HHS Public Access

Author manuscript

Alcohol Clin Exp Res. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:

Alcohol Clin Exp Res. 2017 February ; 41(2): 359–368. doi:10.1111/acer.13293.

Comparison of parent, peer, psychiatric, and cannabis use influences across stages of offspring alcohol involvement: Evidence from the COGA Prospective Study

Kathleen K. Bucholz, Ph.D.[1], **Vivia V. McCutcheon, Ph.D.**[1], **Arpana Agrawal, Ph.D.**[1], **Danielle M. Dick, Ph.D.**[2], **Victor M. Hesselbrock, Ph.D.**[3], **John R. Kramer, Ph.D.**[4], **Samuel Kuperman, M.D.**[4], **John I. Nurnberger Jr., M.D., Ph.D.**[5], **Jessica E. Salvatore, Ph.D.**[2], **Marc A. Schuckit, M.D.**[6], **Laura J. Bierut, M.D.**[1], **Tatiana M. Foroud, Ph.D.**[5], **Grace Chan, Ph.D.**[3], **Michie Hesselbrock, Ph.D.**[3], **Jacquelyn L. Meyers, Ph.D.**[7], **Howard J. Edenberg, Ph.D.**[5], and **Bernice Porjesz, Ph.D.**[7]

[1]Washington University School of Medicine, St. Louis MO USA

[2]Virginia Commonwealth University, Richmond VA, USA

[3]University of Connecticut, Farmington CT USA

[4]University of Iowa Carver College of Medicine, Iowa City, IA USA

[5]Indiana University School of Medicine, Indianapolis IN USA

[6]University of California San Diego, San Diego CA USA

[7]SUNY Downstate Medical Center, Brooklyn NY USA

Abstract

Background—All stages of development of alcohol use disorder (AUD) have not been equally studied. While initiation of drinking has been given considerable attention, other stages have not

Correspondence should be addressed to: KK Bucholz, Ph.D., Department of Psychiatry, Washington University School of Medicine, 4560 Clayton Ave., Suite 1000, St. Louis MO 63110-1547, USA, Tel: 314-286-2284, Fax: 314-286-2213, bucholzkk@wustl.edu.

Declarations of conflicts of interest: AA has previously received peer-reviewed funds, travel and honorarium from ABMRF (ended 12/2012) which receives support from the brewing industry. LJB is listed as an inventor on Issued U.S. Patent 8,080,371, “Markers for Addiction” covering the use of certain SNPs in determining the diagnosis, prognosis and treatment of addiction. The other authors have no conflicts to report.

The Collaborative Study on the Genetics of Alcoholism (COGA), Principal Investigators B. Porjesz, V. Hesselbrock, H. Edenberg, L. Bierut, includes eleven different centers: University of Connecticut (V. Hesselbrock); Indiana University (H.J. Edenberg, J. Nurnberger Jr., T. Foroud); University of Iowa (S. Kuperman, J. Kramer); SUNY Downstate (B. Porjesz); Washington University in St. Louis (L. Bierut, J. Rice, K. Bucholz, A. Agrawal); University of California at San Diego (M. Schuckit); Rutgers University (J. Tischfield, A. Brooks); Department of Biomedical and Health Informatics, The Children's Hospital of Philadelphia; Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia PA (L. Almasy), Virginia Commonwealth University (D. Dick), Icahn School of Medicine at Mount Sinai (A. Goate), and Howard University (R. Taylor). Other COGA collaborators include: L. Bauer (University of Connecticut); J. McClintick, L. Wetherill, X. Xuei, Y. Liu, D. Lai, S. O'Connor, M. Plawecki, S. Lourens (Indiana University); G. Chan (University of Iowa; University of Connecticut); J. Meyers, D. Chorlian, C. Kamarajan, A. Pandey, J. Zhang (SUNY Downstate); J.-C. Wang, M. Kapoor, S. Bertelsen (Icahn School of Medicine at Mount Sinai); A. Anokhin, V. McCutcheon, S. Saccone (Washington University); J. Salvatore, F. Aliev, B. Cho (Virginia Commonwealth University); and Mark Kos (University of Texas Rio Grande Valley). A. Parsian and M. Reilly are the NIAAA Staff Collaborators.

We continue to be inspired by our memories of Henri Begleiter and Theodore Reich, founding PI and Co-PI of COGA, and also owe a debt of gratitude to other past organizers of COGA, including Ting-Kai Li, P. Michael Conneally, Raymond Crowe, and Wendy Reich, for their critical contributions. This national collaborative study is supported by NIH Grant U10AA008401 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA).

been as thoroughly investigated. It is not clear if the same factors are associated consistently across early and late transitions in AUD involvement. High risk family samples that are enriched for AUD vulnerability and transitions in AUD development offer an opportunity to examine influences across multiple stages of AUD development.

Methods—Data from adolescents and young adults from high risk families were used to study four transitions in AUD development –time to first drink, first drink to first problem, first drink to first diagnosis, and first problem to first diagnosis. Cox modeling was used to compare associations of parental AUD, parental separation, peer substance use, offspring ever-use of cannabis, trauma exposures and internalizing and externalizing psychopathology across transitions.

Results—Hazards of most transitions were elevated for those who had ever used cannabis, those who attributed substance use to their peers, those with externalizing disorders and those with parents with AUD. Many risk factors were linked to early initiation of alcohol, particularly cannabis use. Internalizing disorders were associated with later stages. Non-assaultive trauma was associated only with early initiation; assaultive trauma was not associated with any transition. .

Conclusions—In this large, ethnically-diverse sample of high risk youth, significant influences across transitions were fairly consistent, with externalizing disorders and cannabis ever-use elevating the likelihood of each stage, and peer and parental (and especially maternal AUD) influences linked to initiation and some later stages. Finally, in light of the increasingly permissive legal and social stances toward cannabis in the U.S., the marked elevations of all alcohol outcomes observed for cannabis use underscore the importance of studying the underpinnings of this relationship.

Introduction

Development of Alcohol Use Disorder (AUD), a highly heritable psychiatric disorder, may be decomposed into a series of transitions, beginning with initiation of drinking, progressing to acquisition of a first problem, and culminating in the clustering of specific problems that comprise the current AUD definition. Identifying factors that promote -- or inhibit -- each transition may provide targets for prevention and early intervention. However, understanding of the influences underlying stages of AUD development is limited. Initiation of drinking, and particularly of early drinking (e.g. Kuperman et al 2005; Trim 2010; Waldron 2014a,b), has received considerable attention, while other stages in AUD progression have been somewhat overlooked. Data from samples enriched for AUD vulnerability and thus for AUD transitions – that is, high risk family samples - offer an ideal opportunity to examine influences on the multiple stages of AUD development.

