

The Impact of Peer Substance Use and Polygenic Risk on Trajectories of Heavy Episodic Drinking Across Adolescence and Emerging Adulthood

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Background: Heavy episodic drinking is developmentally normative among adolescents and young adults, but is linked to adverse consequences in later life, such as drug and alcohol dependence. Genetic and peer influences are robust predictors of heavy episodic drinking in youth, but little is known about the interplay between polygenic risk and peer influences as they impact developmental patterns of heavy episodic drinking.

Methods: Data were from a multisite prospective study of alcohol use among adolescents and young adults with genome-wide association data ($n = 412$). Generalized linear mixed models were used to characterize the initial status and slopes of heavy episodic drinking between age 15 and 28. Polygenic risk scores (PRS) were derived from a separate genome-wide association study for alcohol dependence and examined for their interaction with substance use among the adolescents' closest friends in predicting the initial status and slopes of heavy episodic drinking.

Results: Close friend substance use was a robust predictor of adolescent heavy episodic drinking, even after controlling for parental knowledge and peer substance use in the school. PRS were predictive of the initial status and early patterns of heavy episodic drinking in males, but not in females. No interaction was detected between PRS and close friend substance use for heavy episodic drinking trajectories in either males or females.

Conclusions: Although substance use among close friends and genetic influences play an important role in predicting heavy episodic drinking trajectories, particularly during the late adolescent to early adult years, we found no evidence of interaction between these influences after controlling for other social processes, such as parental knowledge and broader substance use among other peers outside of close friends. The use of longitudinal models and accounting for multiple social influences may be crucial for future studies focused on uncovering gene-environment interplay. Clinical implications are also discussed.

Key Words: Heavy Episodic Drinking, Peer Influences, Development, Polygenic Risk Score, Gene-Environment Interaction.

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HEAVY EPISODIC DRINKING behaviors, defined as the consumption of large volumes of alcohol (e.g., 5 or more standard drinks) within a set period of time (Gmel et al., 2011; Murgraff et al., 1999), are common among adolescents and young adults. In the United States, approximately 20% of high-school seniors reported engaging in heavy episodic drinking and nearly 11% reported extreme heavy episodic drinking (i.e., 10 or more drinks on a single occasion) in the past 2 weeks (Patrick et al., 2013). Compared to adolescents who abstain from heavy episodic drinking, adolescents who engage in heavy episodic drinking earlier in life and with high frequency are elevated for multiple risk factors (e.g., parental psychopathology, family conflict, and stress; Chassin et al., 2002) and are at the highest risk for developing negative outcomes in later life, including a higher incidence of adult drug and alcohol dependence (Chassin et al., 2002; Schulenberg et al., 1996) and health and medical problems (Oesterle et al., 2004). As the

initiation and progression in heavy episodic drinking coincide with several hallmarks of normative adolescent development (e.g., puberty, autonomy from adults, increased impulsivity; Chassin et al., 2002), understanding its etiology requires a developmental perspective that accounts for individual, family, and peer influences (Shin et al., 2009). The current investigation focused on understanding how genetic and environmental influences impact developmental patterns of heavy episodic drinking during this critical developmental period.

