Keywords: mortality; alcohol tolerance; alcohol intoxication; binge drinking; birth cohort study

Recent statistics indicate that alcohol use results annually in some 3 million deaths worldwide (5.3% of all deaths), with men experiencing 2.3 million and women 0.7 million of these deaths [1]. Mortality resulting from alcohol consumption globally is higher than that caused by diseases such as tuberculosis, HIV/AIDS and diabetes. Young adults are more seriously affected by alcohol compared to older persons and 13.5% of all deaths among those 20–39 years old are attributed to alcohol.

Consuming a large amount of alcohol in a defined timeframe is often referred to as binge drinking. However, the definitions of binge drinking, e.g. using cut-offs for the volume of consumed alcohol, vary somewhat in literature and not all definitions include a set timeframe. The term binge drinking does not assess whether an individual experiences intoxication from alcohol or not. Binge drinking puts an individual at risk for acute alcohol related harm, specifically unintentional and intentional injuries including road traffic crashes, violence, suicides and fatal alcohol-related injuries [1]. Approximately half of all deaths from both unintentional and intentional injuries among 15–69 year-old Finnish men are alcohol-related [2].

The acute effects of binge drinking are quite well established. Binge drinking has been shown to be associated with an increased long-term risk of fatal injuries [3] and it plays a large role also in long-term health conditions that can lead to death, e.g. cardiovascular illness [4]. However, less is known about the relationship between binge drinking in adolescence and longer-term risk of death. The mortality associated with alcohol use has more traditionally been evaluated according to diagnoses or by average volume of consumption. For example, alcohol use disorders (AUD) are associated with a three to five fold increase in all-cause mortality compared with controls [5, 6]. In addition, recent studies have shown that the association between volume of consumption and mortality is likely linear [7].

In the year 2011, a mean 17% of European adolescents reported binge drinking three or more times during the past 30 days [8]. Binge drinking in adolescence is associated with various adverse outcomes in adulthood, including psychiatric morbidity, convictions, lower social class and underachieving [9].

Adolescent binge drinking has also been linked to an increased risk of suicide attempts surpassing the influence of depression and other stressful life events [10].

As noted above, the risks conferred by binge drinking have been well documented. However, these previous studies have focused on the behavior (i.e., how many drinks were consumed within a short period of time) rather than on the individual's experience. Studying subjective experience of tolerance (i.e., number of drinks needed to feel intoxicated) and frequency of intoxication could potentially capture drinkers who can become intoxicated with fewer drinks than the typical definitions of binge drinking. This could potentially add to our understanding of the relationship between drinking during adolescence and adverse outcomes in young adulthood.

Alcohol tolerance can be divided into different classes based on timeframe and pattern of exposure, with underlying mechanisms also being different [11]. Acute tolerance occurs within minutes and hours of alcohol exposure while chronic tolerance is the result of prolonged exposure over days or weeks. Enhanced acute tolerance appears to some extent to be a trait feature, i.e. an intrinsic characteristic of an individual, and may be linked to the risk of development of AUD [12]. Chronic alcohol tolerance, on the other hand, is among the diagnostic criteria of AUD. However, adolescents may report withdrawal symptoms and rate their alcohol tolerance to be high without necessarily meeting the diagnostic criteria of AUD [13]. Previous literature has suggested that this may be the result of confusing the sequelae of acute intoxication with alcohol withdrawal and rapid initial tolerance with the chronic tolerance reported in the context of AUD. A recent study found that high self-reported alcohol tolerance in adolescence is associated with subsequent SUD in young adulthood [14]. However, very little is known about the link between alcohol tolerance in adolescence and subsequent mortality.

McCambridge et al. reviewed the literature regarding the adult consequences of adolescent alcohol consumption [15]. The review concluded that an urgent need exists for long-term prospective cohort

studies to evaluate the health burden that is consequent on adolescent drinking. This study was set within that context and aimed to study the adolescent alcohol use and subsequent mortality. We examined the predictive association between self-reported alcohol tolerance, i.e. association between number of drinks in relation to subjective experience of intoxication, and frequency of alcohol intoxication at age 15–16 years and the risk of subsequent death by the age of 33 in the Northern Finland Birth Cohort Study 1986 (NFBC1986).

Methods

A multidisciplinary NFBC1986 follow-up study was conducted when the adolescents were 15–16 years of age. The NFBC Studies are epidemiological and longitudinal research programs which aim to promote the health and well-being of the population. The NFBC1986 study was begun in 1985 and was originally called as "The mother-child cohort study of morbidity and mortality during childhood with the special purpose of preventing mental and physical handicap". A wide range of data beginning from the gestational period onwards to this date has been collected. The final sample used in this study included 6,615 individuals (49.3% male). The study was approved by the ethics committee of the Northern Ostrobothnia Hospital District in Finland. Informed consent for participation including the follow-ups was obtained from all participants and their parents. Only participants who signed the informed consent form were included in the analyses.

