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Research paper

Reciprocal relationships between substance use and disorders and suicidal ideation and suicide attempts in the Collaborative Study of the Genetics of Alcoholism

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ABSTRACT

Background: Substance use and misuse and suicidal thoughts and behaviors tend to co-occur. The purpose of this study was to examine whether (a) suicidal ideation and attempt are related to onset of alcohol, nicotine and cannabis use and dependence; (b) early use of alcohol, nicotine and cannabis is associated with onset of suicidal ideation and attempt; and (c) whether these associations persist while controlling for covariates, such as family history of alcohol problems, major depression and other internalizing and externalizing disorders.

Methods: The prospective cohort of the Collaborative Study of the Genetics of Alcoholism (COGA; N=3277) was used. Cross-sectional and discrete time logistic regression (i.e. survival) analyses examined associations between suicidal ideation and attempt and onset of alcohol, nicotine and cannabis use and dependence. Survival models also examined whether individual early substance use was related to onset of ideation and attempt.

Results: Ideation was related to 0.71–0.77 odds of onset of subsequent alcohol, nicotine and cannabis use. Attempt was associated with 1.44–1.61 odds of later alcohol, nicotine and cannabis dependence, even after accounting for covariates. Evidence for early substance use being related to subsequent onset of ideation or attempt was limited. Several sex and race differences emerged.

Limitations: The sample was ascertained for family history of alcoholism; not all participants had been followed up allowing for censored observations; reporting bias.

Conclusion: Suicide attempts are associated with increased likelihood of onset of substance dependence.

1. Introduction

Suicide is the second leading cause of death in individuals aged 15–29 years (World Health Organization, 2016). In the United States, rates of documented suicide have increased by 24% between 1999 and 2014 (Curtin et al., 2016). A history of past suicide attempts (SA) are among the most prominent risk factors leading to suicide death and, in and of themselves, contribute to approximately $33,000 in health care and disability costs per attempt (Palmer et al., 1995; Shepard et al., 2015). According to data from the National Comorbidity Survey, about 4.6% of

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U.S. adults report SA (Kessler et al., 1999); however, a more considerable proportion, 13.5%, report a lifetime history of suicidal ideation (SI; Nock et al., 2008). SI often precedes SA. However, many SAs occur in the absence of significant SI and indeed, the etiology of SI and SA have been characterized to be partially distinct (Nock et al., 2016). Some have posited that SA, in the absence of SI, may reflect a liability to impulsive behaviors (Conner et al., 2006; Rimkeviciene et al., 2015; Turecki, 2005), risk for which may be exacerbated in those with a family history of substance use.

Alcohol, nicotine and cannabis use and use disorders have been inconsistently linked to both SI (Nock et al., 2008) and SA (Borges and Loera, 2010). For instance, alcohol use and related problems during adolescence and early adulthood have been prospectively linked to SI (Fergusson et al., 2013) and, cross-sectionally, to SI and SA (Darvishi et al., 2015). Current smoking is associated with SI and SA as well (Poorolajal et al., 2016). Studies have also found that smokers with severe nicotine dependence are more likely than non-smokers to report more frequent and serious SA (Berlin et al., 2015; Lopez-Castroman et al., 2016). Some longitudinal studies have found profound elevations in risk for SI and SA in chronic, heavy and early-onset cannabis users (Delforterie et al., 2015; Silins et al., 2014; van Ours et al., 2013) while other studies have attributed these associations to confounding measures (Price et al., 2009), thus the evidence is inconclusive (Borges et al., 2016). In contrast to this literature, little is known about whether SI and SA are themselves associated with the onset of substance use and substance use disorders. While rates of substance use and use disorders are typically elevated in individuals reporting suicidal thoughts and behaviors, such associations have been primarily attributed to possible pathways that lead from substance use to SI and SA, and evidence for reverse "causality" (i.e. SI/SA leading to increased substance involvement) has not been supported by a limited longitudinal literature (e.g. Covey et al., 2012; van Ours et al., 2013).

The present study examines reciprocal associations between substance involvement (alcohol, nicotine and cannabis use and dependence) and SI and SA in a longitudinal cohort which was partially derived from families at high genetic risk for alcohol use disorders. In a sample of 3277 participants, we examined the extent to which early substance use was associated with subsequent onset of SI and SA, and conversely, whether SI and SA that preceded onset of substance involvement was associated with alcohol, nicotine and cannabis use and dependence.

2. Methods and materials

2.1. Sample

Data were drawn from the baseline through 10-year follow-up data collection conducted with the prospective cohort of the Collaborative Study of the Genetics of Alcoholism (COGA), which is characterized in detail elsewhere (Bucholz et al., 2017). Briefly, the parent COGA study (Begleiter et al., 1995; Reich, 1996) aimed to delineate the genetic and environmental underpinnings of alcoholism and comorbid psychiatric disorders. High risk families were identified through probands who were in inpatient or outpatient clinics for alcohol problems; families with 2 additional relatives with alcoholism were further prioritized. Control families were ascertained from a variety of sources (e.g., driver's license records) and alcoholism was not an exclusion criterion. First degree relatives and, in some cases, members from the extended pedigree, were interviewed. The prospective component of COGA is an ongoing data collection project that aims to understand the impact of genes and environment on substance use and related milestones in youth and young adults, most of whom (86.7%) are at high familial risk for alcoholism. In 2005, adolescent and young adult offspring born from 1982 onwards were recruited from alcoholic and control COGA families described above. The prospective study was designed to be conducted on offspring of ages 12–22 years at their baseline assessment, with at least one parent who was interviewed in the first phases of the parent COGA study. Subsequent assessments occur every two years with data available on 3277 participants (aged 12–26 years; there were some offspring who required repeat tracking and multiple invitations over several years to participate in the baseline interview and as a result 1.3% of offspring were older than age 22 at their first interview). Currently, 2759, 2238, 1733, 1093 and 409 individuals have participated in the 2, 4, 6, 8 and 10 year follow-ups respectively, reflecting data collected between January 2005 and June 2016. For the present study, we used all available data, across all interviews, such that as long as individuals had participated in the baseline, their data were included.

