UC San Diego
UC San Diego Previously Published Works

Title

Associations of parental alcohol use disorders and parental separation with offspring initiation of alcohol, cigarette and cannabis use and sexual debut in high-risk families

Permalink

Journal

ISSN

Authors

McCutcheon, Vivia V
Agrawal, Arpana
Kuo, Sally I-Chun
et al.

Publication Date

DOI

Peer reviewed

Associations of parental alcohol use disorders and parental separation with offspring initiation of alcohol, cigarette and cannabis use and sexual debut in high-risk families

Vivia V. McCutcheon[1] (ID), Arpana Agrawal[1], Sally I-Chun Kuo[2], Jinni Su[2], Danielle M. Dick[2], Jacquelyn L. Meyers[3], Howard J. Edenberg[4], John I. Nurnberger[4], John R. Kramer[5], Samuel Kuperman[5], Marc A. Schuckit[6], Victor M. Hesselbrock[7], Andrew Brooks[8], Bernice Porjesz[3] & Kathleen K. Bucholz[1]

Washington University School of Medicine, Department of Psychiatry, St Louis, MO, USA,[1] Virginia Commonwealth University, Departments of Psychology, African-American Studies, & Human and Molecular Genetics, Richmond, VA, USA,[2] SUNY Downstate Medical Center, Department of Psychiatry, Brooklyn, NY, USA,[3] Indiana University School of Medicine, Departments of Biochemistry and Molecular Biology, Psychiatry, Indianapolis, IN, USA,[4] University of Iowa Carver College of Medicine, Department of Psychiatry, Iowa City, IA, USA,[5] University of California San Diego, Department of Psychiatry, San Diego, CA, USA,[6] University of Connecticut, Department of Psychiatry, Farmington, CT, USA[7] and Rutgers University, Department of Genetics, New Brunswick, NJ, USA[8]

ABSTRACT

Background and Aims   Parental alcohol use disorders (AUDs) and parental separation are associated with increased risk for early use of alcohol in offspring, but whether they increase risks for early use of other substances and for early sexual debut is under-studied. We focused on associations of parental AUDs and parental separation with substance initiation and sexual debut to (1) test the strength of the associations of parental AUDs and parental separation with time to initiation (age in years) of alcohol, tobacco and cannabis use and sexual debut and (2) compare the strength of association of parental AUD and parental separation with initiation. **Design**   Prospective adolescent and young adult cohort of a high-risk family study, the Collaborative Study on the Genetics of Alcoholism (COGA). **Setting**   Six sites in the United States. **Participants**   A total of 3257 offspring (aged 14–33 years) first assessed in 2004 and sought for interview approximately every 2 years thereafter; 1945 (59.7%) offspring had a parent with an AUD. **Measurements**   Diagnostic interview data on offspring substance use and sexual debut were based on first report of these experiences. Parental life-time AUD was based on their own self-report when parents were interviewed (1991–2005) for most parents, or on offspring and other family member reports for parents who were not interviewed. Parental separation was based on offspring reports of not living with both biological parents most of the time between ages 12 and 17 years. **Findings**   Parental AUDs were associated with increased hazards for all outcomes, with cumulative hazards ranging from 1.19 to 2.71. Parental separation was also an independent and consistent predictor of early substance use and sexual debut, with hazards ranging from 1.19 to 2.34. The strength of association of parental separation with substance initiation was equal to that of having two AUD-affected parents, and its association with sexual debut was stronger than the association of parental AUD in one or both parents. **Conclusions**   Parental alcohol use disorders (AUDs) and parental separation are independent and consistent predictors of increased risk for early alcohol, tobacco and cannabis use and sexual debut in offspring from families with a high risk of parental AUDs.

Keywords   Alcohol use disorders, cannabis, COGA, early substance use, familial, parent AUD, sexual debut, tobacco.

INTRODUCTION

Early initiation of substance use is associated with many negative outcomes, including increased risk for developing substance use disorders [1–6], lower educational attainment [7,8], early sexual debut and risky sexual behaviors [9–11]. Age at onset of alcohol, cigarette and cannabis use is influenced by genetic and familial environmental

factors [12,13], some of which are common across substances [3,14]. A recent twin study found that a common factor accounted for 15–43% of the genetic influences on age at initiation of alcohol, tobacco and cannabis, and also contributed 18–77% of the shared environmental variance in initiation of each substance, suggesting that the family environment plays a significant role in age at initiation of multiple substances [14]. Parental alcohol use disorders (AUDs) affect the family environment shared by offspring in multiple ways that increase the likelihood of early substance use. In households where one or both parents has an AUD, there is a greater incidence of parental separation [15,16], childhood trauma [15,17] and decreased parental monitoring of child behavior [18,19], factors which have also been associated with earlier ages at first drink [1,16,20], first cigarette, first use of cannabis [20] and earlier age at sexual debut [21]. Parental separation in particular is a potent factor related to early age at first substance use [20,22,23] and sexual debut [21] even after adjustment for parental AUDs. While parental AUDs are associated with earlier age at initiation of alcohol use [16,24–28], few studies examine whether they also increase risk for early use of other substances and other risky behaviors [29,30] or adjust for the strong effect of parental separation on early initiation [20–23]. In the current study, we focus on associations of parental AUDs and parental separation with substance initiation and sexual debut to (1) test the strength and independence of the associations of parental AUDs and parental separation with time to initiation of alcohol, tobacco and cannabis use and sexual debut, and (2) compare the strength of association of parental AUD and parental separation with initiation.

METHODS

Design

The outcomes were time, in years since birth, to initiation of alcohol, tobacco and cannabis use and to sexual debut. The joint associations of parental AUDs and parental separation with each of the outcomes were first tested to determine their independence and strength, then compared to determine their relative strength for each outcome.