Data collection

A multidisciplinary NFBC field study was conducted when the adolescents were 15–16 years of age. Data on substance use was collected in 2001–2002 in two different surveys. First, the participants received a postal questionnaire, which included questions on smoking habits. All the participants were then invited to a field

study where they completed self-report questionnaires including questions on alcohol and illicit substance use.

Thus, the final sample is comprised of children born alive in 1986 who had known addresses at age 15-16, completed questionnaire data including information on alcohol tolerance and provided consent for use of the data. More information about the study and its design is available in Supplement 1 and on the NFBC1986 webpage at <http://www.oulu.fi/nfbc/node/40696>.

Measures

Outcome: Death

Information on causes of death until the end of 2018, i.e. follow-up to the age of 33 years, was obtained from the Population Register Data and Registry for Causes of Death which covers all deaths in Finland. An autopsy is routinely carried out in all unclear cases in Finland. The deaths were categorized based on cause of death according to the International Classification of Disease, 10th revision (ICD-10) [16], and categorized into deaths due to somatic causes, accidents and suicide. In the cases of accidents where suicidal intent was unclear (n=3), the deaths were included in the accident- category.

Alcohol tolerance and frequency of alcohol intoxication

The data on alcohol tolerance was collected using questionnaires that the participants received during the field study in adolescence. 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 was given. The participants were also asked how many times in the previous 30 days they had been intoxicated. Alcohol intoxication was defined in this study according to a self-reported, subjective experience of intoxication.

Participants were classified into four groups according to self-reported tolerance: low tolerance (1-4 drinks for males, 1-3 drinks for females), intermediate (5-8 drinks for males, 4-6 drinks for females) and high tolerance (≥ 9 drinks for males and ≥ 7 drinks for females). Participants who had never consumed alcohol or had never been intoxicated were considered the reference group. Frequency of intoxication was classified into three groups: infrequent intoxication (1-2 times in the previous 30 days) and frequent intoxication (≥ 3 times in the previous 30 days). Participants who had not consumed alcohol or had not been intoxicated in the past 30 days were considered the reference group.

Confounding variables

Socioeconomic status and structure of the family

Alcohol related harm is mediated by socioeconomic status [1]. The socioeconomic status of the family was estimated by the highest education level achieved by either parent when the child was an adolescent. This variable was categorized into ≥ 12 years of education corresponding to vocational or university studies and < 12 years corresponding to primary school without a secondary degree. Information on family structure was gathered by combining information collected from parents at birth and when the cohort member was an adolescent. The classification of the family pattern included families with (a) both parents living with the participant all the time (intact families) and (b) all other family types (non-intact families).

Smoking and illicit substance use

Mortality among daily smokers is 2 to 3 times higher than among persons who never smoked [17]. Information on smoking was ascertained in postal questionnaires and data on substance use were collected via questionnaire that the participants completed during the field study. Information on tobacco smoking was studied and the participants were categorized into 'daily smoking (no/yes)'.

Persons with substance use disorders have a significantly shorter life expectancy than the general population [18]. Data on lifetime illicit substance use at age 15-16 years were collected with several questions (no/yes) concerning, for example, cannabis use, prescription drug use, use of inhalants and other illicit drugs. These were combined as 'Illicit substance use (no/yes)'.

Psychiatric disorders

Individuals suffering from mental illness are at a greater risk for premature death when compared to the general population [18]. Diagnoses of psychiatric disorders according to ICD-10 [16] were obtained from four national registers until the end of 2018, i.e. by the age of 33 years: The Register of Primary Health Care Visits 2011 – 2018 and the Care Register for Health Care 2001 – 2018 of the National Institute for Health and Welfare, the medication reimbursement register of the Social Insurance Institution of Finland 2001 – 2018 and disability pensions of the Finnish Centre for Pensions 2001 – 2018. 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.

Five classification groups were formed according to the obtained diagnoses: any psychiatric diagnosis, psychosis, mood disorder, anxiety disorder and any substance use disorder (SUD). The SUD group included those with alcohol and/or substance dependence or harmful use. Grouping was done prioritizing the diagnoses in the following order: psychosis, SUD, mood disorder and anxiety disorder meaning participants with psychosis could also have an SUD and/or mood and/or anxiety disorder, participants with SUD could also have a mood and/or anxiety disorder (but no psychosis) and participants with a mood disorder could also have an anxiety disorder (but no psychosis or SUD) and individuals with an anxiety disorder could not have any of the other diagnoses.