In one of the few studies to use family data to investigate several alcohol transitions, Lieb et al (2002) observed that paternal AUD elevated the likelihood of progression to regular use, to hazardous use, and to abuse and dependence, while maternal AUD increased the likelihood of the transition only to regular use. However, other offspring characteristics were not included in analyses, and the number of affected mothers was small. In a novel study by Olfson et al. (2014), high levels of peer drinking reduced the well-established protective effect of rs1229984, a missense variant in ADH1B, for progression to first intoxication and

to first AUD problem. However, only gender and ethnicity were included in models, which precluded evaluation of other offspring and family characteristics on AUD development. Sartor et al (2007), studying initiation of drinking and progression to alcohol dependence, found that the externalizing diagnosis of conduct disorder was the sole common risk factor for both transitions, while the internalizing disorder Generalized Anxiety Disorder was related to progression to alcohol dependence but not to initiation. Still, not all offspring had passed through the period of highest risk by the time of analysis, making it likely that not all cases of alcohol dependence had occurred. In studying the influence of parental divorce/ separation on 3 stages of alcohol involvement, Grant et al. (2015) included many covariates that were reported in supplemental tables but not discussed in the paper. Our examination of those tables revealed that conduct disorder was associated with a higher risk for all 3 transitions, while internalizing disorders were related to the transition to disorder but not to initiation or to an AUD problem. In summary, the findings across studies to date suggest that risk factors differ across stages of alcohol involvement, that parental AUD may promote transition to the later but not to the early stages, and that distinguishing paternal from maternal AUD influences is important. In short, these findings support stage-specific study of AUD development.

The present report expands upon the literature in several ways. We investigate four transitions in AUD development– time to initiation of drinking, time from initiation of drinking to first AUD problem, time from initiation of drinking to first AUD diagnosis, and time from first AUD problem to first AUD diagnosis. We include covariates that cover the major domains of influence implicated in the literature (but not always studied together), including family, peer, offspring psychopathology, ever-use of cannabis, and traumatic experiences. Of particular interest are the influences on various transitions of internalizing and externalizing disorders that are prominent in two models of AUD etiology- negative affect regulation (Sher 1991) and deviance proneness (Zucker, 1986). A main objective of these analyses is to characterize risk factors associated with each outcome, identifying those common and unique to each. A secondary objective is to provide detailed information about the data source that has not been fully described in the literature to date.

Materials and Methods

Sample

The data are from the Prospective Study of the Collaborative Study on the Genetics of Alcoholism (COGA). The COGA study, which began in 1989 to identify the vulnerability and protective genes for alcoholism, has been described elsewhere (Begleiter et al 1995; Reich et al 1998; Nurnberger et al 2004); only a brief overview is provided here. High risk families were ascertained through probands in inpatient or outpatient treatment for alcoholism at 7 sites across the United States, with all first degree relatives who were aged 7 or older interviewed with a comprehensive, highly reliable and valid assessment (Bucholz et al. 1994; Hesselbrock et al. 1999). In families with at least 2 affected first degree relatives of the proband, recruitment was extended to additional relatives with an expanded protocol that included neuropsychological and neurophysiological evaluations and collection of blood for

DNA. Comparison families, drawn from various sources (e.g., dental clinics, drivers' registries), were studied with the same protocol.

Beginning in late 2004, adolescent and young adult offspring in the COGA families who were born from 1982 onward (aged 12-22 at inception) and with at least one parent who had been interviewed in the original COGA study, were recruited into the Prospective Study. Every 2 years, participants are administered a comprehensive structured psychiatric diagnostic interview covering histories of alcohol, tobacco and illicit drug use, problems and disorders, as well as other psychiatric disorders, to obtain DSM-IV and DSM-5 (for substances) diagnoses. Questionnaires that focus on personality, impulsivity, drinking motives, response to ethanol, among others, are included. Subjects undergo neuropsychological and neurophysiological protocols that focus on resting state and cognitive function, including aspects of frontal lobe functioning. About 75% of the sample has been genotyped. Supplemental Table 1 contains the specific assessments included. All subjects provided written informed consent, and the study was approved by institutional review boards at each COGA site.

In targeting the age range that covers the period of highest risk for initiation and progression of drinking and associated problems, the Prospective Study has several advantages. Its inclusion of a wide range of birth cohorts, as opposed to a few or even a single cohort as in other designs (e.g. Golding et al., 2001; Poulton et al., 2015), permits the study of multiple developmental periods in a short time period. It is a high-risk sample, with many youth having at least one parent with AUD, and the parents and other adult generations are well characterized for substance use and other psychiatric disorders. The subjects are diverse, with over 25% of non-European American heritage. Lastly, longitudinal assessments cover not only self-reported behaviors but also neurophysiological, neuropsychological and genetic measures (although not used in this report). These attributes distinguish the Prospective Study from others and underscore its ability to characterize AUD development over time from a multi-faceted perspective.

The data analyzed here were collected from January 2005—June 2016; 3573 offspring from 2147 nuclear families in 901 extended pedigrees are included. Characteristics across 5 assessment waves are displayed in Table 1. For these analyses, information across all interviews was used, selecting data from the interview at which the behavior, problem, or disorder was first reported.

Offspring alcohol use transitions

Four transitions were defined: (1) time to first full drink, (2) time from first drink to first DSM-5 AUD problem, (3) time from first drink to first DSM-5 AUD diagnosis, and (4) time from first AUD problem to first DSM-5 AUD diagnosis. The age of occurrence for each transition was drawn from the interview at which the behavior or problem was first reported.

Risk factors—Selection of risk factors was guided by prior findings in the literature.

Parents' AUD status

Information from parent interview, family history reports (most obtained at prior COGA waves), and offspring questionnaires was used to classify parental AUD status, with interview data given the highest priority, and family history and offspring reports used only for uninterviewed parents. Interviewed parents were coded as affected or unaffected based on whether they met lifetime criteria for DSM-5 AUD at interview. For uninterviewed parents, those with 2 or more family history reports (obtained from all subjects across all COGA assessment waves) of DSM-IV lifetime alcohol dependence ("FHAM", Rice et al 1995) were added as affected. For the remainder, a "possible-AUD" category was created based on 1 positive FHAM or on the most recent offspring report of the parent as a heavy drinker or recovering alcoholic from the Important People and Activities (IPA) questionnaire (Clifford et al, 1992). Uninterviewed parents with negative FHAM or IPA reports were coded as unaffected. All others were coded as missing. Ninety percent of offspring had mothers coded unaffected (56.9%) or affected (33.2%) based on interview (33.0%) or by 2+ FHAM reports (0.2%) . About 2% were possible-AUD, 6.5% were unaffected based on negative FHAM/IPA and 1.6% were missing. Comparable proportions for fathers were unaffected (26.3%) or affected (39.1%) from interview (34.5%) or 2+ FHAM (4.6%), 7.5% possible-AUD, 19.5% unaffected from negative FHAM/IPA, and 7.5% missing. Cross classification of mother's and father's statuses led to 6 dummy variables for analysis: both AUD; fathers AUD mothers not/missing; mother AUD, fathers not/missing; one parent AUD-possible, co-parent unaffected; one unaffected, co-parent missing; with both unaffected as the referent group. Distributions of these variables are presented in Table 1 and Supplemental Table 2.