Sample

Data were from participants in the ongoing prospective cohort of the Collaborative Study of the Genetics of Alcoholism (COGA), a multi-site family study which began in 1989 with the purpose of identifying genes that increase the risk for AUDs. Families were identified through probands in treatment for alcoholism at six sites in the United States. Probands and their first-degree relatives were interviewed with a comprehensive, structured interview, the Semi-Structured Assessment for the Genetics of Alcoholism

(SSAGA) [31,32], and in families where two or more first-degree relatives were also affected, additional branches of the family were recruited into the study. Comparison families recruited from a variety of sources (e.g. dental clinics, drivers' registries) participated in the same protocol. Because these families were intended to represent a subset of the general population, family members were not excluded if they met criteria for an AUD or other psychiatric disorder. Further details concerning the study have been published [33,34].

The prospective component of the COGA study began in 2004 and is ongoing [35]. Offspring from high-risk and comparison families who are aged 12–22 (born 1982 or later) at intake, and who have at least one parent who was interviewed for the COGA study (1991–2005), are enrolled, with new subjects added as they reach the age of 12. Subjects are interviewed every 2 years with the SSAGA or, for subjects younger than 18, the childhood version (C-SSAGA), which covers alcohol and other substance use problems and disorder and other psychiatric disorders [36]. This study focused on 3257 offspring from 1912 nuclear families with one (51.9%), two (31.8%) or three or more (16.3%) participating offspring as of June 2016 who had data on both parents; 1945 (59.7%) had a parent with an AUD. The data set included 2-, 4-, 6-, 8- and 10-year follow-up data for 2851, 2337, 1812 and 1153 and 442 individuals, respectively. Sixty-four per cent of the sample had three or more follow-up interviews, 16.4% had two, 15.7% had one and 12.4% had not yet had a follow-up interview. Sample demographics are available in Table 1.

Measures

Outcomes: offspring substance use and sexual debut

Data from all offspring interviews were used to obtain lifetime reports of substance use and consensual sexual debut; age at onset for each behavior was based on first report. For subjects who had already initiated a particular substance or sexual debut at the baseline interview or had only one interview (52.9%), retrospectively reported age at first use or first sex was used. Age was recorded in years since birth, in yearly increments. Substance use variables came from the alcohol, cannabis and tobacco assessments of the SSAGA and C-SSAGA interviews, and sexual debut from a question in the antisocial behaviors section about age at first sexual intercourse. Subjects were first asked: 'Have you ever had sexual intercourse voluntarily?' and, if 'yes': 'How old were you when you first had sexual intercourse (voluntarily)?'.

Independent variables: parental AUD status and parental separation

Parental AUD was a life-time measure based on parents' self-report from direct diagnostic SSAGA interviews when available (65.3% of fathers and 90.5% of mothers). For

Table 1 Demographics, parental separation, and substance use characteristics of 3257 offspring overall and by parental alcohol use disorder (AUD) status.

| | Total sample n = 3257 | Parental AUD status | | | | Test of differences by parental AUD status |
		None n = 1160	One parent only AUD n = 1273	Both parents AUD n = 672	One parent AUD possible, co-parent unaffected n = 152	Design-based statistic and P-value
Female, %	51.1	50.8	51.0	51.5	53.3	$F_{(3, 5726)} = 0.13$, $P = 0.94$
European American, %	65.9	64.4	63.8	76.0	50.0	$F_{(6, 1906)} = 4.9$, $P < 0.001$
African American, %	25.8	27.2	28.4	15.8	37.5	
Other race/ethnicity, %	8.3	8.4	7.9	8.2	12.5	
Age at study entry, mean (SD, range)	16.1 (3.3, 12–26)	15.8 (3.3, 12–24)	16.4 (3.3, 12–26)	16.2 (3.3, 12–25)	15.7 (3.2, 12–25)	$F_{(3, 1909)} = 6.7$, $P < 0.001$
Age at most recent follow-up, mean (SD, range)	22.8 (4.5, 14–33)	22.5 (4.6, 14–33)	23.1 (4.4, 14–32)	22.7 (4.4, 14–32)	22.1 (4.4, 13–31)	$F_{(3, 1704)} = 3.2$, $P = 0.02$
Parental separation, %	47.9	32.5	54.5	56.8	73.3	$F_{(3, 1900)} = 34.8$, $P < 0.0001$
Ever had drink of alcohol, %	82.5	75.6	87.3	85.4	81.6	$F_{(3, 1909)} = 13.44$, $P < 0.0001$
Ever smoked full cigarette, %	48.3	36.6	52.2	61.8	46.0	$F_{(3, 1909)} = 28.6$, $P < 0.0001$
Ever used cannabis, %	65.1	54.5	71.1	71.0	70.4	$F_{(3, 1909)} = 20.8$, $P < 0.0001$
Ever had voluntary sexual intercourse, %	79.3	72.4	83.4	82.9	81.6	$F_{(3, 1909)} = 11.2$, $P < 0.0001$
Timing of first substance use, sexual debut						
Age first drink, mean (SD, range)	15.7 (2.5, 7–30)	16.3 (2.5, 7–30)	15.6 (2.5, 7–25)	15.1 (2.5, 7–26)	15.6 (2.5, 8–22)	$F_{(3, 1680)} = 16.3$, $P < 0.0001$
First drink ≤ age 15, %	38.7	29.2	41.3	49.5	40.1	
First drink ≥ age 16, %	43.8	46.4	46.0	35.9	41.5	
Age first cigarette, mean (SD, range)	15.6 (3.0, 7–30)	16.2 (2.6, 9–24)	15.7 (3.0, 7–28)	15.0 (3.1, 7–30)	15.3 (3.1, 8–24)	$F_{(3, 1139)} = 9.6$, $P < 0.0001$
First cigarette ≤ age 15, %	23.5	14.3	25.1	36.1	25.6	
First cigarette ≥ age 16, %	24.8	22.3	27.1	25.7	20.4	
Age first use cannabis, mean (SD, range)	15.9 (2.7, 8–29)	16.5 (2.7, 8–27)	15.9 (2.7, 8–29)	15.4 (2.8, 8–26)	15.8 (2.6, 8–23)	$F_{(3, 1436)} = 12.5$, $P < 0.0001$
First cannabis ≤ age 15, %	29.5	19.8	33.6	37.3	34.9	
First cannabis ≥ age 16, %	35.6	34.7	37.5	33.6	35.5	
Age sexual debut, mean (SD, range)	16.3 (2.3, 10–27)	16.9 (2.5, 10–27)	16.1 (2.2, 10–25)	15.8 (2.1, 10–24)	15.7 (2.0, 10–22)	$F_{(3, 1657)} = 21.3$, $P < 0.0001$
First sex ≤ age 15, %	30.0	20.8	33.8	36.5	39.5	
First sex ≥ age 16, %	49.3	51.6	49.6	46.4	42.1	

