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Comparison of Parent, Peer, Psychiatric, and Cannabis Use Influences Across Stages of Offspring Alcohol Involvement: Evidence from the COGA Prospective Study

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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 been as thoroughly investigated. It is not clear whether 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 4 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. Nonassaultive 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 United States, the marked elevations of all alcohol outcomes observed for cannabis use underscore the importance of studying the underpinnings of this relationship.

Key Words: Alcohol Involvement, Parental Alcohol Use Disorder, Externalizing Disorders, Internalizing Disorders, High-Risk Families.

DEVELOPMENT OF ALCOHOL use disorder (AUD), a highly heritable psychiatric disorder, may be decomposed into a series of transitions, beginning with

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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 et al., 2010; Waldron et al., 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 and colleagues (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 and colleagues (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 and colleagues (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 and colleagues (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 4 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 2 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; Nurnberger et al., 2004; Reich et al., 1998); 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 to 22 at inception) and with at least 1 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. Table S1 contains the specific assessments included. All subjects provided written informed consent, and the study was approved by institutional review boards (IRBs) 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 1 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. Last, 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 multifaceted perspective.

The data analyzed here were collected from January 2005 to June 2016; 3,573 offspring from 2,147 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: (i) time to first full drink, (ii) time from first drink to first DSM-5 AUD problem, (iii) time from first drink to first DSM-5 AUD diagnosis, and (iv) time from first AUD problem to first DSM-5 AUD diagnosis (American Psychiatric Association, 2013). 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.

Table 1. Cross-Sectional Characteristics of the Sample at Each Assessment Wave. All Numbers Reflect Percentages Unless Otherwise Noted

	Baseline (n = 3,573)	2 years (n = 3,030)	4 years (n = 2,465)	6 years (n = 1,901)	8 years (n = 1,197)
Mean age (SD)	16.05 (3.29)	18.39 (3.54)	20.62 (3.58)	22.65 (3.48)	24.67 (3.29)
12 to 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 to 86	23.68	23.33	24.54	25.36	28.65
Born 1987 to 89	22.19	22.97	23.69	25.46	26.65
Born 1990 to 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 nonassaultive trauma	33.61	27.96	27.45	26.49	28.43
Peer substance use 12 to 17	53.60	66.34	70.75	68.39	63.83
Did not live with both parents from age 12 to 17	47.48	50.22	50.47	49.55	46.49
Household income (parent report)					
Low (\leq 29,999)	25.37	25.52	25.18	25.15	24.25
Middle (30,000 to 74,999)	54.86	54.56	54.44	54.68	54.77
High (\geq 75,000)	19.77	19.93	20.37	20.18	20.99

^aParent 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. *AUD-possible*: 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.

^bInternalizing—Lifetime history of major depressive disorder, panic, social phobia, and suicidal ideation.

^cExternalizing—Lifetime history of conduct disorder or oppositional defiant disorder.

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 AUD-possible 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 AUD-possible, 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% AUD-possible, 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; 1 parent AUD-possible, co-parent unaffected; 1 unaffected, co-parent missing; and with both unaffected as the referent group. Distributions of these variables are presented in Tables 1 and S2.

Other Risk Factors

Parental separation was based on offspring report of not living with both biological parents for the majority of time from 12 to 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; American Psychiatric Association, 1994), *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 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 school-mates) from ages 12 to 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 as follows: offspring sex, birth cohort (4 cohorts born 1982 to 86 [referent], 1987 to 89, 1990 to 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 to 74,999 [referent]), or high (\geq \$75,000) categories.