Attrition

An analysis of attrition for this sample of the NFBC1986 has been previously described [19]. 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 a 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.

Statistical analyses

Basic statistical methods including cross-tabulation and Chi-square-tests were used for studying the associations of background variables and psychiatric diagnoses with death. Effect sizes were computed using Cramer's V with >0.25 reflecting very strong, >0.15 , strong, >0.10 moderate, >0.05 weak and >0 no or very weak associations [20]. Univariate Cox regression was used to analyze differences between survival rates for the groups categorized according to alcohol tolerance and frequency of alcohol intoxication.

Univariate Cox regression for survival was used to calculate univariate hazard ratios (HRs) with 95% confidence interval (CI) and determine the associations between the studied variables and age at death. The confounding variables were included in the multivariable models when they were associated with mortality in this study ($p < 0.1$). The confounding variables considered were gender, family structure (intact vs. non-intact), parental education (over or under 12 years), psychiatric diagnoses, history of illicit substance use and daily smoking.

Multivariable Cox regression for survival was used to analyze the risk of death by age 33 after adjusting for confounding variables. HRs with 95% CI were calculated. Separate multivariable models were created to evaluate the predictive significance of alcohol tolerance and frequency of alcohol intoxication on mortality after adjusting for confounders in order to control for the collinearity between alcohol tolerance and frequency of alcohol intoxication (please see Supplement 2 for additional information on the correlations between substance use related variables).

Results were considered statistically significant at $p < 0.05$. All statistical analyses were performed using SPSS version 24.

Results

Of all participants, 49.3% were male and 79.0% lived with both parents (Table 1). Daily smoking was reported by 12.5% of participants. Any psychiatric diagnosis according to register data available was reported for 16.8% and a diagnosis of substance use disorder for 1.8% of participants.

By the age of 33, of all 6,615 participants, 53 (0.8%) were deceased. The deceased were predominantly male (83.0%) and the most common causes of death were suicide (43.4% of all deaths) and accidents (37.7%). Accidental deaths occurred at a slightly older age than suicides or death due to somatic causes (Table 2).

Male gender, higher alcohol tolerance, more frequent intoxication, any psychiatric disorder, psychotic disorder, a diagnosis of SUD and history of illicit substance use in adolescence were significantly more common among those deceased by age 33 (Table 1). Survival from baseline to age 33 according to alcohol tolerance and frequency of alcohol intoxication is depicted in Figures 1 and 2.

Table 3 presents the results of univariate analyses to identify potential confounders. Based on these analyses, gender, maternal education, a history of illicit drug use during adolescence, any psychiatric disorder (incl. substance use disorders) and daily smoking were added to the multivariable models.

High alcohol tolerance was significantly associated with both all-cause mortality and mortality due to accidents or suicide after adjusting for confounding variables (Table 4). Likewise, frequent alcohol intoxication was significantly associated with both all-cause mortality and mortality due to accidents or suicide after adjusting for confounding variables.

Male gender and any psychiatric diagnosis were significant predictors of mortality in all models. The risk for death among males was the highest in all models with HRs from 6.29 to 9.82, and the HRs for psychiatric diagnoses, from 2.94 to 3.47, were also substantial. After adjusting for confounders, the associations between mortality and daily smoking, or a history of illicit substance use during adolescence did not reach statistical significance.

Discussion

High self-reported alcohol tolerance and frequent alcohol intoxication during adolescence were significant predictors of death by age 33, after adjusting for the potential confounders measured in this study. This association was found for both all-cause mortality and mortality due to accidents or suicide. The association of daily smoking or a history of illicit substance use during adolescence with all-cause mortality or mortality due to accidents or suicide did not reach statistical significance, but male gender and having a psychiatric diagnosis did. Males had a higher risk of death due to accidents or suicides compared to females. Mortality among adolescents with a subsequent psychiatric diagnosis was higher than among those without psychiatric diagnoses.

Previous research has shown that drinking habits during adolescence typically continue into later life and binge drinking during adolescence is a risk-factor for development of subsequent AUD as well as problems with other substance use [21]. Binge drinking is highly correlated with high volume alcohol consumption in

general in adolescents [9]. High volume consumption is likely associated with high alcohol tolerance as reported in this study, but individual differences also play a role in how tolerance is acquired [12]. It has been hypothesized that poorer inhibitory functioning could explain why these adolescents subsequently transition to high volume consumption [22]. These reductions continue after such drinking commences. The affected areas are central for executive functions, including inhibitory functioning, attention, impulsivity and self-regulation [22].