SD = standard deviation.

parents who were not interviewed, at least two positive family history reports, based on the Family History Assessment Module [37], were used to code parents as affected (5.1% of fathers and 0.3% of mothers). If fewer than two family history reports were available, parents were coded as 'possible AUD' if there was just one positive family history report (5.9% of fathers and 0.9% of mothers) or if offspring reported that the parent was a heavy drinker or recovering alcoholic in the Important People and Activities interview [38] (2.3% of fathers and 1.1% of mothers). The combined AUD status of both parents was represented with dummy variables coded 0/1 for father only AUD, mother only AUD, both parents AUD and one parent negative and other parent possible AUD (see Supporting information, Table S1 for details on parental AUD coding). Parental separation was represented by a dummy variable coded 1 for offspring who reported they did not live with both biological parents most of the time between ages 12 and 17 years, and 0 for all others.

Control variables

Internalizing (any among major depressive disorder, panic disorder, social phobia or suicidal ideation) and externalizing (either conduct disorder or oppositional defiant disorder) domains based on offspring data about DSM-IV life-time criteria [39] from the SSAGA interviews were included to account for potential effects of self-medication on substance use [40,41] and associations of externalizing and internalizing problems with sexual debut [42] and with parental AUDs [43,44]. Assaultive and non-assaultive trauma variables were based on a trauma screen which preceded the post-traumatic stress disorder section of the interview. Based on evidence that interpersonal assaultive events have a stronger and more enduring effect on psychopathology and substance use than non-assaultive events [45–49] and that traumatic events cluster together [50], we created two composite variables representing report of one or more life-time assaultive traumas (stabbed, shot, mugged, threatened with a weapon, robbed, kidnapped, held captive, raped or molested) and non-assaultive traumas (life-threatening accident, disaster, witnessing someone seriously injured or killed and unexpectedly finding a dead body). The earliest reported age of occurrence of an internalizing or externalizing disorder or traumatic event was selected to represent age at onset of the respective composite variable. These control variables were modeled as time-varying (i.e. coded '0' before onset and '1' during year of onset and thereafter), so that only disorders or events that preceded or occurred at the same time as the outcome contributed to risk. Demographic control variables were yearly family income [low ($30 000), middle (referent), high (≥ $75 000)], sex, ethnicity (African American and other versus European

American), case family (versus comparison) and birth cohort. Age in years is implicit in the models where interactions with age were necessary to satisfy the proportional hazards assumption, described below in Statistical methods.

Statistical methods

First, we estimated frequencies of parental separation, substance use and sexual debut and average age at initiation of each substance and at sexual debut, in the sample as a whole and as a function of parental AUD status. Secondly, we used survival analysis to estimate the strength of association of parental separation and parental AUDs with each of the four outcomes: time in years since birth to initiation of alcohol, cigarette and cannabis use and sexual debut. Within this step, we (i) used Cox regression to test the associations of mother-only and father-only AUD with each outcome, then performed *post-hoc* Wald χ^2 tests to assess the equality of the coefficients. As the coefficients for mother-only and father-only AUD did not differ for any outcome (*P*-values ranging from 0.17 to 0.94), we combined them into a single variable representing alcohol problems in either parent; and (ii) graphed cumulative failure rates using the Kaplan–Meier survival function. Thirdly, we estimated Cox proportional hazards regression models predicting age at first use of alcohol, cigarettes, cannabis and age at sexual initiation from parental AUD (modeled with three dummy variables representing AUD in one parent, both parents or possible AUD in one parent) and parental separation, before and after adjustment for control variables. Observations were censored at first use of substance or first sex; subjects who had not yet used substances or had sex were censored at their most recent age. Fourthly, we performed *post-hoc* Wald χ^2 tests to compare the relative strength of association with each outcome of parental separation with AUD in one parent and AUDs both parents. Significance for *P*-values was adjusted for multiple testing (*P* = 0.05/two tests = 0.025). Tests of proportional hazards, i.e. the assumption that the risk associated with different levels of a variable remain proportional over time, were computed using Schoenfeld residuals [51]. Where such variations in risk were found for parental AUDs and parental separation, interactions with age that correspond to key developmental periods were created and entered into the model [i.e. early childhood (aged 12 and younger), puberty (13–15), early adolescence (16–18) and young adulthood (19 and older)] [52]. For example, subjects with two AUD-affected parents may have greater cumulative incidence of alcohol initiation before age 16 than later, and that difference in cumulative incidence before and after age 16 is modeled with an age interaction (see Supporting information, Fig. S1 for visual representation). For control variables, the average

association with the outcome across time was used, as violations of the proportional hazards assumption did not affect the interpretation of the association of parental AUDs and parental separation with outcomes [53,54]. Standard errors were adjusted for the non-independence of observations within families using the Huber–White robust variance estimator, and analyses were performed using Stata statistical software version 14 [55].