The importance of genetic factors for alcohol-related phenotypes has been well-established through twin studies (Kno-pik et al., 2004; Prescott and Kendler, 1999) and more recently through genome-wide association studies (GWAS). For instance, twin studies have shown that additive genetic influences account for 18 to 30% of the variance in alcohol-related phenotypes (i.e., heavy episodic drinking) for young adult females and 39 to 57% for young adult males (King et al., 2005), while GWAS have identified several single-nucleotide polymorphisms (SNPs) that may contribute to this variance, including those involved in the transcription of enzymes responsible for alcohol metabolism (Bierut et al., 2012; Gelernter et al., 2014). However, genetically associated markers identified through GWAS only account for a fraction of the total genetic variance. Using a method called genome-wide complex trait analysis (Yang et al., 2011) and data from Netherlands Twin Register, 1 study estimated that the total variance explained by common SNPs for adult alcohol use problems was 33%, suggesting that a large portion of the heritability can be explained by variations in common SNPs in aggregate, rather than in isolation (Mbarek et al., 2015). These findings reinforce the idea that complex traits are largely influenced by polygenic variation, rather than 1 or a few SNPs (Plomin et al., 2009; Purcell et al., 2009). Researchers can index the composite effects of common SNPs by computing polygenic risk scores (PRS), which represent a quantitative distribution of aggregate genetic liability to predict the phenotypic variance in 1 sample using genome-wide information from a separate, independent sample. The PRS approach was first applied to predict the risk of bipolar disorder and schizophrenia (Purcell et al., 2009), but has since been applied to predict risk for alcohol-related phenotypes (Kos et al., 2013; Salvatore et al., 2014b; Vink et al., 2014), explaining about 0.63 to 1.1% of variation in alcohol use behaviors. Although this is a relatively small amount of the total variance, it still constitutes a larger effect than single SNPs confer independently (Plomin et al., 2009).

Furthermore, genetic influences are known to interact with the environment (gene-environment interaction [$G \times E$]; Dick and Kendler, 2012). Twin studies have provided evidence of these effects with respect to peer substance use and genetic risk for adolescent alcohol use behaviors. Adolescents with high genetic liability for alcohol and other substance use were more vulnerable to the adverse influences of their best friends' substance use than adolescents with low genetic liability (Harden et al., 2008). The interplay between

genetic and peer influences for adolescent alcohol use behaviors is also evidenced by genetic association studies, where for example, adults carrying at least 1 copy of the long allele of the dopamine D4 receptor gene (*DRD4*) were more influenced by their close friends' alcohol use in the development of their own heavy episodic drinking than those without the long allele (Mrug and Windle, 2014), although this study was limited by a relatively small sample size and focused on only a single polymorphism in *DRD4*. Investigations with respect to PRS in the context of $G \times E$ have recently emerged as well, as high PRS for alcohol problems was recently shown to be more robust in predicting alcohol problems in an adolescent twin sample (i.e., Finnish Twin Study) under conditions of high peer deviance and low parental knowledge (Salvatore et al., 2014b), although the magnitude of these interactive effects was small (~0.30% of the variance in alcohol problems). Collectively, the evidence suggests that genetic risk may be moderated by peer influences in predicting more broadly defined alcohol-related phenotypes in adolescents.

Importantly, $G \times E$ studies as they relate to peer influences on adolescent alcohol use behaviors have not widely controlled for concomitant processes that may confound their effects. For instance, adolescents and their closest friends strongly model and influence each other's attitudes and perceptions toward drinking (i.e., socialization effects; Brechwald and Prinstein, 2011; Jaccard et al., 2005). Close friends are typically embedded within a broader peer group (e.g., school settings), and this broader peer context influences the magnitude of socialization effects from close friends (Brechwald and Prinstein, 2011; Urberg et al., 1995). Furthermore, socialization effects are also influenced by parental factors; the negative effects of close friends' substance use are amplified when the quality of the parent-child relationship is strained (Jaccard et al., 2005). Thus, without accounting for concomitant processes (e.g., broader peer group and parental relationship), previous findings in the peer substance use literature more generally may have overestimated the effects of peer influences (Jaccard et al., 2005).

The goal of the current study was to use a developmental framework to investigate the relationship between polygenic influences, close friend substance use, and their interaction on heavy episodic drinking patterns during the period from adolescence to young adulthood, while simultaneously controlling for other social processes (i.e., parental knowledge, broader peer group substance use) that may confound close peer effects. Generalized linear mixed models were used to account for age-related variability in heavy episodic drinking patterns (Chassin et al., 2002), as well as to examine genetic and environmental influences on the initial status and subsequent trajectories. In line with previous $G \times E$ investigations on adolescent substance use (e.g., Harden et al., 2008; Mrug and Windle, 2014; Salvatore et al., 2014b), it is hypothesized that individuals with high PRS for alcohol dependence will have a more rapid escalation of heavy episodic drinking over time compared to individuals with low PRS and that close

friend substance use will moderate this association such that the increased prevalence of substance use among close friends will accelerate heavy episodic drinking trajectories among these individuals.