2.2. Measures

Substance use, DSM-IV (American Psychiatric Association, 1994) diagnosis of alcohol, nicotine and cannabis dependence and of other psychiatric disorders (as well as covariates) and measures of suicidal thoughts and behaviors were assessed using the child and adult versions of the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994; Hesselbrock et al., 1999). The assessment is available at: ⟨https://zork.wustl.edu/niaaa/coga_instruments/resources.html⟩.

2.3. Substance use

Respondents were queried about whether they had ever used alcohol, tobacco cigarettes (i.e. nicotine) or cannabis. Those who had used each substance were further asked to recall the age at which they had first used the substance. For all three substances, the median age of onset was 16 years. For analyses (i.e. model 1) in which SI or SA were the dependent variables, early substance use was defined as onset of each substance prior to age 15, based on the bottom quartile of the distribution of ages of onset. Supplemental Fig. S1A–S1C show the distribution of ages of onset for each substance.

2.4. Substance dependence

DSM-IV criteria, assessed with the SSAGA, were used to ascertain lifetime history of alcohol, nicotine and cannabis dependence.

2.5. Suicidal ideation and attempt

All participants were queried about (a) whether they had "ever thought about taking their own life" (ideation: SI) and (b) whether they had "ever tried to kill" themselves (attempt: SA). SA was queried regardless of a history of SI. Importantly, SI and SA items were not nested within the diagnostic section for major depressive disorder (MDD) although individuals who reported SI and SA in that section were coded accordingly as having reported the behavior. For the current analyses, individuals reporting any SA (e.g. even those reporting drug-related SA, 14%) were included. The distribution of ages of onset for SI and SA are shown in Supplemental Figs. S2A and S2B respectively.

2.6. Other covariates

Several additional variables were included to adjust the association between substance use, dependence, SI and SA. These included (a) demographic factors (self-reported sex, African-American ancestry (race), Hispanic ethnicity, and age at last assessment wave (range 12 – 33 years, coded as a median split at 22 years); (b) family history of alcohol use disorder (neither parent, mother only, father only, or both parents); (c) psychiatric disorders, including those broadly defined as externalizing (meeting criteria for any one of the following: conduct, oppositional defiant, or the hyperactivity-impulsivity component of

Table 1
Demographics and Rates of Suicidal Ideation, Suicide Attempt, and Substance Use and Dependence, across all interviews (N=3277).

	All Subjects (N=3277)	Race			Gender		
		European-American (N=2296)	African-American (N=981)	p	Male (N=1615)	Female (N=1662)	p
Age at baseline, mean (SD)	16.1 (3.3)	16.1 (3.3)	16.0 (3.3)	0.1510	16.0 (3.3)	16.1 (3.3)	0.2386
Age at last assessment, mean (SD)	21.7 (5.0)	21.7 (5.0)	21.6 (4.8)	0.6672	21.3 (4.9)	22.1 (5.0)	< 0.0001
Male, %	49.3	49.1	49.7	0.7293	–	–	–
African-American, %	29.9	–	–	–	30.2	29.7	0.7293
Hispanic, %	6.7	5.7	9.2	0.0002	7.9	5.6	0.0090
Lifetime suicidal thoughts and behaviors							
Suicidal ideation, %	30.2	31.6	27.1	0.0104	25.9	34.4	< 0.0001
Suicide attempt, %	5.8	5.6	6.3	0.4278	4.0	7.6	< 0.0001
Lifetime substance use and use disorders							
Alcohol use, %	80.3	81.2	78.3	0.0561	79.8	80.8	0.4752
Early alcohol use, %	22.2	24.7	16.2	< 0.0001	23.4	21.0	0.0974
Alcohol dependence, %	13.3	15.2	8.9	< 0.0001	14.6	12.1	0.0339
Nicotine use, %	46.6	50.3	37.7	< 0.0001	51.1	42.2	< 0.0001
Early nicotine use, %	14.7	16.6	10.5	< 0.0001	14.8	14.7	0.9243
Nicotine dependence, %	20.0	22.0	15.3	< 0.0001	22.9	17.2	< 0.0001
Cannabis use, %	62.9	61.0	67.4	0.0006	66.3	59.7	< 0.0001
Early cannabis use, %	17.3	15.4	21.8	< 0.0001	20.4	14.3	< 0.0001
Cannabis dependence, %	17.4	16.9	18.8	0.1889	23.1	11.9	< 0.0001
Other lifetime characteristics							
Parental alcohol use disorder				< 0.0001			0.2825
Neither parent AUD, %	38.3	36.8	41.9		38.6	38.0	
Maternal-only AUD, %	17.4	15.0	23.0		16.2	18.7	
Paternal-only AUD, %	27.2	27.7	26.0		27.6	26.8	
Both parents AUD, %	17.1	20.6	9.1		17.7	16.6	
Major depressive disorder	22.9	24.7	18.6	0.0001	16.9	28.7	< 0.0001
Externalizing disorders[a]	20.1	17.7	25.6	< 0.0001	25.2	15.1	< 0.0001
Internalizing disorders[b]	7.0	8.0	4.8	0.0011	5.0	9.0	< 0.0001
Number of assessment waves				0.0306			< 0.0001
Baseline only	15.7	16.1	14.9		17.6	14.0	
Baseline+1 wave	15.7	15.3	16.6		16.6	14.9	
Baseline+2 waves	15.8	15.9	15.6		17.5	14.1	
Baseline+3 waves	19.4	18.5	21.4		19.2	19.6	
Baseline+4 waves	21.1	20.8	21.8		18.9	23.2	
Baseline+5 waves	12.3	13.4	9.7		10.2	14.3	

[a] Conduct, oppositional defiant, hyperactivity-impulsivity component of attention-deficit hyperactivity-impulsivity disorder;
[b] Panic, social phobia.

attention-deficit hyperactivity-impulsivity disorder), internalizing disorders (either panic disorder or social phobia) and MDD.