Other risk factors—*Parental separation* was based on offspring report of not living with both biological parents for the majority of time from 12-17. Principal component analyses (results available on request) supported combined measures for *Internalizing conditions* (any DSM-IV lifetime diagnosis of major depressive disorder, panic disorder, social phobia, or any report of suicidal ideation), *externalizing disorders* (conduct disorder and oppositional defiant disorder), and 2 dichotomous variables of offspring trauma exposures. These latter were distinguished by whether the trauma was assaultive or nonassaultive in nature. *Assaultive traumas* included being raped or sexually assaulted, stabbed, shot, mugged, wounded in combat, threatened with a weapon, or robbed, kidnapped or held captive), while *nonassaultive traumas* included being in a fire, flood, earthquake or other natural disaster, serious accident, witnessing someone being seriously injured or killed, or discovering a dead body. Questions specific to childhood physical abuse and childhood sexual abuse were not asked at only 4 out of 6 sites due to IRB restrictions and thus not included in analyses; childhood neglect was not assessed. *Substance use:* Offspring report of ever use of cannabis was included in the model. *Perceived substance use of peers* was based on respondent report at first interview (for those 18 and older) or at the interview obtained closest to age 17 (for those under 18 at baseline) that "most" or "all" peers (best friends, romantic partners and schoolmates) from ages 12-17 used any substance (tobacco, alcohol, cannabis or other drugs). High correlations (r's > 0.8) precluded substance-specific estimates.

Other covariates

Other characteristics included in all models were: offspring sex, birth cohort (4 cohorts born 1982-86 (referent), 1987-89, 1990-93, 1994+), race/ethnicity (coded as white (referent)/ black/other), case family status (i.e., ascertained through a proband in treatment) and overall household income in the family of origin based on mother's report at her interview (if no mother's report, father's report was used), classified into low (less than $29,999), middle ($30,000-74,999- referent) or high (≥ $75,000) categories.

Statistical analysis

All modeling was conducted in Stata, version 14.0 (Stata Corp, 2015). Cox proportional hazards multivariate regression was used, including time-varying covariates to account for the temporal ordering of events preceding each of the transition outcomes – first drink, first drink to first AUD problem, first drink to first AUD diagnosis, and first AUD problem to first AUD diagnosis. Variables for which age of onset was obtained were coded as time-varying; that is, they were counted as "risk factors" only if they occurred either prior to or at the same age as the outcome. For example, if age at onset of cannabis use preceded/occurred at the same time as the age of onset of first drink, it was coded as an event, but if it occurred after the age of first drink, it would not contribute toward the risk of transitioning to using alcohol. Variables modeled in this way included ever-use of cannabis, internalizing conditions, externalizing disorders, and assaultive and nonassaultive traumas. Maternal and paternal AUD statuses were lifetime measures and were time-invariant; parental separation and perceived peer substance use were also time-invariant as only an age range (12-17), and not a specific onset age, were obtained. To assess whether there were differential associations based on gender, interactions between each risk factor and gender were studied; those that met significance after adjusting for multiple comparisons were retained.

For the transition from no alcohol use to first full drink, participants entered the analysis at birth and "failed" at the age of their first drink, or were censored otherwise. For models of the timing of advanced transitions, individuals were included from the time of their first drink to the occurrences of the transition. To adjust for variability in risk period from age at first drink to other transitions, variables representing age at first drink (12 and younger, 13, 14, 15, 17, 18 and 19 and older; 16 was the median age and was used as the referent category) were included as covariates. Age categories were combined when their associations were not statistically different. (see Supplemental Tables 3-6). Risk factors and covariates were entered into the models simultaneously, and the same variables were included in all models. Violations of the proportional hazards assumption, that the hazard associated with a risk factor remains proportional over time, were investigated using Schoenfeld residuals as assessed by the Grambsch & Therneau test (Grambsch & Therneau, 1994). Identified violations were resolved by modeling age interactions with the pertinent variable. Age risk periods were chosen based on developmental cutoffs (e.g., menarche, entering middle or high school) and on examination of graphical representations of the data to observe failure rates to see where hazards diverged. Once violations were resolved, post hoc tests were conducted to ensure that the hazard ratios could not be equated across risk periods to provide additional confidence that the defined risk periods were distinct. Survival ties were handled by the Efron approximation (Efron, 1977). All analyses were adjusted for

familial clustering via the Huber-White robust standard errors as implemented in Stata (StataCorp, 2015).

Results

Description across assessment waves

In Table 1, characteristics of the sample at each assessment wave are displayed. (In Supplemental Table 2, data are presented by age at assessment.) Of those eligible for the 8 year follow-up, 73% were interviewed. Female participants comprised a somewhat greater proportion at each successive wave. As expected, use of alcohol, tobacco and cannabis increased across the waves as the sample became older. Ever use of cannabis was more prevalent than ever use of cigarettes, consistent with the latest data from the Monitoring the Future study (Johnston et al, 2016). Overall, the data revealed maintenance of the high risk nature of the sample over time.

Cox model for time to first drink

Results are displayed in Table 2. About 81% of the sample had ever had a drink, and the mean age of first drink was 15.7 years (SD=2.56). Parental AUD, whether defined by 1- or 2-affected parents, significantly increased the hazard of initiating alcohol use by 16-22% over that for no affected parents, and this effect did not vary by risk period. In contrast, for several risk factors, violations of the proportional hazards assumption were observed, requiring interactions that modeled differential hazard coefficients across age periods. Two were associated with significant increases in the hazards of initiating alcohol use before age 13; ever-use of cannabis was associated with an 852% increase, and parental separation was associated with an 84% increase. Ever-use of cannabis increased the hazard of initiation at other age periods as well. Nonassaultive trauma, externalizing disorders and perceived peer substance use significantly increased the hazards of alcohol initiation before age 16 by 15%, 53% and 145% respectively. Perceived peer substance use also increased the hazard by 60% from age 16-18, but not thereafter.

Time from first drink to first AUD problem

Sixty-five percent of ever-drinkers had an alcohol problem, which occurred at a mean age of 17.5 (sd 2.56), with an average of 2.4 years elapsing from first drink to first problem. Maternal AUD, regardless of paternal AUD status, increased the hazard of transitioning from alcohol use to an AUD problem by 27%, but paternal AUD in the absence of maternal AUD did not. (Table 3). A violation of the proportional hazards assumption was observed, where the likelihood of transitioning to having an alcohol problem in the first year after starting to drink was increased by 39% among those with externalizing disorders, but not thereafter. Ever-use of cannabis, internalizing disorders in females only, and peer substance use were associated with 111%, 40% and 56% (respectively) increased hazards of transitioning to an alcohol problem, and these did not vary across the risk period. Those who experienced parental separation were significantly less likely to transition to having an alcohol problem. Neither nonassaultive nor assaultive trauma was significantly related to the transition to having an alcohol problem.

