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Age of first alcohol intoxication and psychiatric disorders in young adulthood – A prospective birth cohort study

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ABSTRACT

Objective: Early onset of alcohol use is associated with an increased risk of substance use disorders (SUD), but few studies have examined associations with other psychiatric disorders. Our aim was to study the association between the age of first alcohol intoxication (AFI) and the risk of psychiatric disorders in a Finnish general population sample.

Methods: We utilized a prospective, general population-based study, the Northern Finland Birth Cohort 1986. In all, 6,290 15–16-year old adolescents answered questions on AFI and were followed up until the age of 33 years for psychiatric disorders (any psychiatric disorder, psychosis, SUD, mood disorders and anxiety disorders) by using nationwide register linkage data. Cox-regression analysis with Hazard Ratios (HR, with 95% confidence intervals (CI)) was used to assess the risk of psychiatric disorders associated with AFI.

Results: Statistically significant associations were observed between AFI and any psychiatric disorder, psychosis, SUDs, and mood disorders. After adjustments for other substance use, family structure, sex and parental psychiatric disorders, AFIs of 13–14 years and ≤12 years were associated with SUD (HR = 5.30; 95%CI 2.38–11.82 and HR = 6.49; 95%CI 2.51–16.80, respectively), while AFI ≤ 12 years was associated with any psychiatric disorder (HR = 1.59; 95%CI 1.26–2.02) and mood disorders (HR = 1.81; 95%CI 1.22–2.68). After further adjustments for Youth Self Report total scores, AFI ≤ 14 was associated with an increased risk of SUD and AFI ≤ 12 with an increased risk of any psychiatric disorder.

Conclusions: We found significant associations between the early age of first alcohol intoxication, later SUD and any psychiatric disorder in a general population sample. This further supports the need for preventive efforts to postpone the first instances of adolescent alcohol intoxication.

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1. Introduction

Alcohol is the most commonly used substance among adolescents in mid- and high-income countries and also the most frequent form of very early onset substance use (Kraus et al., 2015; Miech & Johnston, 2018; Toumbourou et al., 2018). The early use of alcohol coincides with a period of neurodevelopmental vulnerability, during which typical maturational processes for the brain and related circuitry of the central nervous system may be disrupted by substance use (Gray & Squeglia, 2018; Hamidullah, Thorpe, Frie, Mccurdy, & Khokhar, 2020). This may increase the later risk of substance use and mental health problems (Gray & Squeglia, 2018; Hamidullah et al., 2020), increasing the burden of disease associated with early use of alcohol (Degenhardt et al., 2018; Griswold et al., 2018).

Research on adolescent exposure to alcohol and mental health outcomes has applied the age of first drink (AFD) to study early alcohol-related harm. Longitudinal studies have typically yielded associations of AFD with later alcohol use behaviors and alcohol use disorders (AUD) (DeWit, Adlaf, Offord, & Ogborne, 2000; Grant & Dawson, 1997; Hingson, Heeren, & Winter, 2006; Pitkänen, Lyyra, & Pulkkinen, 2005). However, the usefulness of AFD as an early marker of alcohol-related harm has been debated due to unclear definitions across studies and weak theoretical arguments and empirical evidence to support causative inferences (Kuntsche, Rossow, Engels, & Kuntsche, 2016). A recent study by Newton-Howes et al. (2019) examined the age of first intoxication (AFI) alongside AFD as predictors of substance use and mental health disorders in adulthood in a prospective birth cohort design, with AFI proving to be superior in predicting these outcomes (Newton-Howes, Cook, Martin, Foulds, & Boden, 2019). The researchers reported an association between AFI and substance use disorders (alcohol use disorder, nicotine and cannabis dependence) in adulthood. Furthermore, they reported a crude association between AFI and anxiety and depression, which diminished after adjustments for confounders.

Alcohol use and other substance use disorders are highly comorbid with other psychiatric disorders (McGrath et al., 2020; Plana-Ripoll et al., 2019). There is evidence of the influence of adolescent substance use on the onset of psychiatric disorders and some evidence that alcohol use in adolescence may predict future depression (Hamidullah et al., 2020). It is thus possible that early onset of alcohol use could influence trajectories of psychiatric disorders, given the dynamic period of brain development in adolescence. Nonetheless, any association may also be due to the confounding effects of environmental or individual factors.

Our aim was to study whether AFI is independently associated with any psychiatric disorder, psychosis, substance use disorders (SUD), mood disorders and anxiety disorders until age 33 years. We used the linkage of Northern Finland Birth Cohort 1986 and national register data that provides substantial coverage of diagnosed psychiatric disorders. Our sample is based on the general population. The prospective Northern Finland Birth Cohort 1986 (n = 6290) also provides a large dataset on possible confounders, including parental history of psychiatric disorders, emotional and behavioral problems in adolescence (YSR) and other substance use, allowing us to investigate the independent contribution of age of first alcohol intoxication.