2.7. Data analysis

We took a lifetime perspective for all analyses. Data across all reports made by an individual were included, spanning the baseline through 10-year follow-up period and positive endorsement of a behavior, at any wave, was considered as lifetime history for that behavior. Thus, any individual (N=3277) who had participated in the baseline interview was included.

First, we examined the cross-sectional relationship between substance use, dependence, SI and SA, while accounting for covariates, using logistic regression. For these analyses, there was no requirement for independent variables to have occurred prior to the onset of the dependent measure.

Second, to examine reciprocal and time-varying relationships between substance involvement and suicidal thoughts and behaviors, we adopted a survival analytic approach. Because onset of substance use and SI and SA temporally clustered around age 13–16 years, a time-varying approach was adopted whereby an independent variable was considered a "predictor" only if it had an onset age prior to the age of onset of the dependent variable. For instance, in order for SI to be a predictor for onset of alcohol use, age at onset of SI was required to be less than the age at onset of alcohol use (Supplemental Table S1 provides proportions of individuals reporting substance involvement prior to SI/SA and vice versa). There were multiple reports of age of onset; for the current analyses, the report that was closest in age to the age at interview was taken, assuming that it would minimize recall bias. All covariates were also coded to precede the onset of the dependent measure as well.

Person-year data were fitted to discrete time logistic regression models using PROC SURVEYLOGISTIC (SAS v9), which adjusts for complex survey designs, such as data clustered in families, by using a robust variance estimator. After an initial analysis that only included gender, AA race/ethnicity, Hispanic status and age at last interview as covariates, a model that included all covariates was fitted to the data to obtain an adjusted odds-ratio. In addition, we tested for interactions with sex (female as reference group) and race (European-American as reference group) in separate models that only accounted for demographic variables. Significant interaction terms were further adjusted for other covariates. The models fitted to the data are described below. For Model 1, SI and SA were the dependent variables and early substance use was the independent variable; in other words, we examined whether early substance use "predicted" onset of SI and SA, as has been frequently done in prior longitudinal studies. We elected to focus on early substance use for Model 1 because, as shown in Supplemental Figures, the median age of onset of SI and SA preceded the typical median age of onset of alcohol, nicotine and cannabis use. In contrast, in Models 2–3, substance involvement

Table 2
Odds-ratios with their 95% confidence intervals from logistic regression documenting cross-sectional association between a lifetime history of suicidal ideation, suicide attempt and use and dependence of alcohol, nicotine and cannabis (N=3277).

	Adjusted for gender, race, Hispanic, age	Adjusted for all covariates[a]
Suicidal ideation (SI)		
Alcohol use	2.14 (1.67, 2.74)	1.42 (1.05, 1.93)
Early alcohol use	2.22 (1.86, 2.64)	1.80 (1.45, 2.24)
Alcohol dependence	2.91 (2.35, 3.61)	2.03 (1.56, 2.64)
Nicotine use	2.50 (2.12, 2.95)	1.81 (1.48, 2.21)
Early nicotine use	2.00 (1.63, 2.44)	1.83 (1.43, 2.34)
Nicotine dependence	2.79 (2.32, 3.36)	2.10 (1.67, 2.64)
Cannabis use	2.34 (1.95, 2.80)	1.74 (1.40, 2.16)
Early cannabis use	2.22 (1.83, 2.69)	2.07 (1.64, 2.62)
Cannabis dependence	3.25 (2.67, 3.96)	2.22 (1.74, 2.82)
Suicide attempt (SA)		
Alcohol use	6.92 (2.76, 17.31)	4.42 (1.70, 11.49)
Early alcohol use	3.26 (2.40, 4.44)	2.41 (1.72, 3.37)
Alcohol dependence	3.17 (2.26, 4.45)	1.93 (1.33, 2.79)
Nicotine use	3.71 (2.59, 5.31)	2.39 (1.63, 3.52)
Early nicotine use	3.01 (2.17, 4.17)	2.71 (1.89, 3.89)
Nicotine dependence	3.51 (2.56, 4.82)	2.39 (1.69, 3.38)
Cannabis use	3.58 (2.29, 5.58)	2.25 (1.41, 3.58)
Early cannabis use	3.17 (2.30, 4.36)	2.56 (1.80, 3.66)
Cannabis dependence	2.50 (1.79, 3.49)	1.47 (1.02, 2.13)

[a] Covariates: AA: race is African-American; H: Hispanic; EDx: Externalizing disorders (conduct, oppositional defiant, hyperactivity-impulsivity component of attention-deficit hyperactivity-impulsivity disorder); IDx: Internalizing disorders (panic, social phobia); MDD: Major depressive disorder; M-AUD: Maternal-only history of alcohol use disorder; P-AUD: Paternal-only history of alcohol use disorder; B-AUD: Both maternal and paternal history of alcohol use disorder; 22-yrs: aged < 22 at current last assessment; 2, 4, 6, 8, 10-yr FU: participation in 10 year follow-up assessments; S: Male sex.

measures were the dependent variables, and we examined the reciprocal pathway from SI and SA to onset of substance use and dependence.