Time from first drink to first AUD diagnosis

About one-third of ever drinkers met criteria for DSM-5 AUD, with an average of 3.3 years between starting to drink and meeting criteria for AUD diagnosis. Offspring with a mother with AUD, whether as the only affected parent or with an affected partner, had from 25-28% significantly increased hazards of transitioning from first drink to an AUD diagnosis. (Table 4) Having just a father with AUD did not significantly increase the hazard of transitioning to AUD, although post hoc testing revealed that the estimates across the parental AUD variations were not significantly different. Increased hazards were observed for ever-use of cannabis, internalizing conditions, externalizing disorders and peer substance use, with increases ranging from 36% (peer use) to 152% (ever-use of cannabis). Neither assaultive nor nonassaultive trauma significantly increased the hazards of transitioning from first drink to AUD.

Time from first AUD problem to first AUD diagnosis

On average, 1.2 years elapsed from the occurrence of the first AUD problem to first AUD diagnosis. As displayed in Table 5, externalizing disorders, ever-use of cannabis and internalizing disorders (but only 3 or more years after first drink) were significantly associated with increased hazards of transitioning from first AUD problem to first AUD diagnosis; the hazards of transitioning were not significantly elevated for the other risk factors.

Discussion

A main objective of the present report was to examine risk factors across distinct transitions in the development of AUD in order to identify those that were common and those that were specific to particular transitions, and to discuss these in light of particular domains of risk influence. In general, we observed considerable consistency of significant influences across transitions, with hazards of all 4 transitions elevated for offspring ever use of cannabis and externalizing disorders, and hazards for 3 transitions elevated for parental AUD, perceived peer substance use and internalizing disorders. Influences related to timing of transitions were especially apparent for initiation of alcohol use, where many were linked to very early use, before age 13, and further, before age 15. For later transitions to AUD problems and to AUD, parental AUD (and especially maternal AUD with or without paternal AUD), cannabis use, internalizing and externalizing disorders, and perceived substance use of peers were associated with increased hazards of transitioning that were for the most part constant. Several findings deserve further comment.

We observed significant associations of parental AUD with all but one transition, with increased hazards ranging from about 16-28%, broadly in line with other estimates reported in the literature (e.g. Grant et al, 2015; Trim et al, 2010; Sartor et al 2007; King & Chassin, 2007). In addition, our analyses extended the literature by estimation of separate effects for AUD in mothers-only, in fathers-only, and in both parents, distinctions made possible by the ample number of offspring from COGA families in which only mothers were affected. Other high risk family studies of AUD have been selected primarily on the basis of affected fathers (e.g., Wong et al, 1999; Jacob et al 2004; Calvert et al 2010), with maternal AUD not

excluded but also not serving as a selection criterion. In the few studies based exclusively on affected mothers (e.g. Hill et al 2011; Bidaut-Russell et al 1994) or on either affected mothers or fathers (Chassin et al 1993; Lieb et al 2002), evidence suggested relationships of maternal AUD with offspring AUD involvement, but often was not definitive owing to small numbers of affected mothers. Our data provided evidence for influences of maternal-only (versus paternal-only) AUD across early and late AUD transitions, with estimated hazard ratios for maternal-only AUD that were similar in magnitude to those for 2 AUD parents. Our findings contrast with a report where maternal AUD influences were limited to initiation (Sartor et al., 2007). Potential explanations for our results are that maternal AUD may reflect a higher genetic loading, or may be linked to greater disruption in the offspring's rearing environment, thus contributing as both a genetic and an environmental risk factor, lines of inquiry that can be investigated in future analyses. We did not observe gender interactions with parental AUD, unlike others who have reported that mothers' AUD may be particularly influential for their daughters' substance involvement (Bohman et al 1983). We did not consider either severity or persistence of AUD, which might have altered our results, nor did we consider outcomes other than alcohol involvement, possibilities that merit examination in future analyses.

A second broad domain of influences found to consistently elevate the hazards for all transitions was externalizing behavior, including ever use of cannabis as well as a combined measure of Conduct and Oppositional Defiant Disorders. While externalizing behaviors increased the hazards of transitioning to initiation (particularly ever-use of cannabis for very early drinking) and to first AUD problem within a year of beginning to drink, the increase was also strong for transitions from ever use to disorder, and from first problem to first diagnosis, consistent with the deviance proneness model of AUD etiology. (Zucker 1986; Sher 1991, Iacono et al. 2008). Quite striking were the independent findings for ever-use of cannabis. As we required measures to be time-varying, cannabis use had to occur prior to or at the same age as the alcohol outcome. For alcohol initiation, this would imply very early initiation of cannabis use, and such early cannabis use has been consistently and strongly associated with drinking initiation (Trim et al. 2010) and with development of alcohol and other substance use disorders (Lynskey et al. 2003, Grant et al., 2010). This finding may not be surprising in light of the strong comorbidity between cannabis and alcohol use disorders (Stinson et al. 2005) and of the genetic overlap between both use of and dependence on the two drugs (Sartor et al. 2010). Early cannabis use may also facilitate use of and problems with alcohol via engagement in other developmentally precocious activities (e.g. early sexual debut) and via delinquent peer affiliations, although the latter did not explain the association observed here. While the present study design cannot disentangle causal and correlative influences, and also did not account for the role of heavier cannabis involvement like frequent or problem use, it underscores the importance of considering cannabis initiation as a potent risk factor for drinking trajectories, a concern that is amplified by the growing legalization of recreational cannabis use in the U. S. and steadily decreasing rates of youth disapproval of regular cannabis use. (Pacek et al., 2015; Wilkinson et al., 2016).

In contrast to the ubiquitous associations observed for externalizing disorders, internalizing conditions were associated only with later transitions, similar to other reports. (Sartor et al, 2007; Edwards et al 2014a). We did not observe a significant association with alcohol

initiation, similar to some (Sartor et al, 2007; Trim et al 2010; Edwards et al 2014 b) but not all (King et al 2004) reports. Our findings are particularly credible because our data are not susceptible to limitations present in other studies, such as inclusion of participants only through the age of 14, thus likely missing the large group who initiate alcohol use in mid to late adolescence, use of a narrow definition of internalizing disorders that was limited to depression symptoms, not considering a time-varying measure of internalizing conditions, or too-small samples that might have been underpowered to detect significant associations. Further, our sample included a large proportion of offspring with parents and many other relatives with AUD who likely had high rates of externalizing and internalizing conditions that are commonly comorbid with AUD, and thus it is a sample enriched for vulnerability not only to AUD but also to its comorbid conditions.