The most common causes of death in this study were suicide and accidents, which is in concordance with existing literature. Previous findings have found that heavy drinking where a pattern of binge drinking is included, is a risk factor for death due to unintentional and intentional injuries [1]. Alcohol-related deaths due to both unintentional and intentional injuries are common among Finnish men [2]. Male gender was significantly associated in this study with both all-cause mortality risk and risk of death due to accidents or suicide.

In this study, neither daily smoking during adolescence nor history of illicit drug use were associated with mortality after adjusting for confounders, even though smoking and illicit substance use are both associated with increased mortality in the general population [17, 23]. It is possible, however, that the adolescents with frequent alcohol intoxication and high alcohol tolerance in this study, are to some extent the same adolescents who reported daily smoking and a history of illicit substance use. Thus, collinearity between daily smoking, history of illicit drug use at age 15-16 and the alcohol variables could explain this finding.

Both psychiatric diagnoses and frequency of alcohol intoxication during adolescence were significant predictors of mortality in this study. Individuals reporting being intoxicated 1-2 times in the past month had a higher risk of death compared to those who had not been intoxicated. The largest HR was observed among those who had been intoxicated three or more times. Although the results of this study are

predictive associations only and causality of these associations cannot directly be determined, it is important to examine these results in the framework of previous findings regarding causality. A twin-study conducted by Rose et al. [24] tested whether between-family confounds of family structure and status, familial history and household and community environments could explain the association of adolescent alcohol abuse with adverse outcomes in adulthood, including poor health, life dissatisfaction, truncated education and substance abuse. They found that the associations found in comparisons of twins as singletons replicated in drinking-discordant twin pairs, providing more compelling evidence than previously available that adolescent alcohol abuse disrupts transitions into early adulthood [24]. Further, a Finnish twin-study by Sipilä et al. [25], found that among twins as individuals, high monthly alcohol consumption was associated with earlier all-cause mortality and that between-family association replicated in comparisons of all informatively drinking-discordant twin pairs and, separately, in all discordant monozygotic twin pairs with comparable effect size. The conclusion was that the associations “cannot be explained by familial or genetic confounds: the explanation appears to be causal” [25]. These earlier findings offer indirect support for attributing a causal nature to our associative results.

This study has several strengths. The alcohol measures used in this study regarding intoxication relied on subjective reporting of experienced inebriation. This enabled us to study the subjective experience of intoxication. This is novel approach that differs from studies which have focused on binge drinking, where the common definitions include consuming a minimum number of standard drinks in a specific timeframe. This approach may identify adolescents who can become intoxicated with relatively few drinks, adolescents who may not meet typical definitions of binge drinking; studying tolerance in this way could advance research on sequelae of underage drinking. Thus, the current study can potentially add to our understanding of the relationship between drinking during adolescence and adverse outcomes in young adulthood.

Further strengths include utilization of the NFBC 1986, one of the largest birth cohort studies with high genetic and ethnic homogeneity as well as the use of several nationwide registers where missing information is low. The wide range of information included in this data made it possible to address many potential confounders.

Limitations of this study include an attrition rate of 26.2% at the 15–16-year field study. Individuals from non-intact families and urban areas were less likely to participate, which is likely a source of bias, however, this missing information is more likely to weaken the associations found in this study, rather than spuriously enhance them. The use of a hierarchical psychiatric outcome variable may underestimate the latter outcomes such as anxiety disorders due to loss of cases. Data for all substance use disorders was pooled due to power issues, and thus we were not able to study these disorders independently. We were not able to adjust for potential confounding due to childhood or familial adversity. Finally, information on substance abuse was collected using self-reports. Self-reports typically underestimate substance use [26], however this is likely to lead to underestimation, rather than overestimation, of true associations.

Reducing heavy drinking during adolescence is important for preventing long-term adverse consequences [15], including the mortality risk observed in this study. Regulatory policies, i.e. increasing price, restricting access to alcohol and raising legal purchase age have been found to be effective in reducing adolescent alcohol use and related harms [27, 28]. Developmental interventions include strategies aimed at reducing the risk of alcohol use through, e.g., efforts targeted at reduction of poverty and social isolation [27]. These can be used in primary prevention in conjunction with other measures, such as regulatory approaches and with treatment and harm-reduction programs. Screening of high-risk alcohol use is not routinely implemented [29], even though brief interventions, including motivational interviewing are effective among adolescents engaged in high-risk alcohol use [27]. Screening is necessary also to identify those individuals with diagnosable disorders who could benefit from more intensive interventions. Psychosocial treatment of AUD among adolescents is more effective than no treatment at all, but the evidence for who would benefit from which type of intervention remains unclear [30].