MATERIALS AND METHODS

Participants

The original Collaborative Study on the Genetics of Alcoholism (COGA) study recruited probands through inpatient or outpatient substance use treatment programs at 7 sites across the United States and were included in the study if they met diagnostic criteria for alcohol dependence specified in the DSM-III-R (American Psychiatric Association, 1987) as well as criteria for alcoholism specified by Feighner and colleagues (1972). Control families (2 parents and 3 or more offspring over the age of 14) were also selected from the community. All participants were interviewed across various psychiatric domains using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA-IV) (Bucholz et al., 1994). Adolescents (younger than 18 years of age) were interviewed with a modified version of the SSAGA-IV that incorporated age-appropriate wording. A more detailed description of the COGA study is included elsewhere (Begleiter et al., 1995). The institutional review boards for all 7 data collection sites, and additional data analysis sites, approved the study.

This study uses data from the prospective study of COGA, which consists of 3,444 offspring or relatives of the probands and control families from the original COGA study, followed biennially since 2004. Data collection is ongoing, although 33% of the study sample had been assessed 4 or more times as of 2013 (63% had >3 assessments). Of those 3,444 individuals, only a subset had GWAS data ($n = 412$). Furthermore, only participants of European descent were initially genotyped to avoid confounds due to population stratification. See Table 1 for demographic information of the Prospective Study GWAS subsample.

Measures

Heavy Episodic Drinking. The frequency of heavy episodic drinking was assessed via the item “How often did you have 5 or more [standard] drinks in a 24-hour period in the last 12 months?” in the Alcohol Use Disorder section of the SSAGA-IV. Participants were first queried as to whether or not they ever consumed any alcoholic drinks (e.g., beer, wine, liquor) in their lifetime. A positive response was followed by additional queries regarding their alcohol use; otherwise, the interviewer skipped to the next section of the SSAGA-IV. Participants who stated they had “never had even one full drink of alcohol” at the time of the assessment were included in the analyses so that the sample more fully captured the diversity of drinking patterns and did not reflect an *exclusively* high-risk group. Participants were then given a card with definitions for a standard drink and asked to recall the number of days they consumed 5 or more standard drinks in a 24-hour period in the last 12 months. Their response was then converted onto a 13-point quasi-continuous scale, where higher numbers corresponded to greater frequency of heavy episodic drinking (e.g., “never” = 1, “1 day per week” = 6, and “every day” = 13). Data from baseline and 3 follow-up assessments were used in the longitudinal analysis (see Statistical Analysis section for coding procedures).

Close Friend Substance Use. Close friend substance use was assessed from the Home Environment section of SSAGA-IV. Four items, adapted from the *FinnTwin* studies (Rose and Dick, 2004), were queried to participants pertaining to the prevalence of (i) cigarette smoking, (ii) alcohol use, (iii) marijuana use, and (iv) other illicit

drug use among the participants’ best friends. For instance, participants were asked “how many of your best friends smoke?” and responded to the question on a 4-point scale: “none of them” (1), “a few of them” (2), “most of them” (3), and “all of them” (4). If participants were over the age of 18, they were instead asked to report on the prevalence of substance use among their close friends retrospectively, between the age of 12 and 17. As data from adults were retrospective, specifying close friend substance use as a time-varying covariate would not have been appropriate for the full sample. Hence, only the data from baseline assessment were used for the analysis. A composite score was used.