We also found that internalizing disorders were associated with greater risk for AUD symptom onset in females, but not males. A recent study found that the association of heavy episodic drinking with depressive symptoms was stronger in females than in males between ages 14-17, but this association disappeared once cannabis and tobacco use were included. (Schuler et al 2015). In contrast, the sex difference remained in our study after adjustment for cannabis and other covariates, a robust association that may be due to the high risk nature of the sample and attendant comorbidities of AUDs and other psychiatric disorders (Nurnberger et al 2004). Further, our findings are consistent with investigations that have identified female-predominant subtypes of alcoholism characterized by negative affect (Del Boca and Hesselbrock, 1996), and stronger associations between negative affect and alcoholism for women than for men (Kessler et al 1997). Overall, our results emphasize the role of negative affect in later AUD transitions, drawing attention to youth (and especially females) that may have been neglected in evaluations of problem drinking because they are considered to be outside the externalizing risk domain.

We found a reduced likelihood for the hazard of an alcohol problem among offspring whose parents did not remain together, similar to a report by Grant et al (2015) in an offspring of twins study. There are several possible explanations for this result. Decreased economic circumstances associated with single parent households might reduce affordability of heavy drinking and thus quick progression to alcohol problems. Dissolution of the parental relationship, with the (likely) departure of the AUD parent, may improve the home environment of offspring, which may lower the likelihood of problem development. Also, offspring in non-intact families are more likely to begin drinking earlier, which is linked to a slower progression to alcohol problems due to limited opportunities for heavy drinking in such early initiators (e.g., Sartor et al, 2007; Jackson 2010). However, determining the likely explanations will await further analyses.

Our findings regarding trauma exposures were unexpected in light of a growing literature pointing to childhood assaultive traumas of sexual and physical abuse as risk factors for initiation of alcohol and other substances and for persistence and severity of disorder as well. (e.g. Elliott et al 2014; Sartor et al 2013; Schwandt et al, 2013; Werner et al 2016). We found that non-assaultive but not assaultive trauma was linked to early initiation, and neither trauma was significantly associated with the hazard of later progressions. However, due to

IRB restrictions, questions specific to childhood physical and sexual abuse were not asked at most sites, a limitation of the assaultive trauma measure that may account for the results.

The findings should be considered in light of seven caveats. First, the sample consists of offspring from high risk, densely AUD-affected families, and as such findings may not be generalizable to a less selected sample. Second, although all data across multiple waves of assessment were included in the analyses, some participants have not passed through the period of risk, and thus some individuals who may eventually develop AUD or an AUD problem are treated here as unaffected and censored at their last assessment. However, survival analyses appropriately account for these censored data. Third, the interview data do not provide details about timing and duration of offspring exposure to parental AUD in their rearing environment. Fourth, the severity of parental AUD and its persistence have not been taken into account in the analyses. It is not clear whether the effects observed for parental AUD would differ if severity, duration, and/or remission of parental AUD were considered. Fifth, our data reflect risk factors for transitions without consideration of potentially inhibitory/protective influences. Sixth, effects of maternal AUD may reflect in part in utero exposures which are not available for most offspring. Lastly, due to IRB restrictions, questions specific to childhood sexual and physical abuse were not collected across all sites and thus not included in analyses reported here, and there were no questions about childhood neglect. Thus, we are not able to add to the evidence accumulating in the literature on the importance of these factors in stages of alcohol and other drug involvement.

Despite these limitations, there are a number of strengths to our study. The sample is large, ethnically diverse, at very high risk as indicated by a majority whose parents and other relatives are affected with AUD, and in the peak age range for AUD transitions. The detailed phenotypic information permits characterization of offspring on a variety of attributes that promote transitions, and the definition of these as time-varying strengthens the inferences drawn from the hazard ratios as antecedent and not simply correlated influences. We have examined four stages in the development of AUD with the same covariates included in each model, permitting comparison of associations across early and late stages of AUD development. Overall, our findings indicate that externalizing influences were observed at all stages of AUD development, while internalizing characteristics were associated with later stages and were more potent for females with respect to problem acquisition. Findings also highlight the influence of maternal AUD in the progression of alcohol involvement, motivating further work into what may underlie such associations. Lastly, in light of the increasingly permissive legal status of and attitudes toward cannabis in the U.S., the elevations of all alcohol outcomes associated with cannabis use support prioritization of studying the underpinnings of this relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The support of NIH grants U10AA08401; DA032573 and AA021235 (AA); K02AA018755(DMD); F32 AA022269(JES); K01DA037914 (JLM); K01AA02415 (JES) is gratefully acknowledged.

Citations

Begleiter H, Reich T, Hesselbrock VM, Porjesz B, Li T-K, Schuckit MA, Edenberg HJ, Rice JP. The Collaborative Study on the Genetics of Alcoholism. Alc Health Res World. 1995; 19:228–236.

Bidaut-Russell M, Bradford SE, Smith EM. Prevalence of mental illnesses in adult offspring of alcoholic mothers. Drug Alc Depend. 1994; 35:81–90.

Bohman M, Sigvardsson S, Cloninger CR. Maternal inheritance of alcohol abuse: Cross fostering analysis of adopted women. Arch Gen Psych. 1981; 38:965–969.

Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI, Reich T, Schmidt I, Schuckit MA. A new, semi-structured psychiatric interview for use in genetic linkage studies: A report of the reliability of the SSAGA. J Stud Alcohol. 1994; 55:149–158. [PubMed: 8189735]

Calvert WA, Bucholz KK, Steger-May K. Early drinking and its association with adolescents' participation in risky behaviors. J Am Psychiatric Nurses Assn. 2010; 16:239–251.

Chassin L, Pillow DR, Curran PJ, Molina BSG, Barrera M. Relation of parental alcoholism to early adolescent substance use: A test of three mediating mechanisms. J Abnorm Psychol. 1993; 102:3–19. [PubMed: 8436697]

Clifford PR, Longabaugh R, Beattie M. Social support and patient drinking: a validation study. Alcohol Clin Exp Res. 1992; 116:403.

DelBoca FK, Hesselbrock M. Gender and alcoholic subtypes. Alcohol Health & Research World. 1996; 20:56–62.

Edwards AC, Joinson C, Dick DM, Kendler KS, Macleod J, Munafo M, Hickman M, Lewis G, Heron J. The association between depressive symptoms from early to late adolescence and later use and harmful use of alcohol. Eur Child Adolesc Psychiatry. 2014a; 23:1219–1230. [PubMed: 25130265]

Edwards AC, Latendresse SJ, Heron J, Cho SB, Hickman M, Lewis G, Dick DM, Kendler KS. Childhood internalizing symptoms are negatively associated with early adolescent alcohol use. Alcohol Clin Exp Research. 2014b; 38:1680–88.