Implications and Contribution

Our findings that high subjectively experienced alcohol tolerance and frequent intoxication are associated with death by age 33 suggests that 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. Further, 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. Associations of background and alcohol related variables and psychiatric diagnoses to mortality, (Chi-squared test).

	Total n	All n=6,615		Alive n=6,562		Deceased n=53		p-value	Effect size ¹
		n	%	n	%	n	%		
Gender	6,615								
Male		3,259	49.3	3,215	49.0	44	83.0	<0.001	0.061
Female		3,356	50.7	3,347	51.0	9	17.0		
Family type	5,647								
Two parents		4,463	79.0	4,431	79.1	32	71.1	0.190	0.017
One parent or other		1,184	21.0	1,171	20.9	13	28.9		
Mother's education	5,623								
≥12 years		1,865	33.2	1,857	33.3	8	17.8	0.028	0.029
<12 years		3,758	66.8	3,721	66.7	37	82.2		
Father's education	5,390								
≥12 years		1,030	19.1	1,023	19.1	7	16.7	0.686	0.006
<12 years		4,360	80.9	4,325	80.9	35	83.3		
Alcohol tolerance²	6,615								
No alcohol / intoxication		2,119	32.0	2,108	32.1	11	20.8	0.001	0.048
1-4 (males) / 1-3 (females)		1,228	18.6	1,219	18.6	9	17.0		
5-8 (males) / 4-6 (females)		2,505	37.9	2,487	37.9	18	34.0		
≥9 (males) / ≥7 (females)		763	11.5	748	11.4	15	28.3		
Frequency of alcohol intoxication³	6,441								
0 times		3,847	59.7	3,828	59.9	19	37.3	<0.001	0.049
1-2 times		1,962	30.5	1,942	30.4	20	39.2		
≥3 times		632	9.8	620	9.7	12	23.5		
History of illicit substance use	6,594								
No		6,212	94.2	6,167	94.3	45	84.9	0.004	0.036
Yes		382	5.8	374	5.7	8	15.1		
Daily smoking	6,106								
No		5,340	87.5	5,304	87.6	36	75.0	0.009	0.033
Yes		766	12.5	754	12.4	12	25.0		
Any psychiatric disorder	6,337								
No		4,985	78.7	4,954	78.8	31	60.8	0.002	0.039
Yes		1,352	21.3	1,332	21.2	20	39.2		
Any psychosis	6,580								
No		6,440	97.9	6,395	98.0	45	84.9	<0.001	0.081
Yes		140	2.1	132	2.0	8	15.1		
Mood disorder	6,545								
No		6,056	92.5	6,008	92.5	48	92.3	0.951	0.001
Yes		489	7.5	485	7.5	4	7.7		
Anxiety disorder	6,566								
No		6,203	94.5	6,152	94.5	51	96.2	0.575	0.007
Yes		363	5.5	361	5.5	2	3.8		
Substance use disorder	6,578								
No		6,446	98.0	6,400	98.1	46	86.8	<0.001	0.072
Yes		132	2.0	125	1.9	7	13.2		

¹ Cramer's V; very strong >0.15, strong, >0.10 moderate, >0.05 weak and >0 no or very weak associations ² Number of drinks needed in order to feel intoxicated ³ In the last 30 days

Table 2. Causes and ages of death.

	Suicide n=23		Accident n=20		Somatic disease n=10	
	n	%	n	%	n	%
	Gender					
Male	20	87.0	18	90.0	6	60.0
Female	3	13.0	2	10.0	4	40.0
Age of death, mean (sd)	23.9	3.2	24.6	5.5	23.9	3.9

Table 3. Hazard ratios for death calculated using univariate Cox regression analyses.