2. Materials and methods

2.1. Participants

The Northern Finland Birth Cohort (NFBC) 1986 is an ongoing prospective follow-up study comprising 99% of all live-born children (n = 9432) from the two northernmost provinces in Finland with an expected date of birth between 1st of July 1985 and 30th of June 1986. In all, 7344 adolescents (48.8% male) participated in the follow-up study in 2001–2002, when the study members were aged 15–16 years. At that stage, data collection was conducted in two phases. First, adolescents completed a self-report postal questionnaire about their health and wellbeing, which included items about physical health, psychosocial wellbeing, and smoking habits (n = 7344). Thereafter, all participants were invited to a clinical study, where they completed self-report questionnaires including the Youth Self Report (YSR) (Achenbach & Rescorla, 2000) and a questionnaire concerning, e.g., substance use (n = 6798). Participants who signed the informed consent form and answered the questions on the age of first alcohol intoxication were included in the study. To account for the effect of prior mental health disorders on study variables, we excluded those, who had been diagnosed with any psychiatric disorder before the age of 16.

The final sample was 6290 (48.7% male) (Fig. 1). The 15–16 -year follow-up study was approved by the Ethics committee of the Northern Ostrobothnia Hospital District in Finland (17th May 2006). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. We have used the STROBE reporting guidelines for cohort studies. The STROBE checklist is included in the online supplement.

2.2. Measures

2.2.1. Age of first alcohol intoxication

Data on the age of first alcohol intoxication were collected during the clinical study by using a self-report questionnaire. Participants were asked “At what age did you get drunk for the first time? – (at 11 or younger; at 12 years; at 13 years; at 14 years; at 15 years; at 16 years or never)”. The options were pooled into four categories (1. Never; 2. at 15–16 years; 3. at 13–14 years; and 4. at 12 years or before). Participants who reported never having been intoxicated from alcohol were considered as the reference group.

2.2.2. Outcomes

Information on psychiatric diagnoses was collected cumulatively from the participants, starting with the age 15–16 years until the end of 2018, i.e. when the participants were aged 33 years. The onset age of each disorder was based on the first record of the diagnosis in registers. Diagnosed psychiatric disorders were obtained from linkage to four nationwide registers, which provide extensive coverage of diagnosed psychiatric disorders and only minimal attrition: 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 2001–2005; and the 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 previous studies (Filatova et al., 2017; Gissler & Haukka, 2004; Miettunen, Suvisaari, Haukka, & Isohanni, 2011). The data in Finnish national registers are generally reliable (Sund, 2012) and registers typically provide data with minimal attrition (mostly due to deaths and emigration), compared to survey data (Haapea et al., 2008).

Five outcome groups were identified based on the psychiatric disorders recorded. The first group combined all the psychiatric disorders studied, i.e. any psychiatric disorder. For the other outcome groupings, the ICD-10 (World Health Organization, 2019) psychiatric diagnoses were divided into four classes, which were studied hierarchically: 1) any non-organic psychosis; 2) any substance use disorder; 3) any mood disorder; and 4) any anxiety disorder (ICD details; see online supplement Table 1). SUD was defined as dependence (F1x.2) or harmful use (F1x.1) on alcohol or other substances, or both (ICD-10). Similar categorization was used in previous research on alcohol related outcomes in the same