Statistical Analysis

All modeling was conducted in Stata, version 14.0 (StataCorp, 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 to 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 Tables S3 to S6). 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 and 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 Table S2, 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 to 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 to 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 to 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%

Table 2. Hazard Ratios (and 95% Confidence Intervals) from Multivariate Cox Proportional Hazards Models for Time to First Drink

Predictor (risk period [age])	Hazard ratio (95% CI)
Parental AUD	
Father AUD, mother unaffected	1.22 (1.10 to 1.37)
Mother AUD, father unaffected	1.16 (1.01 to 1.32)
Both parents affected	1.22 (1.07 to 1.39)
M or D unaffected, co-parent status AUD-possible	1.02 (0.82 to 1.27)
M or D unaffected, co-parent status unknown	0.99 (0.79 to 1.25)
Neither parent affected	1.00 (referent group)
Parental separation	
(≤12)	1.84 (1.37 to 2.46)
(≥13)	1.09 (0.99 to 1.20)
Cannabis use ^a	
(≤12)	9.52 (6.81 to 13.31)
(13 to 15)	3.92 (3.40 to 4.51)
(16 to 18)	2.81 (2.47 to 3.19)
(≥19)	1.91 (1.47 to 2.48)
Internalizing disorders ^a	1.02 (0.93 to 1.11)
Externalizing disorders ^a	
(≤15)	1.53 (1.31 to 1.78)
(≥16)	1.03 (0.86 to 1.22)
Assaultive trauma ^a	0.97 (0.88 to 1.07)
Nonassaultive trauma ^a	
≤15	1.15 (1.02 to 1.31)
≥16	0.95 (0.85 to 1.07)
Perceived substance use of peers	
(≤15)	2.45 (2.04 to 2.94)
(16 to 18)	1.60 (1.40 to 1.83)
(≥19)	1.07 (0.85 to 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 as follows: offspring birth cohort (1982 to 86 [referent], 1987 to 89, 1990 to 93, 1994, and later; sex; African American v non-African American background; income (<\$30,000, \$30,000 to <\$75,000, >= \$75,000); case (v comparison) family status.

^aDefined as time-varying.

Table 3. Hazard Ratios (and 95% Confidence Intervals) from Multivariate Cox Proportional Hazards 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 (0.97 to 1.25)
Mother AUD, father unaffected	1.27 (1.08 to 1.49)
Both parents AUD	1.24 (1.07 to 1.43)
Mother or father unaffected, co-parent status AUD-possible	1.09 (0.84 to 1.42)
Mother or father unaffected, co-parent status unknown	0.72 (0.50 to 1.05)
Neither parent affected	1.00 (referent group)
Parental separation	0.89 (0.79 to 0.99)
Cannabis use ^a	2.11 (1.88 to 2.36)
Internalizing disorders ^a	
Male	1.00 (0.86 to 1.15)
Female	1.40 (1.21 to 1.62)
Externalizing disorders ^a	
≤1 year	1.39 (1.20 to 1.60)
≥2 years	1.11 (0.93 to 1.34)
Assaultive trauma ^a	1.05 (0.95 to 1.18)
Nonassaultive trauma ^a	1.06 (0.96 to 1.17)
Perceived substance use of peers	1.56 (1.35 to 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 as follows: offspring birth cohort (1982 to 86 [referent], 1987 to 89, 1990 to 93, 1994, and later; gender; African American v non-African American background; income (<\$30,000, \$30,000 to <\$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. Sixteen was the median age and used as the reference group).

^aDefined as time-varying.

Table 4. Hazard Ratios (and 95% Confidence Intervals) from Multivariate Cox Proportional Hazards 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 to 1.39)
Mother AUD, father unaffected	1.25 (1.01 to 1.55)
Both parents AUD	1.28 (1.04 to 1.57)
Mother or father unaffected, co-parent status AUD-possible	1.44 (1.01 to 2.05)
Mother or father unaffected, co-parent status unknown	0.70 (0.38 to 1.32)
Neither parent affected	1.00 (referent group)
Parental separation	0.86 (0.74 to 1.01)
Cannabis use ^a	2.52 (2.07 to 3.06)
Internalizing ^a	1.42 (1.23 to 1.63)
Externalizing ^a	1.80 (1.55 to 2.10)
Assaultive trauma	1.12 (0.96 to 1.30)
Nonassaultive trauma ^a	1.14 (0.99 to 1.32)
Perceived substance use of peers	1.36 (1.08 to 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 as follows: offspring birth cohort (1982 to 86 [referent], 1987 to 89, 1990 to 93, 1994, and later; gender; African American v non-African American background; income (<\$30,000, \$30,000 to <\$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. Sixteen was the median age and used as the referent).