	n	Deceased		HR	95% CI	p-value
		n	%			
Gender	6,615					
Male		44	1.4	ref.		
Female		9	0.3	0.2	(0.1 – 0.4)	<0.001
Family type	5,647					
Two parents		32	0.7	ref.		
One parent or other		13	1.1	1.5	(0.8 – 2.9)	0.193
Mother's education	5,623					
≥ 12 years		8	0.4	ref.		
< 12 years		37	1.0	2.3	(1.1 – 4.9)	0.033
Father's education	5,390					
≥ 12 years		7	0.7	ref.		
< 12 years		35	0.8	1.2	(0.5 – 2.7)	0.687
Alcohol tolerance¹	6,615					
No alcohol / intoxication		11	0.5	ref.		
1-4 (males) / 1-3 (females)		9	0.7	1.4	(0.6 – 3.4)	0.442
5-8 (males) / 4-6 (females)		18	0.7	1.4	(0.7 – 2.9)	0.397
≥9 (males) / ≥7 (females)		15	2.0	3.8	(1.7 – 8.3)	0.001
Frequency of alcohol intoxication¹	6,441					
0 times		19	0.5	ref.		
1-2 times		20	1.0	2.1	(1.1 – 3.9)	0.024
≥3 times		12	1.9	3.9	(1.9 – 8.0)	<0.001
History of illicit substance use	6,594					
No		45	0.7	ref.		
Yes		8	2.1	2.9	(1.4 – 6.1)	0.006
Daily smoking	6,106					
No		36	0.7	ref.		
Yes		12	1.6	2.3	(1.2 – 4.5)	0.011
Any psychiatric disorder	6,337					
No		31	0.6	ref.		
Yes		20	1.5	2.4	(1.4 – 4.2)	0.002
Any psychosis	6,580					
No		45	0.7	ref.		
Yes		8	5.7	8.3	(3.9 – 17.5)	<0.001
Mood disorder	6,545					
No		48	0.8	ref.		
Yes		4	0.8	1.0	(0.4 – 2.9)	0.950
Anxiety disorder	6,566					
No		51	0.8	ref.		
Yes		2	0.6	0.7	(0.2 – 2.7)	0.576
Substance use disorder	6,578					
No		46	0.7	ref.		
Yes		7	5.3	7.6	(3.4 – 16.8)	<0.001

¹ Number of drinks needed in order to feel intoxicated ² In the last 30 days

Table 4. Hazard ratios (HRs) for death calculated with Cox regression for survival analysis.

	All-cause mortality			Mortality due to accidents and suicides				
	HR	95% CI		p-value	HR	95% CI		p-value
		upper	lower			upper	lower	
Alcohol tolerance¹								
Male gender	6.294	2.775	14.275	<0.001	9.817	3.435	28.058	<0.001
Mother's education <12 years	2.008	0.925	4.360	0.078	1.548	0.697	3.439	0.283
History of illicit substance use	2.157	0.876	5.313	0.095	2.313	0.868	6.166	0.094
Daily smoking	1.197	0.516	2.774	0.675	1.155	0.449	2.971	0.765
Any psychiatric diagnosis	2.939	1.574	5.485	0.001	3.176	1.593	6.331	0.001
Alcohol tolerance ¹				0.039				0.034
1-4 (males) / 1-3 (females)	2.055	0.789	5.353	0.140	3.342	1.114	10.028	0.031
5-8 (males) / 4-6 (females)	1.113	0.446	2.778	0.819	1.491	0.499	4.456	0.475
≥9 (males) / ≥7 (females)	3.082	1.177	8.072	0.022	3.810	1.201	12.083	0.023
Frequency of alcohol intoxication²								
Male gender	6.420	2.833	14.548	<0.001	9.710	3.399	27.738	<0.001
Mother's education < 12 years	2.368	1.047	5.356	0.038	1.834	0.793	4.241	0.156
History of illicit substance use	2.019	0.807	5.051	0.133	2.127	0.785	5.762	0.138
Daily smoking	0.984	0.417	2.318	0.970	0.831	0.311	2.219	0.712
Any psychiatric diagnosis	3.173	1.690	5.958	<0.001	3.472	1.726	6.983	<0.001
Frequency of alcohol intoxication ²				0.039				0.022
1-2 times	2.046	1.006	4.160	0.048	2.340	1.047	5.233	0.038
≥3 times	3.015	1.206	7.540	0.018	3.846	1.409	10.499	0.009

¹ Number of drinks needed in order to feel intoxicated, no alcohol use or never been intoxicated as reference

² In the last 30 days, no reported alcohol intoxication used as reference

Figure 1. Alcohol tolerance during adolescence and survival according to COX regression analyses (unadjusted).