RESULTS

Nearly 60% of the sample had at least one parent with an AUD (39.1% one parent, 20.6% both parents), and an additional 4.7% had one parent with possible AUD. Rates of AUDs among fathers and mothers were 41.8 and 33.0%, respectively. Among offspring with just one affected parent, AUD was more prevalent in fathers (64.6%) than mothers (35.4%). Table 1 contains demographics, rates of parental separation and substance use variables for the sample as a whole and by parental AUD status (see Supporting information, Table S2 for all covariates). In general, age at initiation of substance use and sexual debut were youngest among subjects with two AUD-affected parents, slightly older among subjects with one affected or possibly affected parent and oldest among subjects with no parental AUDs. This gradation by parental AUDs is apparent for alcohol initiation in Fig. 1 (see Supporting information, Figures S2–S8 for other outcomes).

Survival analysis results

Parental AUDs and parental separation were associated with initiation of each of the substances and with sexual debut in unadjusted models and in models adjusted for control variables (Table 2; see Supporting information, Table S3 for bivariate associations). Results from Table 2 adjusted models are discussed below.
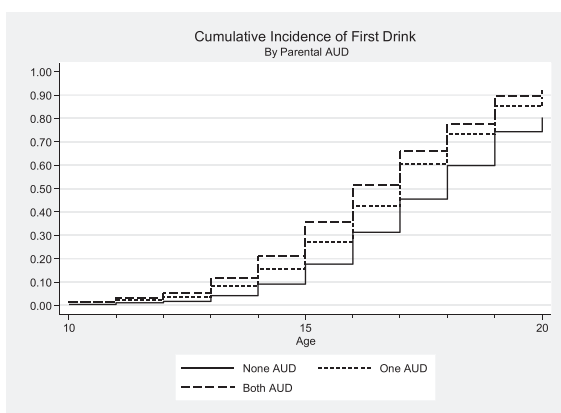

Figure 1 Cumulative incidence of first drink, by parental alcohol use disorder (AUD)

Parental AUDs

The hazard associated with having one parent with an AUD (versus no parental AUD) was similar across all ages and was associated with all outcomes. In adjusted models, the increased risk associated with having one parent with an AUD, versus none, ranged from 20% for age at first consensual sex [hazard ratio (HR) = 1.19] to 32% for age at first use of cannabis (HR = 1.32). The hazards associated with having one parent with possible AUD were similar to the hazards associated with having one parent with diagnostic AUD in regard to alcohol and cannabis initiation and sexual debut.

Having two AUD-affected parents had a stronger association with risk for early than later initiation for all outcomes. AUDs in both parents had a stronger association with risk for use of alcohol and cigarettes before age 16 than later (alcohol: HRs = 1.59 and 1.25; cigarettes: HRs = 1.81 and 1.45). For first use of cannabis, having two parents with an AUD was associated more strongly with beginning use at age 12 and younger than later (HRs = 2.71 and 1.32). Regarding first consensual sex, having two AUD-affected parents was associated with a stable 43% increased risk until age 18, after which there was no significant association (HRs = 1.43 and 0.97).

Parental separation

Parental separation, like parental AUDs, was associated more strongly with early than later age at initiation. Subjects who did not grow up with both biological parents, compared to those who did, were at increased risk for first use of alcohol before age 13 (HR = 2.16) and for initiating cigarette and cannabis use before age 16 (HRs = 1.89 and 2.03, respectively), as well as increased risk for sexual debut before age 16 (HR = 2.34).

Relative strength of associations of parental AUD and parental separation

To determine the relative strengths of association of parental AUDs and parental separation, we used *post-hoc* Wald tests to compare the largest hazard associated with parental separation (i.e. the younger age categories) with (1) the hazard associated with one parent with an AUD and (2) the hazard associated with two AUD-affected parents for the youngest age category, for all outcomes. Parental separation had a stronger association with first use of alcohol than did having one parent with an AUD (HRs = 2.16 versus 1.28, Wald $\chi^2_{(1)} = 10.7$, $P < 0.01$) but did not differ from the hazard associated with two affected parents (HRs = 2.16 versus 1.59, $\chi^2_{(1)} = 3.1$, $P = 0.08$). This pattern was also observed for tobacco and cannabis, where parental separation had a significantly stronger association with initiation risk than did having one AUD-affected parent, and had risk equivalent to that of having two AUD-

Table 2 Associations of parental alcohol use disorder (AUD) with time in years from birth to offspring first use of alcohol, cigarettes, marijuana and sexual debut.

	First drink of alcohol		First cigarette		First use of cannabis		First consensual sex	
	Model 1 HR (95% CI)	*Model 2 HR (95% CI)*	*Model 1 HR (95% CI)*	*Model 2 HR (95% CI)*	*Model 1 HR (95% CI)*	*Model 2 HR (95% CI)*	*Model 1 HR (95% CI)*	*Model 2 HR (95% CI)*
One parent AUD	1.38 (1.24–1.54)	1.28 (1.15–1.43)	1.43 (1.24–1.65)	1.22 (1.06–1.41)	1.43 (1.27–1.61)	1.32 (1.17–1.50)	1.30 (1.17–1.45)	1.19 (1.07–1.33)
Both parents AUD								
≤ Age 12	1.85 (1.57–2.18)	1.59 (1.34–1.88)	2.30 (1.89–2.79)	1.81 (1.49–2.21)	2.90 (2.05–4.12)	2.71 (1.91–3.85)	1.48 (1.30–1.70)	1.43 (1.25–1.63)
Ages 13–15	1.85 (1.57–2.18)	1.59 (1.34–1.88)	2.30 (1.89–2.79)	1.81 (1.49–2.21)	1.44 (1.23–1.67)	1.32 (1.13–1.54)	1.48 (1.30–1.70)	1.43 (1.25–1.63)
Ages 16–18	1.43 (1.19–1.71)	1.25 (1.05–1.50)	1.74 (1.42–2.14)	1.45 (1.18–1.78)	1.44 (1.23–1.67)	1.32 (1.13–1.54)	1.48 (1.30–1.70)	1.43 (1.25–1.63)
> Age 19	1.43 (1.19–1.71)	1.25 (1.05–1.50)	1.74 (1.42–2.14)	1.45 (1.18–1.78)	1.44 (1.23–1.67)	1.32 (1.13–1.54)	0.98 (0.69–1.38)	0.97 (0.66–1.43)
One parent unaffected, co-parent AUD possible	1.33 (1.09–1.64)	1.25 (1.01–1.55)	1.28 (0.98–1.67)	1.15 (0.87–1.51)	1.51 (1.21–1.87)	1.43 (1.14–1.80)	1.54 (1.27–1.87)	1.47 (1.21–1.80)
Parental separation								
≤ Age 12	2.03 (1.52–2.72)	2.16 (1.61–2.91)	1.91 (1.61–2.25)	1.89 (1.59–2.25)	2.29 (1.97–2.67)	2.03 (1.73–2.38)	2.93 (2.51–3.42)	2.34 (1.99–2.75)
Ages 13–15	1.13 (1.03–1.24)	1.23 (1.11–1.37)	1.91 (1.61–2.25)	1.89 (1.59–2.25)	2.29 (1.97–2.67)	2.03 (1.73–2.38)	2.93 (2.51–3.42)	2.34 (1.99–2.75)
Ages ≥16	1.13 (1.03–1.24)	1.23 (1.11–1.37)	1.17 (1.01–1.35)	1.19 (1.01–1.39)	1.18 (1.04–1.34)	1.05 (0.91–1.21)	1.49 (1.34–1.66)	1.19 (1.06–1.34)