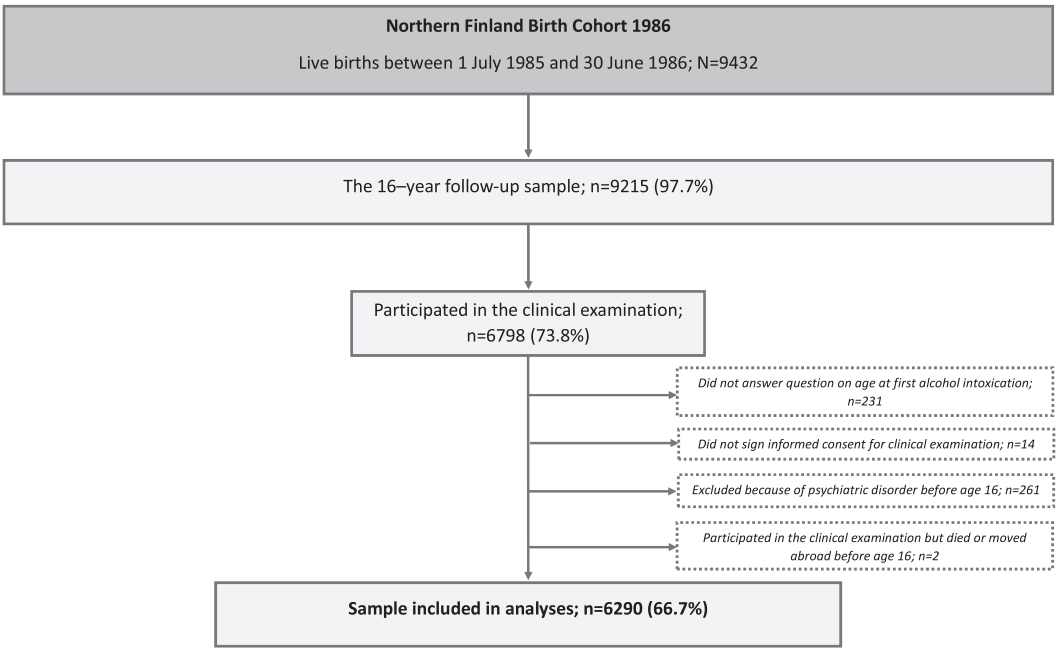

Fig. 1. Flowchart of the current study from the Northern Finland Birth Cohort 1986.

sample (Sarala et al., 2020). The grouping of psychiatric disorders was used to allow for a more robust consideration of their comorbidity.

Individuals with a psychosis diagnosis may thus have had a mood disorder, anxiety disorder or SUD diagnosis at some point during the follow-up. Individuals with SUD may have had a mood disorder or anxiety disorder during the follow-up, but those with psychosis were excluded from the SUD outcome. Individuals with mood disorder may have had an anxiety disorder during the follow-up, but they were excluded from the mood disorder outcome if they had psychosis or SUD. In the anxiety disorder outcome, individuals with psychosis, SUD or mood disorder were excluded. The reference group in all categories consisted of those without any psychiatric diagnosis.

2.2.3. Covariates

Data on lifetime illicit substance use at age 15–16 years were collected during the clinical study by using a self-report questionnaire. The participants were asked: 'Have you used marijuana or hashish?' and 'Have you used ecstasy, heroin, cocaine, amphetamine, LSD or other similar intoxicating drugs?' Individuals were categorized into the yes-group if they had used any of these substances at least once. Information on regular cigarette smoking was collected from postal questionnaires that participants had completed prior to the clinical study (Miettunen et al., 2014). The participants were asked if they currently smoked at least 1 cigarette/day and were considered daily smokers if they reported smoking cigarettes daily.

During the clinical study at age 15–16 years, information was collected on adolescent mental health using the Youth Self Report (YSR) (Achenbach & Rescorla, 2000). The YSR measures symptoms of emotional or behavioral problems in adolescents aged 11–18 years. The adolescents were presented with 118 statements including 29 items for externalizing problems (e.g., 'I am mean to others' and 'I get in many fights') and 30 items for internalizing problems (e.g. 'I worry a lot' and 'I am unhappy, sad or depressed'). Responses were scored on a three-point scale with the statements being not true (0); somewhat/sometimes true (1) or very true (2), reflecting how the adolescents had felt within the past 6 months. Scores for each item were added together to obtain a summary score for each subscale. 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).

Data on family structure were gathered by combining information collected from parents at birth and when the cohort member was aged 15–16. For analyses, they were dichotomized into "family with two parents", where both parents lived together with the participant and "other", which consisted of all other families. Lifetime parental psychiatric diagnoses (including SUD) were obtained from the nationwide registers, which included: 1) Register of Health Care 1972–2018 (including 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 (2011–2018).

2.3. Statistical methods

The covariates were selected based on previous literature (Gobbi et al., 2019; Gurillo, Jauhar, Murray, & MacCabe, 2015; Holst, Tolstrup, Sørensen, Pisinger, & Becker, 2019; Marconi, Di Forti, Lewis, Murray, & Vassos, 2016; McCutcheon et al., 2018; McLaughlin et al., 2012; Whitesell, Bachand, Peel, & Brown, 2013). The relationships of possible covariates (sex, family structure, parental education, daily cigarette smoking, cannabis use, other illicit substance use, parental psychiatric disorder, the YSR total score) with self-reported age of first alcohol intoxication and any psychiatric disorder during the follow-up were examined using crosstabulation and χ^2 or Fisher Exact test, with $p < 0.05$ indicating potential to significantly affect the results. The covariates associated with a $p < 0.05$ significance with self-reported first alcohol intoxication and any psychiatric disorder were included in the multivariable analyses. Linear regression and multicollinearity diagnostics with variance inflation factor (VIF) scores were used to detect correlation between multiple covariates. VIF > 10 was used as an indicator of multicollinearity.