Efron B. The efficiency of Cox's likelihood function for censored data. J Am Stat Assoc. 1977; 72:557–565.

Elliott JC, Stohl M, Wall MM, Keyes KM, Goodwin RD, Skodol AE, Krueger RF, Grant BF, Hasin DS. The risk for persistent adult alcohol and nicotine dependence: the role of childhood maltreatment. Addiction. 2014; 109:842–850. [PubMed: 24401044]

Golding J, Pembrey M, Jones R, et al. ALSPAC- the Avon Longitudinal Study of Parents and Children: I. Study methodology. Paediat Perinatal Epid. 2001; 15:74–87.

Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994; 81:515–526.

Grant JD, Waldron M, Sartor CE, Scherrer JF, Duncan AE, McCutcheon VV, Haber JR, Jacob T, Heath AC, Bucholz KK. Parental separation and offspring alcohol involvement: Findings from offspring of alcoholic and drug dependent twin fathers. Alcohol Clin Exp Res. 2015; 39:1166–73. 2015. [PubMed: 26058573]

Grant JD, Lynskey MT, Scherrer JF, Agrawal A, Heath AC, Bucholz KK. A cotwin-control analysis of drug use and abuse/dependence risk associated with early-onset cannabis use. Addictive behav. 2010; 35:35–41.

Hesselbrock M, Easton C, Bucholz KK, Schuckit MA, Hesselbrock VM. A validity study of the SSAGA- a comparison with the SCAN. Addiction. 1999; 94:1361–1370. [PubMed: 10615721]

Hill SY, Tessner KD, McDermott MD. Psychopathology in offspring from families of alcohol dependent female probands: A prospective study. J Psychiatr Res. 2011; 45:285–94. [PubMed: 20801463]

Iacono WG, Malone SM, McGue M. Behavioral disinhibition and the development of early-onset addiction: common and specific influences. Annu Rev Clin Psychol. 2008; 4:325–48. [PubMed: 18370620]

Jackson KM. Progression through early drinking milestones in an adolescent treatment sample. Addiction. 2010; 105:438–449. [PubMed: 20402987]

Jacob T, Waterman B, Heath A, True W, Bucholz KK, Haber R, Scherrer J, Fu Q. Genetic and environmental effects on offspring alcoholism: New insights using an Offspring-of-twins design. Arch Gen Psychiatr. 2003; 60:1265–72. [PubMed: 14662559]

Johnston, LD., O'Malley, PM., Miech, RA., Bachman, JG., Schulenberg, JE. Monitoring the Future national survey results on drug use, 1975-2015: Overview, key findings on adolescent drug use. Institute for Social Research, the University of Michigan; Ann Arbor: 2016. p. 58-62.

Kessler RC, Crum RM, Warner LA, Nelson CB. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry. 1997; 54:313–321. [PubMed: 9107147]

King SM, Iacono WG, McGue M. Childhood externalizing and internalizing psychopathology in the prediction of early substance use. Addiction. 2004; 99:1548–59. [PubMed: 15585046]

King KM, Chassin L. A prospective study of the effects of age of initiation of alcohol and drug use on young adult substance dependence. J Stud Alc Drugs. 2007; 68:256–65.

Kuperman S, Chan G, Kramer JR, Bierut L, Bucholz KK, Fox L, Hesselbrock V, Nurnberger JI, Reich T, Reich W, Schuckit MA. Relationship of age of first drink to child behavioral problems and family psychopathology. Alcohol Clin Exp Res. 2005; 10:1869–76.

Lieb R, Merikangas KR, Hofler M, Pfister H, Isensee B, Wittchen H-U. Parental alcohol use disorders and alcohol use and disorders in offspring: a community study. Psychol Med. 2002; 32:63–78. [PubMed: 11883731]

Lynskey M, Heath AC, Bucholz KK, Slutske WS, Madden PAF, Nelson EC, Statham DJ, Martin NG. Escalation of drug use in early-onset cannabis users versus co-twin controls. JAMA. 2003; 289:427–433. [PubMed: 12533121]

Nurnberger JI, Wiegand R, Bucholz K, O'Connor S, Meyer ET, Reich T, Rice J, Schuckit M, King L, Petti T, Bierut L, Hinrichs AL, Kuperman S, Hesselbrock V, Porjesz B. A family study of Alcohol Dependence: Coaggregation of multiple disorders in relatives of alcohol-dependent probands. Arch Gen Psychiat. 2004; 61:1246–1256. [PubMed: 15583116]

Olfson E, Edenberg HJ, Nurnberger J, Agrawal A, Bucholz KK, Almasy LA, Chorlian D, Dick DM, Hesselbrock VM, Kramer JR, Kuperman S, Porjesz B, Schuckit MA, Tischfield JA, Wang J-C, Wetherill L, Foroud TM, Rice J, Goate A, Bierut LJ. An *ADH1B* variant and peer drinking in progression to adolescent drinking milestones: Evidence of a Gene-by-Environment Interaction. Alcohol Clin Exp Res. 2014; 38:2541–2549. [PubMed: 25257461]

Pacek LR, Mauro PM, Martins SS. Perceived risk of regular cannabis use in the United States from 2002 to 2012: Differences by sex, age and race/ethnicity. Drug Alc Depend. 2015; 149:232–44.

Poulton R, Moffitt TE, Silva PA. The Dunedin Multidisciplinary Health and Development Study: Overview of the first 40 years, with an eye to the future. Soc Psychiat Psychiat Epidemiol. 2015; 50:679–693.

Reich T, Edenberg HJ, Goate A, Williams JT, Rice JP, Van Eerdewegh P, Foroud T, Hesselbrock V, Schuckit M, Bucholz K, Porjesz B, Li T-K, Conneally M, Nurnberger J, Tischfield J, Crowe R, Cloninger CR, Wu W, Shears S, Carr K, Crose C, Willig C, Begleiter H. Genome-wide search for genes affecting the risk of alcohol dependence. Am J Med Genet. 1998; 81:207–215. [PubMed: 9603606]

Rice JP, Reich T, Bucholz KK, Neuman RJ, Fishman R, Rochberg N, Hesselbrock VM, Nurnberger JI Jr. Schuckit MA, Begleiter H. Comparison of direct interview and family history diagnoses of alcohol dependence. Alcohol Clin Exp Res. 1995; 19:1018–1023. [PubMed: 7485811]

Sartor CE, Lynskey MT, Heath AC, Jacob T, True W. The role of childhood risk factors in initiation of alcohol use and progression to alcohol dependence. Addiction. 2007; 102:216–25. [PubMed: 17222275]

Sartor CE, Grant JD, Bucholz KK, Madden PAF, Heath AC, Agrawal A, Whitfield JB, Statham CJ, Martin NG, Lynskey MT. Common genetic contributions to alcohol and cannabis use and dependence symptomatology. Alcohol Clin Exp Res. 2010; 34:545–54. [PubMed: 20028363]

Sartor CE, Waldron M, Duncan AE, Grant JD, McCutcheon VV, Nelson EC, Madden PAF, Bucholz KK, Heath AC. Childhood sexual abuse and early substance use in adolescent girls: the role of familial influences. Addiction. 2013; 108:993–1000. [PubMed: 23316725]

Schuler MS, Vasilenko SA, Lanza ST. Age-varying associations between substance use behaviors and depressive symptoms during adolescence and young adulthood. Drug Alc Depend. 2015; 157:75–82.