Model 1: Whether early onset (≤14 years) of alcohol, nicotine and cannabis use is associated with onset of (a) SI and (b) SA;.

Model 2: Whether SI is associated with onset of (a) alcohol, (b) nicotine and (c) cannabis use and dependence;.

Model 3: Whether SA is associated with onset of (a) alcohol, (b) nicotine and (c) cannabis use and dependence.

3. Results

3.1. Sample characteristics

Substance use (46.6–80.3%), including early use (onset age≤14 years: 14.7–22.2%) was common by the most recent interview (Table 1). African-American participants were less likely to report early alcohol and nicotine use but more likely to report early cannabis use. Males were more likely to report early cannabis use. Combining data across the six assessments, 13.3%, 20.0% and 17.4% of the respondents met criteria for a lifetime history of alcohol, nicotine and cannabis dependence respectively. Correlations across the substance use measures ranged from 0.77 to 0.88 and from 0.61 to 0.67 across the substance dependence measures. SI was reported by 30.2% while SA was reported by 5.8% of respondents. Despite the items being non-nested, no one reported SA without also reporting SI. Both SI and SA had a median onset age of 15 years and were more commonly reported by females than males; SI was significantly less frequently reported by African-American participants, but no significant ethnic differences emerged for SA. Overall, SI and SA were considerably more common in those reporting early substance use (Supplemental Table S2), while substance use and dependence were more common in those with a prior history of SI and SA (Supplemental Table S3). A matrix of the tetrachoric correlations between all measures is presented in Supplemental Table S4.

3.2. Cross-sectional logistic regression

Even after adjustment for covariates, a history of SI was associated with 1.42–2.22 odds of use and dependence of alcohol, nicotine and cannabis (Table 2). Associations with SA were even stronger, with odds-ratios ranging from 1.47 to 4.42. Early substance use was also associated with both SI and SA, even after adjustment for covariates (Odds Ratio – OR - ranging from 1.80 to 2.71).

3.3. Discrete time logistic regression

Is early substance use associated with onset of suicidal ideation and attempt?

Model 1: As shown in Table 3, early alcohol and nicotine use respectively were associated with 1.49 and 1.66 increased odds of SA (when adjusting for demographic covariates alone), although these associations were no longer significant after adjustment for the full set

Table 3
Early alcohol, nicotine, and cannabis use (independent variables) and onset of suicidal ideation and attempt (dependent) – odds-ratios and 95% confidence intervals from discrete-time hazard analyses (N=3277).

	Onset of Suicidal Ideation	*Onset of Suicide Attempt*
Early Alcohol Use		
Adjusted for gender, race, Hispanic, age	1.09 (0.93, 1.28)	1.49 (1.07, 2.07)
Adjusted for all covariates[a]	0.99 (0.84, 1.17)	1.29 (0.90, 1.84)
	not S, not AA, H, 22-yrs, M-AUD, P-AUD, B-AUD, 8-yr FU, no MDD, IDx, EDx	not S, H, not 22-yrs, M-AUD, B-AUD, no MDD, EDx
Early Nicotine Use		
Adjusted for gender, race, Hispanic, age	1.10 (0.91, 1.33)	1.66 (1.17, 2.37)
Adjusted for all covariates[a]	0.99 (0.81, 1.20)	1.33 (0.91, 1.95)
	not S, not AA, H, 22-yrs, M-AUD, P-AUD, B-AUD, 8-yr FU, no MDD, IDx, EDx	not S, H, M-AUD, B-AUD, no MDD, EDx
Early Cannabis Use		
Adjusted for gender, race, Hispanic, age	1.06 (0.88, 1.27)	1.45 (1.00, 2.12)
Adjusted for all covariates[a]	0.94 (0.77, 1.13)	1.13 (0.76, 1.67)
	not S, not AA, H, 22-yrs, M-AUD, P-AUD, B-AUD, 8-yr FU, no MDD, IDx, EDx	not S, H, M-AUD, B-AUD, no MDD, EDx

[a] Only significant covariates are listed: AA: race is African-American; H: Hispanic; EDx: Externalizing disorders (conduct, oppositional defiant, hyperactivity-impulsivity component of attention-deficit hyperactivity-impulsivity disorder); IDx: Internalizing disorders (panic, social phobia); MDD: Major depressive disorder; M-AUD: Maternal-only history of alcohol use disorder; P-AUD: Paternal-only history of alcohol use disorder; B-AUD: Both maternal and paternal history of alcohol use disorder; 22-yrs: aged < 22 at current last assessment; 2, 4, 6, 8, 10-yr FU: participation in follow-up assessments; S: Male sex.

Table 4
The role of race and gender on the relationship between suicidal ideation and attempt and use as well as dependence of alcohol, nicotine and cannabis, adjusted for main effects of gender, race, Hispanic, and age (N=3277). Results represent odds-ratios (95% confidence intervals).