We studied the association of self-reported age of first alcohol intoxication with the risk for each psychiatric outcome group (any

psychiatric disorder, any psychosis, any SUD, any mood disorder, and any anxiety disorder) separately using Cox regression analysis with hazard ratios (HR) and 95% confidence intervals (95% CI). Time of emigration (n = 234) and death (n = 29) were used as censoring points in survival analyses. Subjects with any prior mental disorder before the age of 16 were excluded (n = 261). To adjust for the effect of covariates, we used the following models for each outcome class: Model 1 included cannabis use, daily smoking, and illicit substance use other than cannabis at baseline; Model 2 further included sex, family structure and any parental psychiatric disorder; and Model 3 further included the YSR total score. This was considered to examine whether the associations between AFI and different outcomes were specifically affected after adjusting for certain groups of covariates. Participants with missing data were excluded if they had not answered the questions used as covariates in the models. This missing data is presented in the online supplement Table 2. Benjamini-Hochberg procedure was used to adjust statistical significance for multiple comparisons.

The Aalen-Johansen cumulative incidence curves were computed for all psychiatric outcomes. The Cox proportional hazard assumption was examined by using hazard logarithms and scaled Schoenfeld residuals. As some AFI – outcome associations violated the assumption, we conducted a sensitivity analysis where a time-dependent interaction term for AFI was constructed and studied with all outcomes by including it in the crude model. As a result of adding the time-AFI interaction term, there was a statistically significant ($p < 0.05$) improvement in fit of the model concerning anxiety disorders. Here the interaction term was statistically significant ($p < 0.05$) for AFI 15–16 years and anxiety disorders.

We also looked for a trend between the age of first alcohol intoxication and outcome categories by using Cox regression analysis, where the categorical AFI variable was used as continuous in the adjusted model 3.

Previous attrition analyses of this sample have shown that fewer males (64% v. 71%; $p < 0.001$), individuals living in urban areas (66% v. 71%, $p < 0.001$) and individuals with parental psychiatric disorder (58% v. 69%, $p < 0.001$) participated in the 15–16 year follow up study (Miettunen et al., 2013). To address this attrition, we weighted our crude analyses by sex, parental psychiatric disorder and urbanicity by using inverse probability weighting (Haukoos & Newgard, 2007) and analyzed these data with logistic regression analysis and odds ratios (OR). All the statistically significant ORs in unweighted analyses of AFI and psychiatric outcomes were also statistically significant in the weighted analyses, and the strength of the associations were of similar magnitude (data available from the authors).

Furthermore, to account for possible unmeasured confounding, E–values were calculated. E – value is an alternative approach for sensitivity analysis in observational studies. E-values with lower bound of the CI indicate the minimum strength of unmeasured confounders' association with independent (here AFI) and dependent variables (here psychiatric disorder groups) that could explain away the observed association between exposure and outcome. Small E-values (lowest possible 1.0) suggest that only relatively weak unmeasured confounding would be required to affect the observed association, while higher E-values indicate robustness of the observed association to unmeasured confounding (Haneuse, Vanderweele, & Arterburn, 2019). E–values calculated from hazard ratios for all models are reported in the online supplement Table 3 (Mathur, Ding, Riddell, & VanderWeele, 2018).

The statistical analyses were performed using SPSS statistical software (IBM SPSS Statistics, version 25; IBM Co., Armonk, New York, USA) with the exception of Aalen – Johansen hazard curves, E-values and examination of cox-proportional hazard assumption that were analyzed using R (R Foundation for Statistical Computing, version 3.6.0; R Core Team., Armonk, Vienna, Austria) packages survival, survminer and Epi.

3. Results

The covariates and their relation to the age of first self-reported alcohol intoxication and onset of any psychiatric disorder are presented in Tables 1 and 2. Of the total sample of 6290 individuals, 4231 had experienced their first alcohol intoxication by the age of 16 years, representing 67.2% of the sample. Of these, 436 adolescents had experienced their first alcohol intoxication at the age of 12 or prior, 2748 adolescents at ages 13–14 and 1047 adolescents at ages 15–16. There were 1345 individuals who had been diagnosed with a psychiatric disorder during the follow up period, representing 21.4% of the sample. In the SUD category, 85/116 (73.3%) were AUD. The VIFs did not indicate presence of multicollinearity (all VIFs < 1.2).

Table 1
Family characteristics, substance use and YSR scores by AFI in the 15- to 16-year follow-up study of the Northern Finland 1986 Birth Cohort.