Close friend substance use was additionally assessed from the Important People and Activities (IPA) questionnaire (Longabaugh et al., 1995). As the IPA was administered to a subset of the COGA prospective study sample (210 out of 412 in the genotypic sample), analyses involving the IPA were included as secondary analyses. Participants were asked to name at least 4 “important people” in their lives (excluding relatives, but including siblings) and then rate the frequency of that person’s alcohol use on a 0 to 7 scale. A score was computed by the average of the frequency of alcohol use among each of the important individuals listed by the participant. Baseline data were used.

Covariates. Parental knowledge was assessed in the Home Environment section of the SSAGA-IV (4 items; “how many of your friends do you parent figures know?” “my parent figures know about my plans,” “my parent figures have a pretty good idea of my interests, activities, and whereabouts,” and “my parent figures know where I am and who I am with when I am not at home”). Parental knowledge items were rated on a 4-point ordinal scale: “always” (4), “usually” (3), “sometimes” (2), and “rarely” (1). School substance use was also measured from the Home Environment section of the SSAGA-IV and was the composite of responses to 4 items pertaining to the perceived prevalence of cigarette smoking, alcohol use, marijuana use, and other illicit drug use among the “kids you go to school with.” These items were virtually analogous to the close friend substance use variables in that participants responded to each question on a 4-point scale: “none of them” (1), “a few of them” (2), “most of them” (3), and “all of them” (4). If participants were over the age of 18, they were instead asked to report on the prevalence of substance use among their peers retrospectively, between the age 12 and 17. Baseline data were used.

Genotyping and PRS Computation

A GWAS on DSM-IV alcohol dependence symptoms was first conducted in the adult European American subsample (age 29 to 88; $n = 1,249$; 45% male) of the original COGA study (for a similar analysis using this sample, see Wang et al., 2013). This sample was genotyped on the Illumina Human OmniExpress array 12.V1 (Illumina, Inc., San Diego, CA), and 587,378 SNPs with minor allele frequency >5% were analyzed. Covariates included sex, age at interview, and cohort. Manhattan and Q-Q plots from the GWAS are provided in the Supplementary section (Figs S1 and S2, respectively). From this GWAS, “weights” were derived from t -scores of the most significant SNPs based on various p -value thresholds, from p -values 0.05 to 0.50, which were then used to calculate a PRS for participants in the prospective study using PLINK software (Purcell et al., 2009). For each SNP, the GWAS-derived t -scores of the associated allele were multiplied by 0, 1, or 2 (depending on the number of risk alleles that individual carried). The final PRS was the sum of the weighted SNPs. Figure 1 shows the proportion of variance explained (in sample size adjusted r^2) in the initial status of heavy episodic drinking by PRS at each p -value threshold. Adjusted r^2 values ranged between 1.9 and 2.3% for males and 0.8 and 1.1% for females, which is about what was expected based on previous