Schwandt ML, Heilig M, Hommer DW, George DT, Ramchandani VA. Childhood trauma exposure and alcohol dependence severity in adulthood: mediation by emotional abuse severity and neuroticism. Alcohol Clin Exp Res. 2013; 36:984–992.

Sher, KJ. Children of alcoholics. University of Chicago Press; Chicago: 1991.

Stinson FS, Grant BF, Dawson DA, Ruan WJ, Huang B, Saha T. Comorbidity between DSM-IV alcohol and specific drug use disorders in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Drug Alc Depend. 2005; 80:105–116.

StataCorp. Stata: Release 14. Statistcial Software. StataCorp LP; College Station TX: 2015.

Trim RS, Schuckit MA, Smith TL. Predicting drinking onset with discrete-time survival analysis in offspring from the San Diego prospective study. Drug Alc Depend. 2010; 107:215–20.

Waldron M, Vaughan EL, Bucholz KK, Lynskey MT, Sartor CE, Duncan AE, Madden PAF, Heath AC. Risks for early substgnace involvement associated with parental alcholism ande parental separation in an adolescent female cohort. Drug Alc Depend. 2014a; 138:130–6.

Waldron M, Grant JD, Bucholz KK, Lynskey MT, Slutske WS, Glowinski AL, Henders A, Statham DJ, Martin NG, Heath AC. Parental separation and early substance involvement: Results from children of alcholic and cannabis dependent twins. Drug Alc Depend. 2014b; 134:78–84.

Werner KB, McCutcheon VV, Agrawal A, Sartor CE, Nelson ECA, Heath AC, Bucholz KK. The association of specific traumatic experiences with cannabis initiation and transition to problem use: Differences bewteen African-American and European-American women. Drug Alc Depend. 2016; 162:162–169.

Wilkinson ST, Yarnell S, Radhakrishnan R, Ball SA, D'Souza DC. Marijuana legalization: Impact on physicians and public health. Annu Rev Med. 2016; 67:453–66. [PubMed: 26515984]

Wong MM, Zucker RA, Puttler LI, Fitzgerald HE. Heterogeneity of risk aggregation for alcohol problems between early and middle childhood: Nesting structure variations. Dev Psychopath. 1999; 11:727–744.

Zucker RA. The four alcoholisms: A developmental account of the etiologic process. Nebr. Symp Motiv. 1986; 34:27–83. [PubMed: 3498124]

Table 1

Cross Sectional Characteristics of the Sample at each assessment wave. All numbers reflect percentages unless otherwise noted

	Baseline (n=3573)	2-yr (n=3030)	4-yr (n=2465)	6-yr (n=1901)	8-yr (n=1197)
Mean age (std dev)	16.05 (3.29)	18.39 (3.54)	20.62(3.58)	22.65 (3.48)	24.67 (3.29)
12-17 years	63.67	44.79	25.19	3.05	-
18 and older	36.33	55.21	74.81	96.95	100.00
Birth cohort					
Born 1982-86	23.68	23.33	24.54	25.36	28.65
Born 1987-89	22.19	22.97	23.69	25.46	26.65
Born 1990-93	26.84	29.04	31.24	33.19	34.84
Born 1994+	27.29	24.65	20.53	15.99	9.86
Gender: % female	51.00	52.81	52.98	54.97	56.81
Family type					
Case	86.51	86.20	85.64	85.53	84.21
Comparison	13.49	13.80	14.36	14.47	15.79
Race					
White	64.06	64.22	65.64	65.97	70.09
Black	27.40	27.66	27.59	27.04	25.90
Other	8.54	8.12	6.77	7.00	4.01
Parent AUD Status (a)					
Both AUD	18.71	19.12	19.11	18.67	18.71
Mom AUD, Dad unaffected	15.77	15.58	15.66	15.31	14.12
Dad AUD, mom unaffected	24.00	24.30	24.83	25.36	24.39
Neither AUD	32.60	33.67	33.67	34.14	37.01
Mom or Dad Unaffected, co-parent status AUD-possible	4.23	4.39	4.26	4.37	3.84
Mom or Dad unaffected, co-parent status unknown	4.70	2.94	2.47	2.16	1.92
Substance use					
Ever had full drink	47.08	64.21	78.90	89.58	94.49
Any AUD problem	22.00	32.57	41.01	45.92	49.21
DSM 5 AUD	9.18	13.76	16.88	19.25	20.38
Ever smoked full cigarette	26.78	34.92	41.74	45.74	48.04
Ever used cannabis	33.01	45.25	57.26	64.58	68.98
Other covariates					
Ever Internalizing (b)	21.59	24.26	26.72	29.81	33.53
Ever Externalizing (c)	8.70	9.31	8.92	9.42	8.44
Ever Assaultive trauma	18.84	21.29	20.69	23.85	25.17
Ever Non assaultive trauma	33.61	27.96	27.45	26.49	28.43
Peer substance use 12-17	53.60	66.34	70.75	68.39	63.83

	Baseline (n=3573)	2-yr (n=3030)	4-yr (n=2465)	6-yr (n=1901)	8-yr (n=1197)
Did not live with both parents from age 12-17	47.48	50.22	50.47	49.55	46.49
Household income (parent report)					
Low (≤ 29,999)	25.37	25.52	25.18	25.15	24.25
Middle (30,000-74,999)	54.86	54.56	54.44	54.68	54.77
High (≥ 75,000)	19.77	19.93	20.37	20.18	20.99

(a): Parent AUD status: coded **affected** if met AUD criteria by own interview report, or if no interview data, by 2 or more reports of AUD from family members. **Unaffected**: did not meet AUD criteria based on own interview report; if no interview data, did not have any family history reports of AUD or no report by any offspring of heavy or problem drinking. **Possible AUD**: defined only among those with no interview data who did not meet definition as affected but had a single family history report or was reported by offspring to be heavy, problem or recovering alcoholic.