	Main effect of Predictor	Predictor x Male	Predictor x Male (adj[a])	Predictor x AA	Predictor x AA (adj[a])
Early Alcohol use -> SI & SA					
Suicidal ideation	1.09 (0.93, 1.28)	0.67 (0.51, 0.88)	0.63 (0.48, 0.84)	0.72 (0.49, 1.04)	–
Suicide attempt	1.49 (1.07, 2.07)	0.54 (0.31, 0.93)	0.43 (0.24, 0.75)	0.76 (0.36, 1.61)	–
Early Nicotine use -> SI & SA					
Suicidal ideation	1.10 (0.91, 1.33)	0.74 (0.53, 1.04)	–	0.50 (0.30, 0.82)	0.52 (0.32, 0.86)
Suicide attempt	1.66 (1.17, 2.37)	0.37 (0.19, 0.71)	0.33 (0.17, 0.64)	0.29 (0.09, 0.94)	0.31 (0.10, 1.00)
Early Cannabis use -> SI & SA					
Suicidal ideation	1.06 (0.88, 1.27)	0.79 (0.58, 1.10)	–	0.64 (0.45, 0.92)	0.70 (0.49, 1.00)
Suicide attempt	1.45 (1.00, 2.12)	0.42 (0.23, 0.77)	0.37 (0.20, 0.69)	0.34 (0.15, 0.77)	0.35 (0.15, 0.79)
SI -> substance use/dependence					
Alcohol use	0.61 (0.50, 0.75)	0.94 (0.63, 1.42)	–	0.77 (0.48, 1.25)	–
Alcohol dependence	1.17 (0.95, 1.44)	1.09 (0.78, 1.53)	–	0.52 (0.34, 0.80)	0.49 (0.32, 0.77)
Nicotine use	0.66 (0.57, 0.77)	1.33 (1.01, 1.74)	1.27 (0.96, 1.67)	0.69 (0.50, 0.94)	0.69 (0.50, 0.95)
Nicotine dependence	1.15 (0.97, 1.36)	1.38 (1.04, 1.84)	1.19 (0.89, 1.58)	0.69 (0.49, 0.98)	0.68 (0.47, 0.97)
Cannabis use	0.68 (0.58, 0.79)	1.14 (0.84, 1.55)	–	1.20 (0.85, 1.71)	–
Cannabis dependence	1.17 (0.97, 1.41)	2.04 (1.50, 2.78)	2.02 (1.47, 2.78)	0.85 (0.59, 1.22)	–
SA -> substance use/dependence					
Alcohol use	0.94 (0.72, 1.25)	0.95 (0.52, 1.71)	–	0.69 (0.40, 1.19)	–
Alcohol dependence	1.68 (1.21, 2.34)	0.99 (0.53, 1.85)	–	0.45 (0.22, 0.92)	0.40 (0.19, 0.84)
Nicotine use	1.02 (0.76, 1.37)	1.26 (0.69, 2.30)	–	0.67 (0.37, 1.21)	–
Nicotine dependence	1.68 (1.28, 2.22)	1.08 (0.61, 1.91)		0.60 (0.34, 1.07)	
Cannabis use	0.94 (0.70, 1.26)	1.13 (0.60, 2.13)	–	1.40 (0.79, 2.46)	–
Cannabis dependence	1.61 (1.21, 2.16)	2.06 (1.19, 3.56)	2.43 (1.41, 4.17)	0.59 (0.31, 1.09)	–

[a] Adjusted for: AA: race is African-American; H: Hispanic, EDx: Externalizing disorders (conduct, oppositional defiant, hyperactivity-impulsivity component of attention-deficit hyperactivity-impulsivity disorder); IDx: Internalizing disorders (panic, social phobia); MDD: Major depressive disorder; M-AUD: Maternal-only history of alcohol use disorder; P-AUD: Paternal-only history of alcohol use disorder; B-AUD: Both maternal and paternal history of alcohol use disorder; 22-yrs: aged < 22 at current last assessment; 2, 4, 6, 8, 10-yr FU: participation in follow-up assessments; S: Male sex.

of covariates (Supplemental Table S5), most notably, MDD (OR=0.33–0.59) and having two parents with alcohol use disorders (OR=1.59–2.22). The negative association between MDD and onset of SI and SA is likely due to its time-varying nature (i.e. the requirement for it to have occurred prior to onset of SI and SA) as a lifetime history of MDD (i.e. occurring before, after or in the same year as SI or SA) resulted in highly significant risk-related associations (OR=5.31–6.10; not shown). Early substance use was not associated with onset of SI. However, across several analyses, there was substantial evidence for interactions of early substance use with sex and race (Table 4). While the main effect of early substance use was not strongly related to onset of SI or SA, males with a history of early substance use that preceded onset of SA were less likely than early substance-using females to report onset of SA (as well as SI for early alcohol use). Furthermore, African-Americans reporting early nicotine and early cannabis use were at 0.31–0.70 adjusted odds of onset of SI and SA relative to their European-American counterparts who had used nicotine or cannabis at an early age.

Are suicidal ideation and attempt associated with onset of substance involvement?

Model 2: Even though SI and SA were associated with increased odds of substance use and dependence, when temporality was taken into account (i.e. SI preceding substance use and dependence), prior history of SI was associated with a lower likelihood of onset of substance use (Table 5; OR=0.61–0.68) and these negative associations remained significant in adjusted models, despite strong contributions of covariates such as externalizing disorders (OR=1.33–1.67), MDD (OR=0.56–0.61) and family history (father-only, mother-only,

Table 5
Lifetime history of suicide ideation (SI - independent) and onset of alcohol, nicotine and cannabis use and dependence (dependent) - odds ratios with their 95% Confidence Intervals from discrete-time hazard analyses (N=3277). Models "adjusted for all covariates" report multivariate (i.e., adjusted odds – ratios; Supplemental Table S5 for covariate odds – ratios).