^aDefined as time-varying.

(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

Table 5. Hazard Ratios (and 95% Confidence Intervals) from Multivariate Cox Proportional Hazards 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 to 1.40)
Mother AUD, father unaffected	1.23 (0.92 to 1.64)
Both parents AUD	1.23 (0.94 to 1.62)
Mother or father unaffected, co-parent status AUD-possible	0.94 (0.55 to 1.62)
Mother or father unaffected, co-parent status unknown	0.80 (0.34 to 1.85)
Neither parent affected	1.00 (referent group)
Parental separation	0.85 (0.69 to 1.05)
Cannabis use ^a	1.42 (1.06 to 1.90)
Internalizing disorders ^a	
≤2 years	1.10 (0.89 to 1.35)
≥3 years	1.85 (1.14 to 3.00)
Externalizing disorders ^a	1.77 (1.41 to 2.22)
Assaultive trauma ^a	1.11 (0.91 to 1.37)
Nonassaultive trauma ^a	1.02 (0.83 to 1.25)
Perceived substance use of peers	1.11 (0.80 to 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 as follows: offspring birth cohort (1982 to 86 [referent], 1987 to 89, 1990 to 93, 1994, and later; gender; African American v non-African American background; income (<\$30,000, \$30,000 to <\$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. Sixteen was the median age and used as the reference group).

^aDefined as time-varying.

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 1 transition, with increased hazards ranging from about 16 to 28%, broadly in line with other estimates reported in the literature (e.g., Grant et al., 2015; King and Chassin, 2007; Sartor et al., 2007; Trim et al., 2010). 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., Calvert et al., 2010; Jacob et al., 2003; Wong et al., 1999), with maternal AUD not excluded but also not serving as a selection criterion. In the few studies based exclusively on affected mothers (e.g., Bidaut-Russell et al., 1994; Hill et al., 2011) 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., 1981). 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 (Iacono et al., 2008; Sher, 1991; Zucker, 1986). 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 (Grant et al., 2010; Lynskey et al., 2003). This finding may not be surprising in light of the strong comorbidity between cannabis and AUDs (Stinson et al., 2005) and of the genetic overlap between both use of and dependence on the 2 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 United States 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 (Edwards et al., 2014a; Sartor et al., 2007). We did not observe a significant association with alcohol initiation, similar to some (Edwards et al., 2014b; Sartor et al., 2007; Trim et al., 2010) 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 in 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 and 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 and colleagues (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 nonintact 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., Jackson, 2010; Sartor et al., 2007). 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 nonassaultive 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 7 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 4

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. Last, in light of the increasingly permissive legal status of and attitudes toward cannabis in the United States, the elevations of all alcohol outcomes associated with cannabis use support prioritization of studying the underpinnings of this relationship.

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CONFLICT OF INTERESTS

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SUPPORTING INFORMATION

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

Table S1. Listing of questionnaires and neuropsychological tests administered to the participants in the prospective study.

Table S2. Lifetime prevalence of substance use and other risk factors by age group at interview, across all assessments (individuals are included more than once based on their age at interviews).

Table S3. Hazard ratios (and 95% confidence intervals) from the final Cox proportional hazards regression model for time to first drink.

Table S4. Hazard ratios (and 95% confidence intervals) from the final Cox proportional hazards regression model for time from first drink to first DSM-5 alcohol problem.

Table S5. Hazard ratios (and 95% confidence intervals) from the final Cox proportional hazards regression model for time from first drink to onset of DSM-5 AUD.

Table S6. Hazard ratios (and 95% confidence intervals) from the final Cox proportional hazards regression model for time from first AUD problem to first AUD diagnosis.