(b) Internalizing- Lifetime history of MDD, Panic, Social Phobia, and Suicidal Ideation

(c) Externalizing – Lifetime history of Conduct disorder or Oppositional Defiant Disorder

Table 2

Hazard ratios (and 95% confidence intervals) from multivariate Cox proportional hazard models for time to first drink

Predictor (risk period [age])	Hazard ratio (95% CI)
Parental AUD	
Father AUD, mother unaffected	1.22 (1.10-1.37)
Mother AUD, father unaffected	1.16 (1.01-1.32)
Both parents affected	1.22 (1.07-1.39)
M or D unaffected, co-parent status AUD possible	1.02 (0.82-1.27)
M or D unaffected, co-parent status unknown	.99 (0.79-1.25)
Neither parent affected	1.00 (referent group)
Parental separation	
(≤12)	1.84 (1.37-2.46)
(≥13)	1.09 (0.99-1.20)
Cannabis use[a]	
(≤12)	9.52 (6.81-13.31)
(13-15)	3.92 (3.40-4.51)
(16-18)	2.81 (2.47-3.19)
(>=19)	1.91 (1.47-2.48)
Internalizing Disorders[a]	1.02 (.93-1.11)
Externalizing Disorders[a]	
(≤15)	1.53 (1.31-1.78)
(≥16)	1.03 (0.86-1.22)
Assaultive trauma[a]	0.97 (.88-1.07)
Non-assaultive trauma[a]	
≤ 15	1.15 (1.02-1.31)
≥ 16	.95 (.85-1.07)
Perceived substance use of peers	
(≤15)	2.45 (2.04-2.94)
(16-18)	1.60 (1.40-1.83)
(≥19)	1.07 (0.85-1.35)

Interactions between predictor variables and age were modeled to satisfy the proportional hazards assumption when the assumption was violated.

Other covariates included were: offspring birth cohort (1982-86 (referent), 1987-89, 1990-93, 1994 and later; Sex; African American v non African American background; Income (<$30,000, $30,000-<$75,000, >= $75,000); case (v comparison) family status

[a]defined as time-varying

Table 3

Hazard ratios (and 95% confidence intervals) from multivariate Cox proportional hazard models for time from first drink to first DSM-5 alcohol problem

Predictor (risk period [years since first drink])	Hazard ratio (95% CI)
Parental AUD	
Father AUD, mother unaffected	1.10(.97-1.25)
Mother AUD, father unaffected	1.27 (1.08-1.49)
Both parents AUD	1.24 (1.07-1.43)
Mother or father unaffected, co-parent status AUD possible	1.09 (0.84-1.42)
Mother or father unaffected, co-parent status unknown	0.72 (0.50-1.05)
Neither parent affected	1.00 (referent group)
Parental separation	.89 (.79-.99)
Cannabis use[a]	2.11 (1.88-2.36)
Internalizing disorders[a]	
Male	1.00 (.86-1.15)
Female	1.40 (1.21-1.62)
Externalizing disorders[a]	
≤ 1 year	1.39 (1.20-1.60)
≥ 2 years	1.11 (.93-1.34)
Assaultive trauma[a]	1.05 (.95-1.18)
Non-assaultive trauma[a]	1.06 (.96-1.17)
substance use of peers	1.56 (1.35-1.79)

Interactions between predictor variable and years since first drink were modeled to satisfy the proportional hazards assumption when the assumption was violated.

Other covariates included were: offspring birth cohort (1982-86 (referent), 1987-89, 1990-93, 1994 and later; Gender; African American v non African American background; Income (<$30,000, $30,000-<$75,000, >= $75,000); case (v comparison) family status; and indicator variables for age at first drink (12 and younger, 13,14,15,17,18, and 19 or older. 16 was the median age and used as the reference group).

[a]defined as time-varying

Table 4

Hazard ratios (and 95% confidence intervals) from multivariate Cox proportional hazard models for time from first drink to onset of DSM-5 AUD

Predictor (risk period [years since first drink])	Hazard ratio (95% CI)
Parental AUD	
Father AUD, mother unaffected	1.15(0.95-1.39)
Mother AUD, father unaffected	1.25 (1.01-1.55)
Both parents AUD	1.28 (1.04-1.57)
Mother or father unaffected, co-parent status AUD possible	1.44 (1.01-2.05)
Mother or father unaffected, co-parent status unknown	0.70 (0.38-1.32)
Neither parent affected	1.00 (referent group)
Parental Separation	0.86 (0.74-1.01)
Cannabis use[a]	2.52 (2.07-3.06)
Internalizing[a]	1.42(1.23-1.63)
Externalizing[a]	1.80 (1.55-2.10)
Assaultive trauma	1.12 (0.96-1.30)
Non-assaultive trauma[a]	1.14 (.99-1.32)
Perceived substance use of peers	1.36(1.08-1.70)

Interactions between predictor variable and years since first drink were modeled to satisfy the proportional hazards assumption when the assumption was violated.

Other covariates included were: offspring birth cohort (1982-86 (referent), 1987-89, 1990-93, 1994 and later; Gender; African American v non-African American background; Income (<$30,000, $30,000-<$75,000, >= $75,000); case (v comparison) family status; and indicator variables for age at first drink (12 and younger, 13,14,15,17,18, and 19 or older. 16 was the median age and used as the referent).

[a] defined as time-varying

Table 5

Hazard ratios (and 95% confidence intervals) from multivariate Cox proportional hazard models for time from first AUD problem to onset of DSM-5 AUD

Predictor (risk period [years since first drink])	Hazard ratio (95% CI)
Parental AUD	
Father AUD, mother unaffected	1.09 (0.84-1.40)
Mother AUD, father unaffected	1.23 (0.92-1.64)
Both parents AUD	1.23 (0.94-1.62)
Mother or father unaffected, co-parent status AUD possible	0.94 (0.55-1.62)
Mother or father unaffected, co-parent status unknown	0.80 (0.34-1.85)
Neither parent affected	1.00 (referent group)
Parental separation	0.85 (0.69-1.05)
Cannabis use[a]	1.42 (1.06-1.90)
Internalizing disorders[a]	
≤ 2 years	1.10 (.89-1.35)
≥ 3 years	1.85 (1.14-3.00)
Externalizing disorders[a]	1.77 (1.41-2.22)
Assaultive trauma[a]	1.11 (0.91-1.37)
Non-assaultive trauma[a]	1.02(0.83-1.25)
Perceived substance use of peers	1.11 (0.80-1.53)

Interactions between predictor variable and years since first drink were modeled to satisfy the proportional hazards assumption when the assumption was violated.

Other covariates included were: offspring birth cohort (1982-86 (referent), 1987-89, 1990-93, 1994 and later; Gender; African American v non African American background; Income (<$30,000, $30,000-<$75,000, >= $75,000); case (v comparison) family status; and indicator variables for age at first drink (12 and younger, 13,14,15,17,18, and 19 or older. 16 was the median age and used as the reference group).

[a]defined as time-varying