Suicidal ideation	Onset of Alcohol Use	Onset of Alcohol Dependence
Adjusted for gender, race, Hispanic and age	0.61 (0.50, 0.75)	1.17 (0.95, 1.44)
Adjusted for all covariates[a]	0.71 (0.55, 0.91)	1.15 (0.90, 1.45)
	not AA, M-AUD, P-AUD, B-AUD, no MDD, EDx	not AA, not 22-yrs, M-AUD, P-AUD, B-AUD, no MDD, IDx, EDx
	Onset of Nicotine Use	**Onset of Nicotine Dependence**
Adjusted for gender, race, Hispanic and age	0.66 (0.57, 0.77)	1.15 (0.97, 1.36)
Adjusted for all covariates[a]	0.74 (0.62, 0.88)	1.13 (0.93, 1.38)
	S, not AA, not 22-yrs, M-AUD, P-AUD, B-AUD, not 6, 8, 10-yr FU, no MDD, EDx	S, not AA, not 22-yrs, M-AUD, P-AUD, B-AUD, not 10-yr FU, no MDD, EDx
	Onset of Cannabis Use	**Onset of Cannabis Dependence**
Adjusted for gender, race, Hispnic and age	0.68 (0.58, 0.79)	1.17 (0.97, 1.41)
Adjusted for all covariates[a]	0.77 (0.65, 0.93)	1.12 (0.90, 1.39)
	S, AA, H, M-AUD, P-AUD, B-AUD, not 10-yr FU, no MDD, EDx	S, H, M-AUD, P-AUD, B-AUD, no MDD, IDx, EDx

[a] Only significant covariates are listed: AA: race is African-American; H: Hispanic; EDx: Externalizing disorders (conduct, oppositional defiant, hyperactivity-impulsivity component of attention-deficit hyperactivity-impulsivity disorder); IDx: Internalizing disorders (panic, social phobia); MDD: Major depressive disorder; M-AUD: Maternal-only history of alcohol use disorder; P-AUD: Paternal-only history of alcohol use disorder; B-AUD: Both maternal and paternal history of alcohol use disorder; 22-yrs: aged < 22 at current last assessment; 2, 4, 6, 8, 10-yr FU: participation in follow-up assessments; S: Male sex.

Table 6
Lifetime history of suicide attempt (SA - independent) and onset of alcohol, nicotine and cannabis use and dependence (dependent) - odds ratios with their 95% Confidence Intervals from discrete-time hazard analyses (N=3277). Models adjusted for all covariates report multivariate (i.e., adjusted odds – ratios; Supplemental Table S5 for covariate odds – ratios).

Suicide Attempt	Onset of Alcohol Use	Onset of Alcohol Dependence
Adjusted for gender, race, Hispanic and age	0.94 (0.72, 1.25)	1.68 (1.21, 2.34)
Adjusted for all covariates[a]	1.17 (0.88, 1.55)	1.60 (1.12, 2.28)
	not AA, M-AUD, P-AUD, B-AUD, no MDD, EDx	not AA, not 22-yrs, M-AUD, P-AUD, B-AUD, no MDD, IDx, EDx
	Onset of Nicotine Use	**Onset of Nicotine Dependence**
Adjusted for gender, race, Hispanic and age	1.02 (0.76, 1.37)	1.68 (1.28, 2.22)
Adjusted for all covariates[a]	1.19 (0.88, 1.61)	1.61 (1.19, 2.17)
	S, not AA, not 22-yrs, M-AUD, P-AUD, B-AUD, not 6, 8, 10-yr FU, no MDD, EDx	S, not AA, not 22-yrs, M-AUD, P-AUD, B-AUD, not 10-yr FU, no MDD, EDx
	Onset of Cannabis Use	**Onset of Cannabis Dependence**
Adjusted for gender, race, Hispanic and age	0.94 (0.70, 1.26)	1.61 (1.21, 2.16)
Adjusted for all covariates[a]	1.04 (0.79, 1.38)	1.44 (1.06, 1.96)
	S, AA, M-AUD, P-AUD, B-AUD, not 10-yr FU, no MDD, EDx	S, H, M-AUD, P-AUD, B-AUD, no MDD, IDx, EDx

[a] Only significant covariates are listed: AA: race is African-American; H: Hispanic; EDx: Externalizing disorders (conduct, oppositional defiant, hyperactivity-impulsivity component of attention-deficit hyperactivity-impulsivity disorder); IDx: Internalizing disorders (panic, social phobia); MDD: Major depressive disorder; M-AUD: Maternal-only history of alcohol use disorder; P-AUD: Paternal-only history of alcohol use disorder; B-AUD: Both maternal and paternal history of alcohol use disorder; 22-yrs: aged < 22 at current last assessment; 2, 4, 6, 8, 10-yr FU: participation in follow-up assessments; S: Male sex.

and both parents; OR=1.57–2.21; Supplemental Table S6). When examining interactions between SI and sex and race, several additional significant findings emerged. Even though there was no main effect of SI on the onset of cannabis dependence, males with SI were more likely than females with SI to meet criteria for cannabis dependence. Likewise, despite an absence of main effects, African-Americans with SI were less likely than their European-American counterparts to meet criteria for alcohol dependence (Table 4). Also, males with SI were more likely than females with SI to meet criteria for both nicotine use and dependence, although these results did not hold after accounting for covariates. Finally, African-Americans with SI were less likely than European-Americans with SI to meet criteria for nicotine use and dependence.

Model 3: A prior history of SA was not associated with onset of alcohol, nicotine or cannabis use (OR=1.04–1.19; Table 6). However, a prior history of SA was associated with 1.44–1.61 adjusted odds of onset of alcohol, nicotine and cannabis dependence. Similar to results for Model 2, males with SA were more likely than their female counterparts to meet criteria for cannabis dependence (Table 4). Also, like in Model 2, MDD (OR=0.47–0.70), externalizing disorders (OR=1.30–2.30) and family history of alcohol use disorders, particularly having two parents with alcohol use disorder (OR=1.73–2.32), were the strongest correlates of onset of substance use and dependence (Supplemental Table S7).