Table 1. Prospective Study (GWAS Subsample) Demographic Information

	Baseline (<i>n</i> = 412)	2-year FU (<i>n</i> = 387)	3-year FU (<i>n</i> = 321)	6-year FU (<i>n</i> = 241)
% Males	50.23	48.18	47.66	42.74
Age (SD)				
Male	16.72 (2.98)	<i>18.88 (3.32)</i>	<i>20.78 (3.22)</i>	<i>22.44 (3.13)</i>
Female	17.10 (3.12)	<i>19.17 (3.27)</i>	<i>21.14 (3.28)</i>	<i>22.85 (3.25)</i>
% 18 years of age and older				
Male	44.24	66.49	78.81	98.04
Female	49.30	65.33	83.23	97.08
% Parent DSM-IV Alcohol Dep.				
Male	46.08	–	–	–
Female	47.44	–	–	–
% DSM-IV Alcohol Dep.				
Male	3.68	11.24	9.92	11.11
Female	7.44	8.56	8.28	10.53
% DSM-IV Marijuana Dep.				
Male	7.58	10.99	10.07	15.15
Female	7.44	7.65	8.43	12.78
% DSM-IV Tobacco Dep.				
Male	8.76	11.89	17.88	24.00
Female	7.44	14.57	16.17	15.56
% DSM-IV Other Drug Dep.				
Male	2.76	6.01	5.33	9.09
Female	6.51	6.06	4.79	10.37
Frequency of heavy episodic drinking means (SD)				
Male	<i>2.43 (2.64)</i>	<i>3.78 (3.32)</i>	<i>4.36 (3.30)</i>	<i>4.49 (3.25)</i>
Female	<i>2.00 (2.28)</i>	<i>2.93 (2.84)</i>	<i>3.25 (2.83)</i>	<i>3.31 (2.77)</i>
School substance use means (SD)				
Male	7.72 (2.40)	<i>8.36 (2.00)</i>	8.59 (1.76)	8.10 (1.87)
Female	7.86 (2.44)	<i>8.52 (2.07)</i>	8.55 (1.83)	8.27 (1.70)
Close friend substance use means (SD)				
Male	<i>9.22 (2.33)</i>	<i>9.27 (2.32)</i>	<i>9.06 (2.36)</i>	<i>8.84 (2.47)</i>
Female	<i>9.84 (2.25)</i>	<i>9.79 (2.28)</i>	<i>9.70 (2.26)</i>	<i>9.69 (2.30)</i>
Parental knowledge means (SD)				
Male	<i>12.10 (2.56)</i>	<i>12.28 (2.38)</i>	12.41 (2.40)	12.30 (2.18)
Female	<i>14.73 (2.48)</i>	<i>12.97 (2.39)</i>	12.54 (2.71)	12.85 (2.74)
Highest level of education (<i>n</i>)				
Less than high school	52	–	–	–
High school/GED	132	–	–	–
Tech school/1-year college	54	–	–	–
Two years of college	56	–	–	–
Three years of college	17	–	–	–
College degree	64	–	–	–
Graduate degree	17	–	–	–
Missing	20	–	–	–
Gross household income (<i>n</i>)				
\$1 to \$9,999/year	33	–	–	–
\$10,000 to \$19,999/year	46	–	–	–
\$20,000 to \$29,999/year	53	–	–	–
\$30,000 to \$39,999/year	78	–	–	–
\$40,000 to \$49,999/year	64	–	–	–
\$50,000 to \$74,999/year	76	–	–	–
\$75,000 to \$99,999/year	22	–	–	–
\$100,000 to \$149,999/year	10	–	–	–
\$150,000 or more/year	7	–	–	–
Missing	23	–	–	–

FU, follow-up; baseline data for parental knowledge, school substance use, and close friend substance use were used in the current analysis (see Materials and Methods section for explanation); DSM-IV Other Drug Dep. = if DSM-IV criteria for stimulant, sedative, opiate, or other drug dependence were met; italicized figures represent significant ($p < 0.05$) mean differences between sexes.

findings (Salvatore et al., 2014b; Vink et al., 2014). SNPs below the $p < 0.05$ threshold were used for the subsequent $G \times E$ analyses, as they explained the highest proportion of variance in initial status of heavy episodic drinking.

Statistical Analysis

Heavy episodic drinking data were first grouped by age, resulting in 14 separate points of measurement from age 15 to 28. However, given the wide age range in the sample and the

fairly restricted sample size, this approach resulted in a large amount of missing data for certain ages. To partially alleviate this concern, and given that assessments were conducted biennially, data were combined into 2-year intervals to create 7 separate points of measurement (ages 15.5, 17.5, 19.5, 21.5, 23.5, 25.5, and 27.5). A generalized linear mixed model with log-link and Poisson distribution was used to model the trajectory of heavy episodic drinking (Fig. 2). Linear, quadratic, and linear piecewise growth parameters were estimated and compared, to determine an optimal model based on information