HR = hazard ratio; '≤ age 12' and other age notations indicate that interactions with age were modeled because the hazard associated with parental AUD or parental separation varied significantly with offspring age [e.g. parental separation was associated with greater risk for first drink at age 12 and younger (HR = 2.16) than at age 13 and older (HR = 1.23)]. Model 1 is unadjusted, model 2 adjusted for externalizing [conduct disorder (CD) or oppositional defiant disorder (ODD)], internalizing/suicidality (life-time major depressive disorder, panic disorder, social phobia, suicidal ideation), assaultive trauma (one or more of stabbed, shot, mugged, kidnapped/held captive, threatened with a weapon, robbed), non-assaultive trauma (one or more of life-threatening accident, disaster, witnessing someone seriously injured or killed and unexpectedly finding a dead body), family income, sex, race/ethnicity, case status of family, birth cohort. Results with all control variables are available in Supporting information, Table S3.

affected parents (tobacco: HRs = 1.89 versus 1.22, $\chi^2_{(1)}$ = 13.0, $P < 0.001$ and HRs = 1.89 and 1.81, $\chi^2_{(1)}$ = 0.08; cannabis: HRs = 2.04 versus 1.33, $\chi^2_{(1)}$ = 16.02, $P < 0.001$ and HRs = 2.04 versus 2.73, $\chi^2_{(1)}$ = 2.0, $P = 0.16$). For sexual debut, parental separation was associated with greater hazard than was having one or two AUD-affected parents (HRs = 2.34 versus 1.19, $\chi^2_{(1)}$ = 44.6, $P < 0.0001$ and versus 1.43, $\chi^2_{(1)}$ = 19.3, $P < 0.0001$).

DISCUSSION

Subjects with two AUD-affected parents were at greater risk for early initiation of alcohol, cigarette and cannabis use and sexual debut than were subjects with no parental AUD. Parental separation was also a consistent predictor of early substance use and sexual debut, with an effect on substance initiation equal to that of having two AUD-affected parents, and associated more strongly with early sexual debut than AUD in one or both parents.

Our work builds upon previous work by documenting that parental AUD is a common risk factor for initiation of multiple substances and early sexual debut. Previous work has focused largely on the association between parental AUD and offspring risk for alcohol initiation and alcohol-related outcomes, with some recent attention to the association of parental AUD with offspring use of other substances [29,30]. Data from the National Epidemiological Study on Alcoholism and Related Conditions (NESARC) showed that subjects who began drinking before age 15 and from ages 15–17 reported more substance use problems in their parents than did subjects who began drinking at age 18 years and older [6]. There is also evidence from twin and offspring-of-twin studies showing associations of parental alcohol problems with earlier age at alcohol use in offspring [22,23,56]. Just one of these studies used diagnostic measures of parental AUD [23]; the rest employed respondent reports of parent drinking behavior [6,22,56]. The present study replicates and extends previous findings in its use of diagnostic measures by self-report in most parents or with family history measures of AUD.

There is less evidence of a link between parental AUD and early cigarette and cannabis use and sexual debut than for early alcohol use. Sartor and colleagues [30] found that maternal alcohol problems were associated with early age at first cigarette in a sample of offspring of twins. In an extension of that same offspring-of-twins study, Scherrer and colleagues [57] found a significant association of maternal alcohol problems with elevated odds of offspring nicotine dependence. Regarding cannabis use, parental alcohol problems were associated independently with opportunity to use cannabis in Australian twins, but not with the transition to cannabis dependence [29]. The present study

broadens the literature on the influence of parental AUD beyond offspring alcohol use to other substances and behaviors that are often correlated with alcohol use.

The finding that AUDs in both parents had a stronger association with earlier than later cannabis use is consistent with a recent study which showed that parental alcohol problems were associated with increased opportunity to use cannabis and with increased risk of initiating use, given the opportunity [29]. Recent evidence showed that the age at initiation of cannabis use was influenced more strongly by shared environment than were ages at initiation of tobacco and alcohol, suggesting that this might be due to the illegality of cannabis (in most states), making it harder to procure [14]. Parents with AUDs may provide less monitoring of child behavior than parents without AUDs [18,19], increasing the likelihood that offspring will have access to cannabis via deviant peers. Parental AUDs may also represent a general risk for psychosocial and substance use problems via increased genetic risk for conduct problems and other substance use [58].