4. Discussion

In a sample enriched for familial liability to substance use, particularly alcohol dependence, we find support for associations between substance involvement, SI and SA. When examined using cross-sectional approaches, these associations were significant and positive, ranging from 1.42 (SI and alcohol use) to 4.42 (SA and alcohol use), and were robust to the inclusion of covariates. These findings suggest that, across the lifetime, substance involvement and suicidal thoughts and behaviors are, somewhat independently, associated. These results are highly consistent with several studies, and in particular, with two recent meta-analyses for alcohol use disorders and tobacco smoking. The first meta-analysis (Darvishi et al., 2015) of 420,732 participants concluded that alcohol use disorders were associated with suicidal ideation (OR=1.86), attempt (OR=3.13) and completion (OR=2.59). The second (Poorolajal and Darvishi, 2016) identified 63 studies on the relationship between current smoking and suicide (N=8,063,634) and found significant associations for suicidal ideation, plan, attempt and completion (OR > 2.0). These findings also support results from another meta-analysis which suggests that chronic, but not acute, cannabis use is associated with suicidal ideation and attempt (Borges et al., 2016).

Next, we examined whether prior early substance use increases the likelihood of onset of SI and SA. In our data, evidence for this hypothesis was limited and most associations, which were with SA, were explained by comorbid factors, such as MDD, family history and externalizing disorders. Evidence that males with early substance use were less likely than females with early substance use to report SA is also consistent with the notion that early substance use in women might be indicative of a liability to both internalizing and externalizing problems (Brady et al., 1999; Kessler et al., 1997). Males with early substance use may be more likely to progress to other externalizing behaviors while females with early substance use may be vulnerable to future problems with depressed mood and suicidal thoughts as well (Kandel et al., 1991). Similarly, early substance use was less likely to be related to SI and SA in African-Americans relative to their European-American counterparts. Future studies with larger sample sizes for African-American participants might be better suited to the identification of aspects of substance use and misuse that relate to SI and SA in this population. Importantly, MDD diagnosis that preceded early substance use and SI as well as SA exerted a protective influence (OR=0.33–0.59; Table S5). We attribute this negative association (i.e. OR < 1) to the time-varying nature of MDD because analyses in which MDD was not required to have occurred prior to the onset of the dependent variable showed OR > 5. Thus, the OR associated with MDD reflects meeting criteria for a diagnosis at a fairly young age, which may be related to even earlier, but not subsequent, onsets of SI and SA. We, unfortunately, did not have age of onset data on first dysphoric or anhedonic symptom to be able to evaluate their time-varying effect on SI and SA.

We also examined whether a history of SI or SA was associated with onset of substance use and dependence. Here, an interesting divergence between SI and SA was noted. Unlike the cross-sectional findings, a prior history of SI was associated with a reduced likelihood of the onset of alcohol, nicotine and cannabis use (OR=0.71–0.77). This was not the case for SA. Because onset of SI and substance use tend to cluster around similar ages (Supplemental Figs. S1A, S1B, S1C, S2A and S2B), we presume that these “protective” effects might reflect a trajectory indicative of escalating problems with internalizing beha-

viors (e.g. MDD) that are independent of experimentation or self-medication with substances. Early SI might represent significant depressed mood which may also reduce the chance that individuals will interface with delinquent peer groups (potentially, due to peer rejection) who might have otherwise promoted substance use (Hussong et al., 2011). In fact, a prior study of these data show similar protective effects of a score assessing difficulties with family and peers on age of onset of alcohol use (Kuperman et al., 2013). This hypothesis is also supported by the stronger correlation between MDD and SI (r=0.74) rather than SA (r=0.52). Alternatively, those with early SI (or MDD, OR=0.47–0.71; Tables S6 and S7) may be at greater risk for very early, but not later, onset of substance use. In other words, these findings may support the idea that early SI is preceded by even earlier substance use and is unlikely to be a "predictor" of it. In addition, this finding may also be sample-specific. Individuals in COGA are at high genetic and environmental liability for onset of substance use; thus, if SI precedes this expected behavior of substance use, it may reflect a developmental pattern of psychopathology that does not increase risk for substance-related onsets.

SA was associated with onset of alcohol, nicotine and cannabis dependence, even after accounting for comorbid psychiatric diagnoses and family history of alcohol use disorder, with the effects on cannabis dependence being stronger in males. This finding is largely, but not entirely, inconsistent with several prior studies that have examined this reciprocal path. For instance, one large-scale longitudinal study found a dose-dependent relationship between frequent cannabis use and SI (van Ours et al., 2013) in males but did not find evidence for prior SI predicting increases in cannabis use. Similarly, while numerous studies have reported that ever and current smoking (Lucas et al., 2013) are prospectively associated with suicide, at least one study found that prior suicide-related outcomes were not associated with subsequent current smoking (Covey et al., 2012). Despite this, increases in smoking subsequent to SA might reflect self-medication for depressed mood (Hughes, 2008). Finally, the role of both acute and chronic alcohol use in SA has also been closely studied (Bagge et al., 2008; Conner et al., 2014). Within this literature, there are several proposed pathways that support our finding. For instance, escalation in alcohol use, subsequent to ideation, may reflect changes in drinking expectancies or motives or to facilitate SA. Distal effects have also been proposed – for instance, alterations in the residential, educational or vocational environment subsequent to SA, as well as other profound environmental changes (e.g., hospitalization) might result in escalations in problematic alcohol use (Bagge and Sher, 2008).