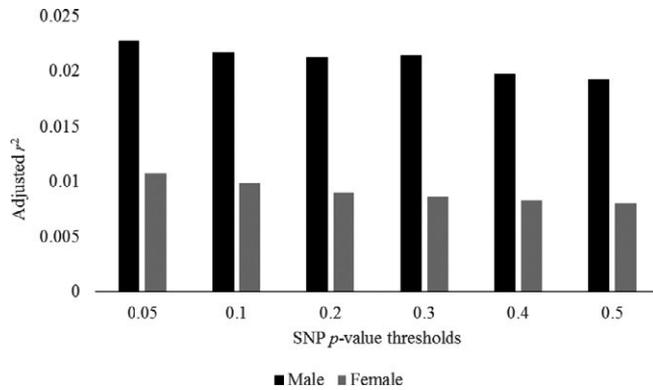


Fig. 1. Variance in heavy episodic drinking (initial status) explained by PRS at each p -value threshold.

criteria fit statistics (i.e., Akaike information criterion and Bayesian information criterion). The piecewise model was specified as follows: The first portion of the slope reflected the change in heavy episodic drinking from adolescence (age 15.5) to early adulthood (age 21.5), and the second portion of the slope reflects adult trajectories of heavy episodic drinking, from age 23.5 to 27.5. The intercept was set at age 15.5. Given the possibility of sex differences in genetic heritability estimates for alcohol use problems (King et al., 2005), analytic models were tested separately for males and females, resulting in 6 total models tested. Hence, direct statistical comparisons (e.g., mean differences) between males and females were not directly tested in this study. Upon selection of the best fitting model, covariates were included into a hierarchical Poisson regression model. In the initial model step, intercept and slopes were estimated. In the second model, covariates (i.e., school substance use, parental knowledge), close friend substance use, and PRS were added. In the final (fully saturated) model, cross products between PRS and close friend substance use variables were included.

RESULTS

Model Fit

Comparisons of model fit were evaluated for linear, quadratic, and linear piecewise growth models, separately for males and females (see Table S1). Similar to previously published findings using the same data (i.e., Dick et al., 2014), the piecewise models were marginally superior to the linear model and quadratic models in males and females. The piecewise growth model was selected for subsequent analyses for a more straightforward interpretation of covariate effects on heavy episodic drinking trajectories across 2 separate development epochs: (i) adolescence (age 15.5) to early adulthood (age 21.5) and (ii) older adult (age 23.5 to 27.5).

Regression

In the base model, only intercepts and slopes terms were estimated, separately for males and females. The mean initial heavy episodic drinking status (i.e., at age 15.5) significantly differed from zero for both males ($b = 1.83$, $SE = 0.02$, $p < 0.0001$) and for females ($b = 1.52$, $SE = 0.02$, $p < 0.0001$). For both sexes, heavy episodic drinking exhibited a positive trajectory from age 15.5 to 21.5 (males: $b = 0.20$, $SE = 0.01$, $p < 0.0001$, females: $b = 0.18$, $SE = 0.01$, $p < 0.0001$) and a slight negative trajectory from age 23.5 to 27.5 (males: $b = -0.08$, $SE = 0.01$, $p < 0.0001$, females: $b = 0.10$, $SE = 0.01$, $p < 0.0001$). In the 2 models, parental knowledge and school substance use prevalence were included as covariates, while close friend substance use and PRS were included as main effects to predict intercepts and slopes for male and female heavy episodic drinking (Table 2). For both sexes, close friend substance use