Parental separation was a stronger predictor of sexual debut than was parental AUD, consistent with evidence that parental separation outweighs the effect of parental AUD on early use of alcohol in offspring of male twins [23], Australian twins [20] and European American female twins [22]. In an ethnically diverse sample of 12–17-year-old adolescents, age at sexual debut was significantly younger among subjects who did not live with both biological parents than among those who did [59], and 15–18-year old African American girls from high-poverty neighborhoods who lived with both parents were less likely than those living with single mothers to have had their sexual debut [60]; neither of these studies included a measure of parental AUD. Our result, showing that parental separation has a stronger effect on sexual debut than parental AUD, is striking, as parental AUD is associated with increased risk for childhood adversities which themselves are associated with earlier sexual debut [61]. Separated parents, like parents with AUDs, may provide less monitoring of their children, so that opportunities for substance use and risky sex are more plentiful. Parental separation may be a marker indexing a broad risk that includes lax parental monitoring as well as potentially greater genetic liability to substance use, as parents with AUD are more likely than parents without to separate [15,16], and parental AUD is associated with increased genetic risk for other substance use in offspring [58].

Limitations and future directions

The results from this sample, selected for high familial risk for AUDs, might not be generalizable to population-based samples. However, the outcomes examined are normative behaviors in population-based data; it is only the timing

of these behaviors that may differentiate this from population-based samples. Furthermore, more than 40% of children in the United States live in homes with a parent or other adult with alcohol problems [62], and these data may be used to infer risks associated with parental AUD for any child. Parental use of substances other than alcohol was not included, and the timing of parental AUDs or parental separation was not modeled in relation to offspring outcomes. It is possible that remitted parental AUDs might have a different association with outcomes (e.g. null or even protective), or that timing of parental separation is associated differentially with risk. Despite these limitations, the high prevalence of parental AUDs in this sample provides the opportunity to examine parental effects on timing of first use. Future work examining the progression of offspring substance involvement including AUDs in relation to the course of parental AUDs will be important.

CONCLUSIONS

Parental AUDs and parental separation are independent and consistent predictors of increased risk for early alcohol, tobacco and cannabis use and sexual debut in offspring, after accounting for other risks associated with early substance use and sexual debut.

Declaration of interests

None.

References

1. Hawkins J. D., Graham J. W., Maguin E., Abbott R., Hill K. G., Catalano R. F. Exploring the effects of age of alcohol use initiation and psychosocial risk factors on subsequent alcohol misuse. *J Stud Alcohol* 1997; **58**: 280–90.
2. King K. M., Chassin L. A prospective study of the effects of age of initiation of alcohol and drug use on young adult substance dependence. *J Stud Alcohol Drugs* 2007; **68**: 256–65.
3. Sartor C. E., Lynskey M. T., Bucholz K. K., Madden P. A., Martin N. G., Heath A. C. Timing of first alcohol use and alcohol dependence: evidence of common genetic influences. *Addiction* 2009; **104**: 1512–8.
4. Grant B. F., Dawson D. A. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: results from the National Longitudinal Alcohol Epidemiologic Survey. *J Subst Abuse* 1997; **9**: 103–10.
5. Hingson R. W., Heeren T., Winter M. R. Age at drinking onset and alcohol dependence: age at onset, duration, and severity. *Arch Pediatr Adolesc Med* 2006; **160**: 739–46.
6. Dawson D. A., Goldstein R. B., Patricia C. S., June R. W., Grant B. F. Age at first drink and the first incidence of adult-onset DSM-IV alcohol use disorders. *Alcohol Clin Exp Res* 2008; **32**: 2149–60.
7. Grant J. D., Scherrer J. F., Lynskey M. T., Agrawal A., Duncan A. E., Haber J. R. *et al.* Associations of alcohol, nicotine, cannabis, and drug use/dependence with educational attainment: evidence from cotwin-control analyses. *Alcohol Clin Exp Res* 2012; **36**: 1412–20.
8. King K. M., Meehan B. T., Trim R. S., Chassin L. Marker or mediator? The effects of adolescent substance use on young adult educational attainment. *Addiction* 2006; **101**: 1730–40.
9. Agrawal A., Few L., Nelson E. C., Deutsch A., Grant J. D., Bucholz K. K. *et al.* Adolescent cannabis use and repeated voluntary unprotected sex in women. *Addiction* 2017; **111**: 2012–20.
10. Bierman K. L., Coie J. D., Dodge K. A., Greenberg M., Lochman J. E., McMahon R. J. *et al.* Trajectories of risk for early sexual activity and early substance use in the fast track prevention program. *Prev Sci* 2014; **15**: S33–S46.
11. Hipwell A., Stepp S., Chung T., Durand V., Keenan K. Growth in alcohol use as a developmental predictor of adolescent girls' sexual risk-taking. *Prev Sci* 2012; **13**: 118–28.
12. Fowler T., Lifford K., Shelton K., Rice F., Thapar A., Neale M. C. *et al.* Exploring the relationship between genetic and environmental influences on initiation and progression of substance use. *Addiction* 2007; **102**: 413–22.

13. Han C., McGue M. K., Iacono W. G. Lifetime tobacco, alcohol and other substance use in adolescent Minnesota twins: univariate and multivariate behavioral genetic analyses. *Addiction* 1999; **94**: 981–93.

14. Richmond-Rakerd L. S., Slutske W. S., Lynskey M. T., Agrawal A., Madden P. A., Bucholz K. K. *et al.* Age at first use and later substance use disorder: shared genetic and environmental pathways for nicotine, alcohol, and cannabis. *J Abnorm Psychol* 2016; **125**: 946–59.

15. Anda R. F., Whitfield C. L., Felitti V. J., Chapman D., Edwards V. J., Dube S. R. *et al.* Adverse childhood experiences, alcoholic parents, and later risk of alcoholism and depression. *Psychiatr Serv* 2002; **53**: 1001–9.

16. Donovan J. E., Molina B. S. Childhood risk factors for early-onset drinking. *J Stud Alcohol Drugs* 2011; **72**: 741–51.