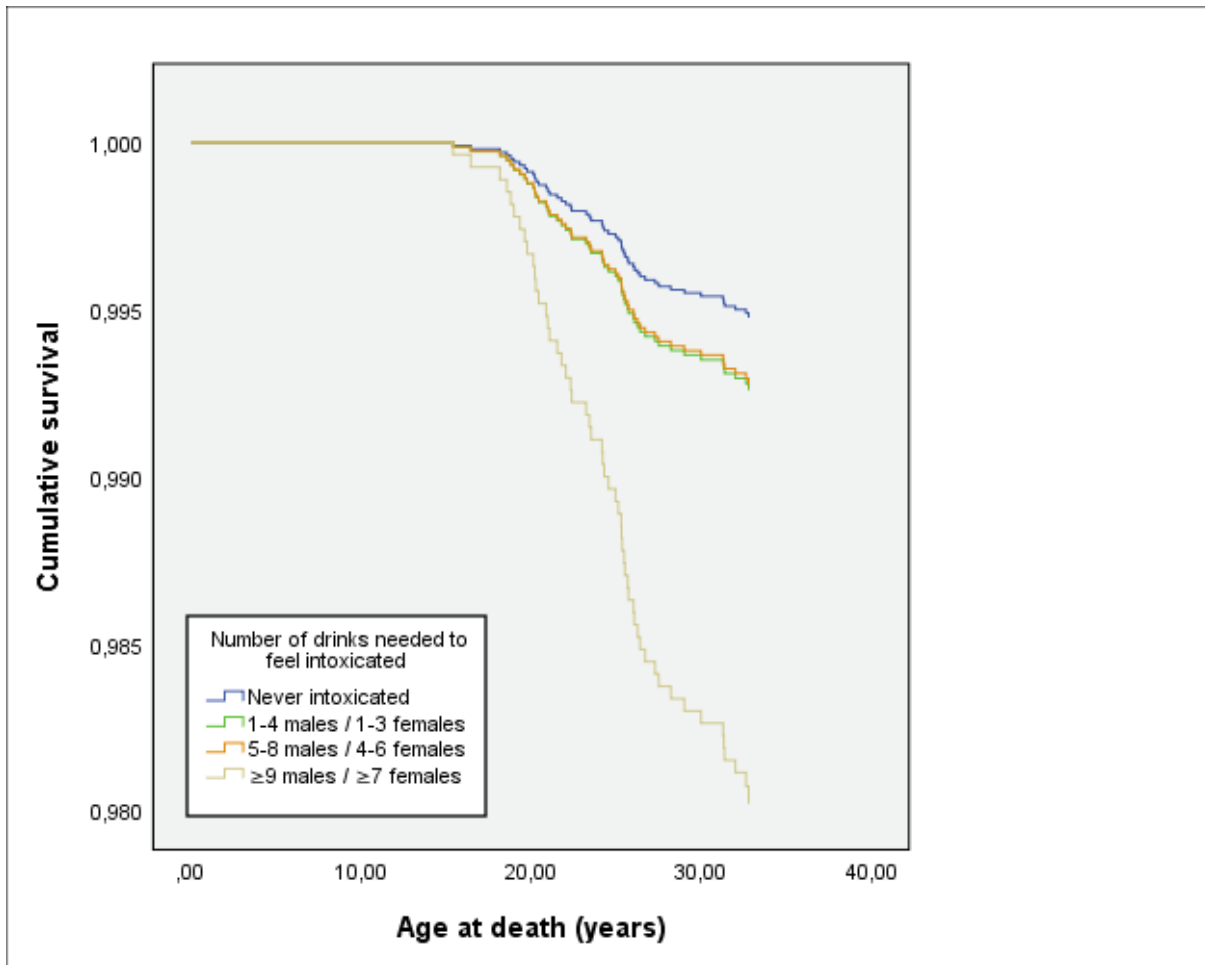


Figure 2. Frequency of alcohol intoxication during adolescence and survival according to COX regression analyses (unadjusted).