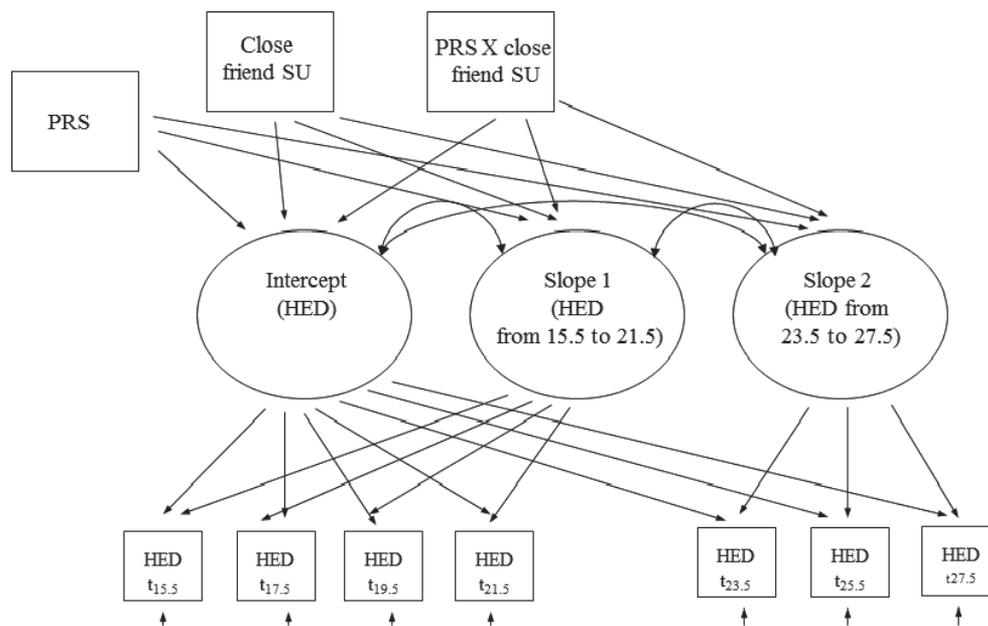


Fig. 2. Longitudinal gene-environment interaction model. Note. HED, heavy episodic drinking; PRS, polygenic risk scores; SU, substance use.

Table 2. Hierarchical Poisson Regression: Main Effects of PRS and Close Friend Substance Use on Heavy Episodic Drinking Intercepts and Slopes

	Males			Females		
	<i>b</i>	SE	<i>p</i>	<i>b</i>	SE	<i>p</i>
Intercept						
PRS	6.76	2.18	<0.01	-2.75	2.52	0.28
Parental knowledge	0.09	0.09	0.31	-0.12	0.14	0.37
School substance use	0.01	0.12	0.96	-0.23	0.16	0.14
Close friend substance use	0.63	0.09	<0.01	0.78	0.12	<0.01
Slope 1 (age 15.5 to 21.5)						
Parental knowledge	-0.01	0.02	0.48	0.00	0.02	0.85
PRS	-0.81	0.38	0.05	0.62	0.44	0.16
School substance use	0.01	0.02	0.70	0.02	0.03	0.40
Close friend substance use	-0.06	0.02	<0.001	-0.09	0.02	<0.01
Slope 2 (age 23.5 to 27.5)						
Parental knowledge	0.01	0.02	0.78	0.02	0.02	0.38
PRS	0.49	0.44	0.27	-0.66	0.51	0.20
School substance use	-0.05	0.03	0.13	0.04	0.03	0.13
Close friend substance use	0.01	0.02	0.76	0.03	0.02	0.23

prevalence strongly predicted a higher initial status of heavy episodic drinking and a greater rate of change in heavy episodic drinking between age 15.5 and 21.5. For males specifically, PRS predicted a higher initial status of heavy episodic drinking and a greater rate of change in heavy episodic drinking between age 15.5 and 21.5. The third and final model (Table 3) included the cross product between PRS and close friend substance use prevalence, while also accounting for their main effects and controlling for parental knowledge and school substance use prevalence. No significant interactions emerged between close friend substance use prevalence and PRS for either males or females for the heavy episodic drinking intercept and slopes.

Secondary Analyses

First, we assessed whether $G \times E$ effects were attenuated due to having included school substance use and parental knowledge as covariates. After removing covariates from the model, results were entirely consistent with the primary models (Table S2).