		Self-reported age of first alcohol intoxication										
	Total n	*n = 6290*		*Reference n = 2059*		*at ages 15–16n = 1047*		*at ages 13–14n = 2748*		*at age 12 or earlier n = 436*		*p-value*
		n	%	n	%	n	%	n	%	n	%	
Sex	6290											
Male		3066	48.7	1073	52.1	515	49.2	1240	45.1	238	54.6	<0.001
Female		3224	51.3	986	47.9	532	50.8	1508	54.9	198	45.4	
Family structure	5392											
Other		1097	20.3	207	11.5	175	19.6	589	25.2	126	35.2	<0.001
Family with two parents		4295	79.7	1595	88.5	719	80.4	1749	74.8	232	64.8	
Parental education	5042											
<12 years		3033	60.2	978	57.1	515	61.6	1336	61.5	204	63.0	0.023
12 years or more		2009	39.8	731	42.9	321	38.4	837	38.5	120	37.0	
Cannabis use	6248											
No		5898	94.4	2045	100.0	1021	97.9	2488	91.3	344	79.3	<0.001
Yes		350	5.6	1	0.0	22	2.1	237	8.7	90	20.7	
Daily smoking	5838											
No		5125	87.8	1904	98.9	904	93.7	2073	81.2	244	61.8	<0.001
Yes		713	12.2	22	1.1	61	6.3	479	18.8	151	38.2	
Other illicit drug use	6252											
No		6222	99.5	2046	100.0	1038	99.8	2718	99.5	420	97.0	<0.001
Yes		30	0.5	1	0.0	2	0.2	14	0.5	13	3.0	
Parental psychiatric disorder	6290											
No		4021	63.9	1373	66.7	671	64.1	1732	63.0	245	56.2	<0.001
Yes		2269	36.1	686	33.3	376	35.9	1016	37.0	191	43.8	
YSR	5813	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	
YSR total score		26.5	15.6	22.2	13.6	25.3	14.7	29.1	15.9	33.3	17.9	

Table 2
Family characteristics, substance use and YSR scores, by any psychiatric disorder in the 15- to 16-year follow-up study of the Northern Finland 1986 Birth Cohort.

	Total n	Any psychiatric disorder during the follow-up						
		n = 6290		*No n = 4945*		*Yes n = 1345*		*p-value*
		n	%	n	%	n	%	
Sex	6290							
Male		3066	48.7	2546	51.5	520	38.7	<0.001
Female		3224	51.3	2399	48.5	825	61.3	
Family structure	5392							
Other		1097	20.3	798	18.8	299	26.2	<0.001
Family with two parents		4295	79.7	3454	81.2	841	73.8	
Parental education	5042							
<12 years		3033	60.2	2394	60.0	639	60.7	0.662
12 years or more		2009	39.8	1596	40.0	413	39.3	
Cannabis use	6248							
No		5898	94.4	4684	95.4	1214	90.9	<0.001
Yes		350	5.6	228	4.6	122	9.1	
Daily smoking	5838							
No		5125	87.8	4090	89.0	1035	83.4	<0.001
Yes		713	12.2	507	11.0	206	16.6	
Other illicit drug use	6252							
No		6222	99.5	4902	99.7	1320	99.0	0.001
Yes		30	0.5	16	0.3	14	1.0	
Parental psychiatric disorder	6290							
No		4021	63.9	3287	66.5	734	54.6	<0.001
Yes		2269	36.1	1658	33.5	611	45.4	
YSR	5813	mean	sd	mean	sd	mean	sd	
YSR total score		26.5	15.6	25.2	14.7	31.3	17.7	

In our univariable analyses, AFI 12 years or earlier was associated with any psychiatric disorder, psychosis, substance use disorder (SUD) and mood disorder until the age of 33, and AFI 13–14 years was associated with any psychiatric disorder and SUD (see Table 3). The Aalen-Johansen curves are presented in Fig. 2.

AFI 12 years or earlier was associated with any psychiatric disorder, SUD and mood disorder, and AFI 13–14 years was associated with SUD after adjusting for cannabis, illicit substance use other than cannabis, and daily cigarette smoking. Further adjustment for sex, family structure and parental psychiatric disorder attenuated associations only minimally. After further adjusting for the YSR total score, only the associations between AFI 12 years or earlier and any psychiatric disorder (HR = 1.40; 95% CI 1.11–1.79), AFI 12 years or earlier and AFI 13–14 years and SUD (HR = 6.18; 95% CI 2.33–17.23 and HR = 5.14; 95% CI 2.17–12.17 respectively) remained statistically significant. For the results, see Table 3.

Furthermore, there was a trend, in which an earlier age of the first alcohol intoxication was associated with an increasing risk of SUD in model 3 (HR = 1.85; 95%CI 1.40–2.45). For all the results of the trend tests, see online supplement Table 4.

Non-response to the questions at 15–16-year follow-up reduced the sample size from 6290 to 5058 from crude to a fully adjusted model 3 concerning the study of any psychiatric disorder. However, the distribution of covariates within the AFI categories was generally similar in the study population in crude model to that in the study population in model 3 (see online supplement Table 2).

E-values for point estimates and lower limits for confidence interval for the association between AFI and psychiatric outcomes are reported in the online supplement Table 3.