17. Fergusson D. M., Lynskey M. T., Horwood L. J. Childhood sexual abuse and psychiatric disorder in young adulthood: I. Prevalence of sexual abuse and factors associated with sexual abuse. *J Am Acad Child Adolesc Psychiatry* 1996; **35**: 1355–64.

18. Chassin L., Curran P. J., Hussong A. M., Colder C. R. The relation of parent alcoholism to adolescent substance use: a longitudinal follow-up study. *J Abnorm Psychol* 1996; **105**: 70–80.

19. Latendresse S. J., Rose R. J., Viken R. J., Pulkkinen L., Kaprio J., Dick D. M. Parenting mechanisms in links between parents' and adolescents' alcohol use behaviors. *Alcohol Clin Exp Res* 2008; **32**: 322–30.

20. Waldron M., Grant J. D., Bucholz K. K., Lynskey M. T., Slutske W. S., Glowinski A. L. *et al.* Parental separation and early substance involvement: results from children of alcoholic and cannabis dependent twins. *Drug Alcohol Depend* 2014; **134**: 78–84.

21. Waldron M., Doran K. A., Bucholz K. K., Duncan A. E., Lynskey M. T., Madden P. A. *et al.* Parental separation, parental alcoholism, and timing of first sexual intercourse. *J Adolesc Health* 2015; **56**: 550–6.

22. Waldron M., Vaughan E. L., Bucholz K. K., Lynskey M. T., Sartor C. E., Duncan A. E. *et al.* Risks for early substance involvement associated with parental alcoholism and parental separation in an adolescent female cohort. *Drug Alcohol Depend* 2014; **138**: 130–6.

23. Grant J. D., Waldron M., Sartor C. E., Scherrer J. F., Duncan A. E., McCutcheon V. V. *et al.* Parental separation and offspring alcohol involvement: findings from offspring of alcoholic and drug dependent twin fathers. *Alcohol Clin Exp Res* 2015; **39**: 1166–73.

24. Capaldi D. M., Tiberio S. S., Kerr D. C. R., Pears K. C. The relationships of parental alcohol versus tobacco and marijuana use with early adolescent onset of alcohol use. *J Stud Alcohol Drugs* 2016; **77**: 95–103.

25. Duncan S. C., Duncan T. E., Strycker L. A. Alcohol use from ages 9 to 16: a cohort-sequential latent growth model. *Drug Alcohol Depend* 2006; **81**: 71–81.

26. Armstrong J. M., Ruttle P. L., Burk L. R., Costanzo P. R., Strauman T. J., Essex M. J. Early risk factors for alcohol use across high school and its covariation with deviant friends. *J Stud Alcohol Drugs* 2013; **74**: 746–56.

27. Hussong A., Bauer D., Chassin L. Telescoped trajectories from alcohol initiation to disorder in children of alcoholic parents. *J Abnorm Psychol* 2008; **117**: 63–78.

28. McGue M., Iacono W. G., Legrand L. N., Elkins I. Origins and consequences of age at first drink. II. Familial risk and heritability. *Alcohol Clin Exp Res* 2001; **25**: 1166–73.

29. Hines L. A., Morley K. I., Strang J., Agrawal A., Nelson E. C., Statham D. *et al.* Onset of opportunity to use cannabis and progression from opportunity to dependence: are influences consistent across transitions? *Drug Alcohol Depend* 2016; **160**: 57–64.

30. Sartor C. E., Xian H., Scherrer J. F., Lynskey M. T., Duncan A. E., Haber J. R. *et al.* Psychiatric and familial predictors of transition times between smoking stages: results from an offspring-of-twins study. *Addict Behav* 2008; **33**: 235–51.

31. Bucholz K. K., Cadoret R., Cloninger C. R., Dinwiddie S. H., Hesselbrock V. M., Nurnberger J. I. J. *et al.* A new, semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. *J Stud Alcohol* 1994; **55**: 149–58.

32. Hesselbrock M., Easton C., Bucholz K. K., Schuckit M., Hesselbrock V. A validity study of the SSAGA—a comparison with the SCAN. *Addiction* 1999; **94**: 1361–70.

33. Reich T., Edenberg H. J., Goate A., Williams J. T., Rice J. P., Van Eerdewegh P. *et al.* Genome-wide search for genes affecting the risk for alcohol dependence. *Am J Med Genet* 1998; **81**: 207–15.

34. Nurnberger J. I. Jr., Wiegand R., Bucholz K., O'Connor S., Meyer E. T., Reich T. *et al.* A family study of alcohol dependence: coaggregation of multiple disorders in relatives of alcohol-dependent probands. *Arch Gen Psychiatry* 2004; **61**: 1246–56.

35. Bucholz K. K., McCutcheon V. V., Agrawal A., Dick D. M., Hesselbrock V. M., Kramer J. R. *et al.* Comparison of parent, peer, psychiatric, and cannabis use influences across stages of offspring alcohol involvement: evidence from the COGA prospective study. *Alcohol Clin Exp Res* 2017; **41**: 359–68.

36. Kuperman S., Chan G., Kramer J. R., Bierut L., Bucholz K. K., Fox L. *et al. Alcohol Clin Exp Res* 2005; **29**: 1869–76.

37. Rice J. P., Reich T., Bucholz K. K., Neuman R. J., Fishman R., Rochberg N. *et al.* Comparison of direct interview and family history diagnoses of alcohol dependence. *Alcohol Clin Exp Res* 1995; **19**: 1018–23.

38. Longabaugh R., Wirtz P. W., Zywiak W. H., O'Malley S. S. Network support as a prognostic indicator of drinking outcomes: the COMBINE study. *J Stud Alcohol Drugs* 2010; **71**: 837–46.

39. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. Washington, DC: American Psychiatric Association; 1994.

40. Khantzian E. J. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harv Rev Psychiatry* 1997; **4**: 231–44.

41. Markou A., Kosten T. R., Koob G. F. Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. *Neuropsychopharmacology* 1998; **18**: 135–74.