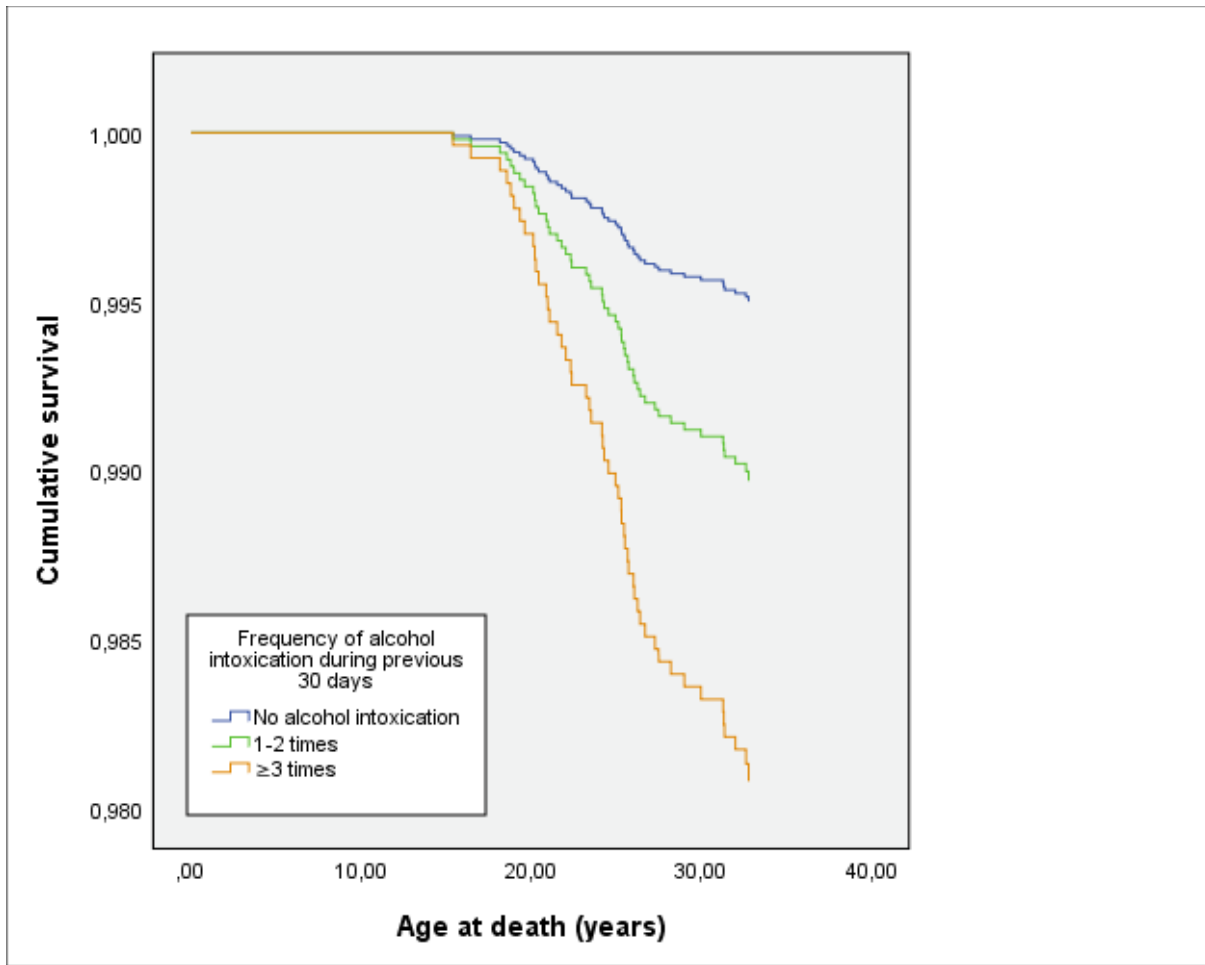


Figure (Suppl. 1). Study flowchart.

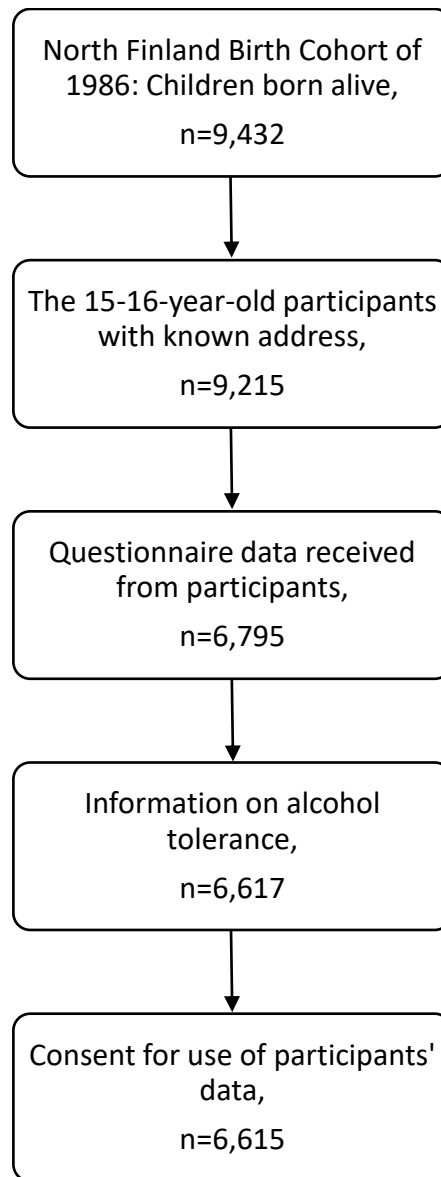


Table (Suppl. 2). Associations and effect sizes of alcohol related variables, history of illicit substance use and daily smoking (Chi-squared test and (Cramer's V).

	Alcohol tolerance¹		Frequency of alcohol intoxication²		History of illicit substance use		Daily smoking	
	Effect size	p-value	Effect size	p-value	Effect size	p-value	Effect size	p-value
Alcohol tolerance¹	--	--	--	--	--	--	--	--
Frequency of alcohol intoxication²	0.439	<0.001	--	--	--	--	--	--
History of illicit substance use	0.231	<0.001	0.285	<0.001	--	--	--	--
Daily smoking	0.376	<0.001	0.340	<0.001	0.273	<0.001	--	--

¹ In the last 30 days ² Number of drinks needed in order to feel intoxicated