4. Discussion

This study used a large prospective birth cohort data to examine the association between the age of first alcohol intoxication (AFI) and psychiatric disorders emerging up to young adulthood. Here, AFI of 14 years or earlier was associated with an increased risk of subsequent SUD while AFI of 12 years or earlier was associated with any psychiatric disorder independent of cannabis use, daily smoking, other substance use, sex, family structure, parental psychiatric disorder, and emotional and behavioral problems in adolescence. Crude associations were seen for psychosis and mood disorders, but they were not significant after adjustments for individual and environmental factors. A statistically significant trend was also observed, in which earlier AFI was associated with an increasing risk of SUD. Together with previous research, this suggests that early AFI increases the risk of future SUD. This study also provides novel findings that early AFI may influence the onset of any psychiatric disorder, providing grounds for future research.

Our results on SUD are consistent with the findings of the previous study by Newton-Howes et al. (2019), which reported statistically significant associations between AFI with the risk of future SUD. Although the point estimates in our study suggest a very strong association, confidence intervals were wide. Therefore, conservative interpretation of the risk increase is recommended. Although the two studies are not entirely comparable due to differing methodology, similar findings support the role of early AFI in the trajectories of SUD.

This study also reported an association of early AFI with any psychiatric disorder. This association was independent of substance use, sex, familial factors and overall measures of adolescent behavioural problems. Furthermore, as seen in the Aalen-Johansen curves (Fig. 2), participants who had reported AFI $\leq$ 12 years represented a separate trajectory compared to other AFI categories. This trajectory associated with early AFI was also observed among mood disorders. This suggests that these individuals, whose first intoxication is earliest, are most vulnerable to the development of such disorders.

Previous literature suggests that offspring of parents with SUDs are at an increased risk of engaging in substance use themselves (Hines et al., 2016; Latvala et al., 2020; McCutcheon et al., 2018), as are children of divorced parents (McCutcheon et al., 2018). Furthermore, research suggests that offspring with a history of parental psychiatric disorders are also at risk of future psychiatric disorders (McLaughlin et al., 2012; Holst et al., 2019). Use of substances other than alcohol, such as cannabis and tobacco, has also been associated with various mental health outcomes in previous systematic reviews and meta-analyses (Esmaeelzadeh, Moraros, Thorpe, & Bird, 2018; Gobbi et al., 2019; Gurillo et al., 2015; Marconi et al., 2016), as well as in this NFBC data (Mustonen et al., 2018a, 2018b, 2018c). Last, adolescent onset substance use may also present with concurrent emotional and behavioral problems (Hussong, Ennett, Cox, & Haroon, 2017). These factors could

Table 3
Association between the age of first alcohol intoxication and psychiatric outcome groups in the Northern Finland Birth Cohort 1986.

		Age of first alcohol intoxication											
		Reference		At age of 15 or 16			At age of 13 or 14			At age of 12 or earlier			
		Sample size	Cases (%)	Sample size	Cases (%)	HR	95% CI	Sample size	Cases (%)	HR	95% CI	Sample size	Cases (%)	HR	95% CI
Any psychiatric disorder	Crude	2059	18.2	1047	19.5	1.07	0.90–1.27	2748	21.9	1.23**	1.08–1.40	436	31.4	1.94**	1.60–2.36
	Model 1	1904	18.1	957	19.3	1.05	0.88–1.25	2522	21.6	1.13	0.98–1.30	393	32.1	1.64**	1.31–2.04
	Model 2	1720	17.8	849	19.2	1.03	0.85–1.25	2221	21.5	1.09	0.93–1.26	342	31.9	1.59**	1.26–2.02
	Model 3	1697	17.9	836	19.4	0.99	0.81–1.19	2188	21.3	0.98	0.84–1.14	337	32.0	1.40*	1.10–1.79
Any psychosis	Crude	1716	2.2	856	2.0	0.89	0.50–1.58	2181	2.1	0.93	0.61–1.44	311	4.5	2.09*	1.13–3.85
	Model 1	1587	2.1	783	1.9	0.83	0.45–1.53	2007	1.9	0.71	0.44–1.17	276	4.0	1.09	0.51–2.35
	Model 2	1442	2.3	695	1.9	0.78	0.41–1.50	1770	1.9	0.70	0.42–1.17	242	4.5	1.20	0.55–2.63
	Model 3	1421	2.3	683	1.9	0.72	0.37–1.37	1749	1.9	0.59	0.35–0.99	238	4.6	0.95	0.43–2.11
Substance use disorder	Crude	1687	0.7	846	0.9	1.43	0.58–3.57	2210	3.4	5.35**	2.84–10.08	318	6.6	10.53**	5.08–21.84
	Model 1	1559	0.5	775	0.9	1.62	0.59–4.48	2036	3.4	5.10**	2.41–10.78	282	6.0	6.69**	2.76–16.25
	Model 2	1414	0.5	689	1.0	1.97	0.69–5.62	1792	3.2	5.30**	2.38–11.82	247	6.5	6.49**	2.51–16.80
	Model 3	1393	0.4	677	1.0	2.13	0.71–6.35	1768	3.1	5.14**	2.17–12.17	243	6.6	6.18**	2.27–16.83
Mood disorder	Crude	1817	7.5	920	8.6	1.13	0.86–1.49	2323	8.0	1.07	0.86–1.33	349	14.6	2.05**	1.49–2.83
	Model 1	1680	7.4	846	8.9	1.16	0.87–1.54	2143	8.2	1.00	0.79–1.27	314	15.3	1.70**	1.18–2.45
	Model 2	1515	6.9	754	9.3	1.23	0.91–1.67	1889	8.1	0.99	0.76–1.28	274	15.3	1.81**	1.22–2.68
	Model 3	1494	6.9	742	9.4	1.16	0.85–1.57	1864	8.0	0.83	0.64–1.09	269	15.2	1.47	0.98–2.19
Anxiety disorder	Crude	1775	5.5	893	6.0	1.09	0.79–1.52	2301	7.0	1.28	0.995–1.64	324	8.0	1.52	0.98–2.34
	Model 1	1645	5.7	817	5.9	1.04	0.73–1.47	2116	6.8	1.20	0.91–1.57	292	8.9	1.55	0.98–2.46
	Model 2	1492	5.6	722	5.4	0.91	0.62–1.34	1864	6.7	1.08	0.81–1.45	254	8.7	1.39	0.84–2.30
	Model 3	1472	5.7	710	5.5	0.90	0.61–1.31	1841	6.6	1.02	0.76–1.37	250	8.8	1.32	0.79–2.20