Our finding that SA is associated with onset of alcohol, nicotine and cannabis dependence might be interpreted in several ways. First, increased likelihood of substance use disorders, particularly in those with SA, might reflect escalations in substance use for negative affect regulation (i.e. self-medication: Khantzian, 1997; or coping: Esposito-Smythers et al., 2004), as has been noted for mood and anxiety disorders (e.g. Bolton et al., 2009; Crum et al., 2013; Dawes et al., 2008; Robinson et al., 2011). Psychiatric disorders such as MDD, especially in their active form (Breslau et al., 2004), predict nicotine dependence (e.g. Breslau et al., 1993). Alternatively, this association may reflect a shared liability to behaviors that include negative affect as a component. Negative affect, including depressed mood (e.g. withdrawal) are hallmark features of substance use disorders (Brady et al., 2005) as well as SI and SA. Studies have also suggested that shared genetic influences may be responsible for the comorbidity across MDD and alcohol (Kendler et al., 1993) and nicotine dependence (Edwards et al., 2011; Thornton et al., 2016). However, adjustment for MDD did not abolish our association suggesting that this shared liability may be more general than MDD (e.g. Ellingson et al., 2016). Third, increased likelihood of substance use disorders in those with a prior history of SA may reflect a general predisposition towards impulsive and aggressive behaviors (Turecki, 2005). It is noteworthy that despite all individuals who reported SA also reporting SI (i.e., no attempts without ideation), results differed for the two outcomes. This finding might indicate that SA represents an escalation in severity of suicidal thoughts and behaviors and that new risk and protective influences might come into play at this more severe stage. Also, that significant effects in our data might relate to ascertainment and individuals being at higher familial liability for substance use and misuse cannot be discounted as such internalizing pathways are commonly noted in offspring of individuals with alcoholism (e.g., Hussong et al., 2011).

Several limitations of the current study are noteworthy. First, the generalizability of our findings, especially the observation of null associations, should be viewed in the context of ascertainment. The sample recruited offspring, many of whom were at high familial liability to alcohol use disorders. Consequently, only 38.3% of the offspring report that neither of their parents had an alcohol use disorder. Given the co-aggregation of other substance use and suicidal thoughts and behaviors with alcohol use disorders, it is not surprising that the prevalence of substance involvement in this sample is higher than estimates from the general U.S. population (e.g. 44.8% in the National Household Survey of Drug Use and Health versus 63% in COGA; U.S. Department of Heath and Human Services, 2014). Similarly, our estimate of SI (30.2%) is considerably higher than that for similarly aged individuals in the National Comorbidity Survey – Replication (18%; (Kessler and Merikangas, 2004)). Even though we control for family history, and it exerts significant effect, it is possible that our study design influenced the pattern of our results. It is also noteworthy that rates of cigarette smoking exceed those of cannabis use in this sample, however, this observation is consistent with estimates from the recent Monitoring the Future Survey (Johnston et al., 2016). Second, even though the study was designed to be longitudinal, it is ongoing, and not all participants have had the opportunity to participate in later follow-ups. Thus, younger participants may have had fewer opportunities to report their substance use behavior and may not have passed the age of risk for onset of cannabis use or of developing substance dependence. To leverage this study design, we employed survival models which allowed for such right censored data and we included age at last interview as a covariate. A related concern is attrition – as the study is ongoing, non-participation in subsequent waves is not necessarily indicative of attrition. However, analyses of those who were eligible to have participated in the 6 year follow-up found no significant differences related to substance use behaviors or psychiatric characteristics. We also adjusted for number of follow-ups in all analyses. Third, recall bias may have influenced reports of all variables, particularly age of onset. We attempted to ameliorate this concern by using multiple reports of age of onset and selecting the one that was closest in age to the age of the respondent at the time of the interview. This may have resulted in higher ages being ascribed to onset. On average, the difference between first, earliest and the age of onset selected by us, for any variable, was 1 year. Fourth, as we required independent variables (and covariates) to be time-varying, we were only able to focus on early substance use as "predictors" of SI and SA, as the onset age for SI and SA was fairly low and typically preceded the onset of substance use and dependence. That is, in many instances, the typical age of onset of substance use and dependence occurred after the onset of SI and SA. Despite this, caution is needed in deriving any causal inference, as recall bias and other unmeasured confounders may be responsible for observed patterns of results. Fifth, due to their low prevalence, particularly at earlier ages, we did not examine illicit drugs other than cannabis. Sixth, when examining early use and dependence, never users were treated the same as late and non-dependent users (i.e., coded as "0") respectively. This creates a confound, in that associations that are specific to early onset of use or onset of dependence cannot be disentangled for associations with onset of any use. Future studies should study substance involvement as a multi-stage process. Seventh, despite the longitudinal design, we did not study whether substance involvement was associated with new onsets of SI and SA, nor do we have data to examine completed suicides. Such

an analysis will be more feasible when greater numbers of participants complete further follow-up assessments. Similarly, we did not examine measures of frequent, chronic or heavy substance use, which have been implicated as risk factors for the onset of SI and SA.

Our analyses call for further studies that outline the nature of these associations – for instance, to what extent are these associations representative of causal pathways or indicative of shared predispositions? Importantly, future efforts should be targeted at understanding the role of both depression and impulsivity (Turecki, 2005), especially when considering the relationship between SA and substance involvement. For instance, studies have reported stronger associations between unplanned SA and substance involvement (Borges et al., 2010; Delforterie et al., 2015) indicating the potential role of impulsivity but a more systematic investigation of potential mediators and modifiers is necessary. Finally, from a clinical perspective, our results suggest that in individuals at high familial risk for substance involvement, a history of SA should be viewed as a potential harbinger of escalating substance use, potentially leading to dependence. Counselling may be required to ensure that environmental alterations subsequent to SA do not result in more frequent substance use. Further, in treating mood disruptions that might be related to SA, clinicians should consider therapies that include components that address the pitfalls of self-medication or account for other shared risk factors that may lead to substance dependence in those with a history of SA.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2016.12.060.

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