42. Skinner S. R., Robinson M., Smith M. A., Robbins S. C., Mattes E., Cannon J. *et al.* Childhood behavior problems and age at first sexual intercourse: a prospective birth cohort study. *Pediatrics* 2015; **135**: 255–63.

43. Chassin L., Pitts S. C., DeLucia C., Todd M. A longitudinal study of children of alcoholics: predicting young adult substance use disorders, anxiety, and depression. *J Abnorm Psychol* 1999; **108**: 106–19.

44. Hill S. Y., Tessner K. D., McDermott M. D. Psychopathology in offspring from families of alcohol dependent female probands: a prospective study. *J Psychiatr Res* 2010; **45**: 285–94.

45. Breslau N., Chilcoat H. D., Kessler R. C., Davis G. C. Previous exposure to trauma and PTSD effects of subsequent trauma: results from the Detroit area survey of trauma. *Am J Psychiatry* 1999; **156**: 902–7.

46. Breslau N., Wilcox H. C., Storr C. L., Lucia V. C., Anthony J. C. Trauma exposure and posttraumatic stress disorder: a study of youths in urban America. *J Urban Health* 2004; **81**: 530–44.

47. Werner K. B., McCutcheon V. V., Agrawal A., Sartor C. E., Nelson E. C., Heath A. C. *et al.* The association of specific traumatic experiences with cannabis initiation and transition to problem use: differences between African-American and European-American women. *Drug Alcohol Depend* 2016; **162**: 162–9.

48. Werner K. B., Sartor C. E., McCutcheon V. V., Grant J. D., Nelson E. C., Heath A. C. *et al.* Association of specific traumatic experiences with alcohol initiation and transitions to problem use in European American and African American women. *Alcohol Clin Exp Res* 2016; **40**: 2401–8.

49. Sartor C. E., Lynskey M. T., Bucholz K. K., McCutcheon V. V., Nelson E. C., Waldron M. *et al.* Childhood sexual abuse and the course of alcohol dependence development: findings from a female twin sample. *Drug Alcohol Depend* 2007; **139**: 44.

50. Benjet C., Bromet E., Karam E. G., Kessler R. C., McLaughlin K. A., Ruscio A. M. *et al.* The epidemiology of traumatic event exposure worldwide: results from the world mental health survey consortium. *Psychol Med* 2016; **46**: 327–43.

51. Grambsch P. M., Therneau T. M. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994; **81**: 515–26.

52. Hosmer D. W., Lemeshow S. *Applied Survival Analysis: Regression Modeling of Time to Event Data*, Wiley Series in Probability and Statistics. New York: John Wiley & Sons, Inc.; 1999.

53. Allison P. D. Survival analysis. In: Hancock G. R., Mueller R. O., editors. *The Reviewer's Guide to Quantitative Methods in the Social Sciences*. New York: Routledge; 2010, pp. 413–25.

54. Allison P. D. *Survival Analysis Using SAS: A Practical Guide*. Cary, NC: SAS Institute; 1995.

55. StataCorp. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP; 2015.

56. Sartor C. E., Lynskey M. T., Heath A. C., 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.

57. Scherrer J. F., Xian H., Pan H., Pergadia M. L., Madden P. A., Grant J. D. *et al.* Parent, sibling and peer influences on smoking initiation, regular smoking and nicotine dependence: results from a genetically informative design. *Addict Behav* 2012; **37**: 240–7.

58. Hicks B. M., Foster K. T., Iacono W. G., McGue M. Genetic and environmental influences on the familial transmission of externalizing disorders in adoptive and twin offspring. *JAMA Psychiatry* 2013; **70**: 1076–83.

59. Upchurch D. M., Levy-Storms L., Sucoff C. A., Aneshensel C. S. Gender and ethnic differences in the timing of first sexual intercourse. *Fam Plann Perspect* 1998; **30**: 121–7.

60. Moore M. R., Chase-Lansdale P. L. Sexual intercourse and pregnancy among African American girls in high-poverty neighborhoods: the role of family and perceived community environment. *J Marriage Fam* 2001; **63**: 1146–57.

61. Fergusson D. M., Horwood L. J., Lynskey M. T. Childhood sexual abuse, adolescent sexual behaviors and sexual revictimization. *Child Abuse Negl* 1997; **21**: 789–803.

62. Grant B. F. Estimates of US children exposed to alcohol abuse and dependence in the family. *Am J Public Health* 2000; **90**: 112–5.

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1 Coding of maternal and paternal alcohol use disorder (AUD) for 3257 offspring.

Table S2 Characteristics of 3527 offspring overall and by parental alcohol use disorder (AUD) status.

Table S3 Bivariate associations of parental alcohol use disorder (AUD), parental separation and control variables with onset of substance use and sexual debut.

Table S4 Associations of parental alcohol use disorder (AUD) with time in years from birth to offspring first use of alcohol, cigarettes, cannabis and sexual debut.

Figure S1 Kaplan–Meier failure estimates of alcohol initiation in subjects with no parental alcohol use disorder (AUD) and subjects with two AUD-affected parents. Black line in center marks age 15 years. Before age 15 (to left of black line), subjects with two AUD-affected parents show a higher failure rate (i.e. greater cumulative incidence of alcohol initiation) than subjects with no AUD-affected parents. After age 15 (to right of black line) their failure rate remains higher, but it is more proportional over time to the failure rate of subjects with no parental AUD.

Figure S2 Cumulative incidence of first drink, by parental separation.

Figure S3 Cumulative incidence of first cigarette, by parental alcohol use disorder (AUD).

Figure S4 Cumulative incidence of first cigarette, by parental separation.

Figure S5 Cumulative incidence of first cannabis use, by parental alcohol use disorder (AUD).

Figure S6 Cumulative incidence of first cannabis use, by parental separation.

Figure S7 Cumulative incidence of sexual debut, by parental alcohol use disorder (AUD).

Figure S8 Cumulative incidence of sexual debut, by parental separation.