Model 1: cannabis use, daily smoking, other illicit substance use; Model 2: cannabis use, daily smoking, other illicit substance use, sex, family structure, parental psychiatric disorder; Model 3: cannabis use, daily smoking, other illicit substance use, sex, family structure, parental psychiatric disorder, YSR Total. Statistical significance at < 0.05* and < 0.01** (Benjamini-Hochberg corrected).

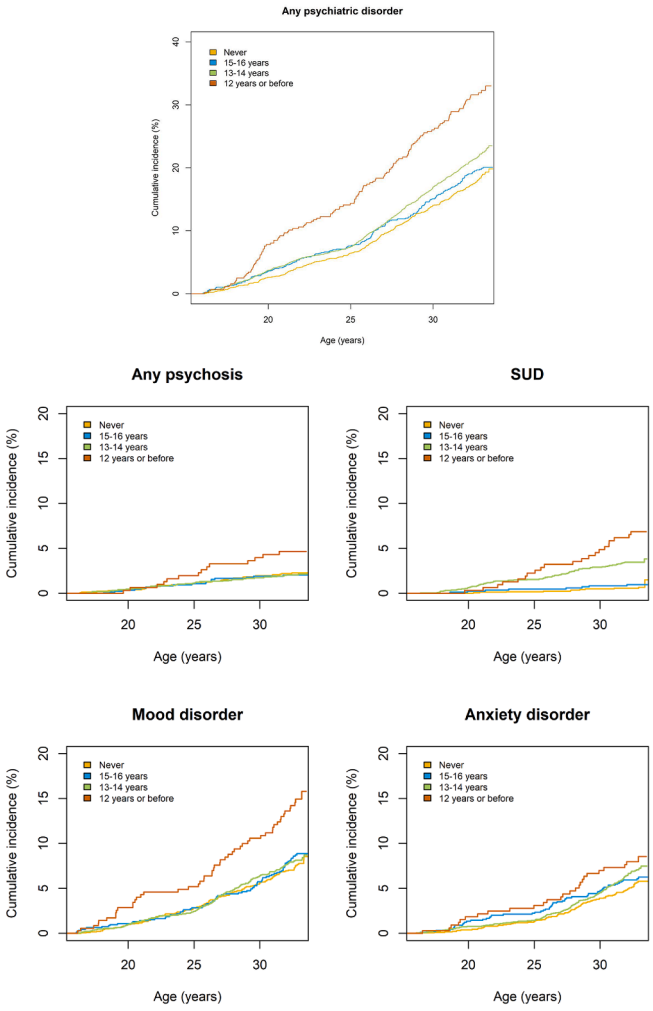

Fig. 2. The Aalen – Johansen curves for the association between AFI and psychiatric outcome categories.

plausibly confound the association between AFI and the psychiatric outcomes studied here.

In this study, cigarette smoking and the use of cannabis and other illicit substances was common especially among those with early AFI, as were elevated YSR total scores (see Table 1), suggesting that individuals with early AFI may be more likely to have emotional and behavioral problems and use multiple substances. In addition, subjects with earlier AFI were more likely to live in families, where the two parents did not live with the study participant or had a history of psychiatric disorders. One could speculate that these adolescents might apply maladaptive coping strategies (e.g. getting drunk to deal with environmental stressors), which in turn could influence trajectories of mental health disorders.

In general, associations between AFI and psychiatric disorders diminished after adjusting for these confounding factors. Although the association between AFI and mood disorders was not independent, participants with early AFI represented a separate trajectory in terms of survival. In fact, the association between AFI with mood disorders was attenuated to non-significance after adjusting for YSR total scores. These findings suggest that there may be a group of individuals with early psychopathology, early onset of substance use and other early life course risk factors that contribute to the onset of mood disorders. Early AFI could be a marker of this development.

However, this study reported statistically significant associations

between AFI ≤ 12 or 13–14 years with SUD on one hand, and between AFI ≤ 12 and any psychiatric disorder on the other hand. Secondly, the association between AFI with SUD followed a trend of earlier AFI associating with a greater risk of a SUD. Together with previous research, our results indicate that early AFI might be one contributing factor in the trajectory of SUD. Furthermore, we introduce novel findings of these links with other psychiatric disorders. Thus, postponing adolescent alcohol intoxication might have beneficial effects on the long-term health of the population.

4.1. Strengths and limitations

The strengths of this study include the size and characteristics of the study sample: the NFBC 1986 is one of the largest birth cohort studies with high genetic and ethnic homogeneity. Secondly, the considerable number of adolescents with data on AFI allows a robust examination of the associations between potentially contributing factors, and adjustment for a range of potentially confounding factors. Furthermore, the E – values suggested that our results concerning SUD were relatively robust to unmeasured confounding. Additionally, the linkage with several nationwide registers, combined with a very small proportion of deceased or emigrated cohort members (during the follow-up), provides high coverage of psychiatric diagnoses within this population during the 17-year follow-up and allows a study of several psychiatric outcomes. Finally, as our study is based on prospective general population-based birth cohort data, with a relatively large sample size, the results are reasonably generalizable to other populations of similar age.

Limitations also exist. Information on lifetime substance use was collected using self-reports at one time-point and we were not able to account for the differential follow-up. If differential follow-up could have been accounted for, the association between AFI with our outcomes might have been weaker. Furthermore, defining the age of first alcohol intoxication as the age of being "drunk" for the first time, versus the age of the first binge episode (≥5 standard drinks consumed) may reduce the predictive power of AFI regarding alcohol drinking outcomes (Morean, L'Insalata, Butler, McKee, & Krishnan-Sarin, 2018). Almost 75% of those in the SUD category were AUD. Thus, the association with AFI might reflect AUD trajectories, rather than other SUD trajectories. The use of a hierarchical outcome variable might lead to an underestimation of some outcomes, especially anxiety disorders, due to loss of cases. This might lead to an underestimation of the true associations. We used a family history of psychiatric disorders to account for possible environmental and genetic confounding due to parental psychiatric disorders. Broad familial outcomes cannot distinguish between environmental and genetic factors, and thus we were not able to study the specific effects of either set of factors as regards parental psychiatric disorders. The data on adolescent emotional and behavioral problems (YSR) reflect participant mental health at 15–16 years, but it is possible that some participants might have experienced symptoms earlier than this and before the onset of substance use, reflective of reverse causality. A previous NFBC study reported that childhood internalizing problems predicted adolescent alcohol use in females (Miettunen et al., 2014). Register data captures individuals who are seeking treatment or have other reasons so significant as to warrant diagnosis. Although unlikely, it is possible that rates of these disorder are similar across AFI groups, but those with early AFI are more likely to seek treatment. However, the study by Newton-Howes et al. (2019) yielded similar findings to ours using the Christchurch birth cohort, in which they conducted structured interviews for psychiatric disorders for participating individuals from the general population, i.e., who were not necessarily linked to treatment services. Last, we were not able to account for the possible influence of childhood or familial adversity.

Despite these limitations, the extensive dataset allowed us to examine the impact of early alcohol intoxication on subsequent psychiatric disorders and to assess the impact of a broad range of possible confounders on this relationship.

5. Conclusions

The first alcohol intoxication before or at age 14 was associated with subsequent substance use disorders, whereas the first alcohol intoxication before or at age 12 was associated with any psychiatric disorder. Based on our findings, we recommend that general and focused strategies to prevent alcohol intoxications should target adolescents as early as possible to reduce the likelihood of later substance use and other mental health disorders.

6. Role of the funding source

Funders of this study had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

7. Contribution

AM and SN developed conception and design of the work. AM performed literature search and provided summary. AM, SN, AEA performed data analysis and interpretation. AM and SN wrote the first manuscript draft. AM, SN, CS, JM, TH, AEA, LJ, JGS supervised conception and design of the work and provided critical revision of the article. All authors contributed approval of the final version of the manuscript.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.addbeh.2021.106910.

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