Second, to address the potential concern that the SSAGA-IV, which is a clinical interview, was not sensitive to adequately assessing environmental domains, we examined interactions between close friend substance use frequency measured from the IPA and PRS for heavy episodic drinking outcomes. Results of these regression models were somewhat consistent with the primary analyses (Table S3), although PRS was not predictive of initial heavy episodic drinking status in these models. This may have been due to the limited power to detect effects (given the small sample size) as well as the possibility of cohort effects, as the smaller sample size was due to the fact that only certain COGA sites administered this instrument. Furthermore, the assessment of close friend substance use frequency was not completely

Table 3. Hierarchical Poisson Regression: PRS \times Close Friend Substance Use Interaction on Heavy Episodic Drinking Intercepts and Slopes

	Males			Females		
	<i>b</i>	SE	<i>p</i>	<i>b</i>	SE	<i>p</i>
Intercept						
PRS	7.54	2.21	<0.01	-2.76	2.52	0.27
Parental knowledge	0.13	0.09	0.16	-0.10	0.14	0.45
School substance use	0.01	0.12	0.93	-0.24	0.16	0.13
Close friend substance use	0.69	0.10	<0.0001	0.81	0.15	<0.0001
PRS \times close friend substance use	-3.22	2.46	0.19	-0.47	2.69	0.86
Slope 1 (age 15.5 to 21.5)						
Parental knowledge	-0.01	0.02	0.45	0.00	0.02	0.83
PRS	-0.82	0.38	0.03	0.77	0.44	0.08
School substance use	0.01	0.02	0.74	0.02	0.03	0.36
Close friend substance use	-0.06	0.02	<0.01	-0.09	0.02	<0.01
PRS \times close friend substance use	0.00	0.43	1.00	-0.18	0.48	0.70
Slope 2 (age 23.5 to 27.5)						
Parental knowledge	0.00	0.02	0.90	0.02	0.02	0.44
PRS	0.41	0.45	0.37	-1.06	0.56	0.06
School substance use	-0.05	0.03	0.11	0.05	0.03	0.10
Close friend substance use	0.00	0.02	0.90	0.01	0.03	0.73
PRS \times close friend substance use	0.31	0.49	0.52	0.70	0.53	0.19

analogous, as the IPA indexed the severity of close friend alcohol use, whereas the SSAGA indexed the number of close friends who use substances.

Third, to account for the possibility of gene-environment correlation, which may confound the interpretation of potential $G \times E$ effects (Knafo and Jaffee, 2013), we examined correlations between PRS and each of the environmental variables assessed in the study. PRS was significantly associated with close friend substance use ($r = 0.23$, $p < 0.01$), parental knowledge ($r = -0.18$, $p < 0.01$), and school substance use ($r = 0.16$, $p < 0.01$). To address concerns that the $G \times E$ results were impacted by the presence of gene-environment correlation, we used standardized residual values from a regression model where each environmental variable was separately regressed on PRS. The use of residualized variables statistically eliminates gene-environment correlation effects in the model because the genetic and environmental effects have been partial from one another (Salvatore et al., 2014a). Parallel analyses (i.e., hierarchical Poisson regressions) were conducted in which growth parameters (i.e., intercepts and slopes) were regressed onto the standardized residual values for close friend substance use, PRS, and their interaction, controlling for the standardized residual values for parental knowledge and school substance use. Results from these analyses were consistent with fully saturated non-residual model (Table S4). That is, the interaction between PRS and close friend substance remained nonsignificant,

including after accounting for the presence of a gene–environment correlation.

DISCUSSION

This investigation examined the interplay between polygenic influences underlying alcohol dependence (i.e., PRS) and the influence of close friends' substance use on the development of heavy episodic drinking in adolescents and young adults. Controlling for parental knowledge and the broader network of peer substance use, close friend substance use predicted a higher initial status and a greater rate of increase in heavy episodic drinking between the age of 15.5 and 21.5 for both males and females. Additionally, PRS predicted a higher initial status and a greater rate of increase in heavy episodic drinking between the age of 15.5 and 21.5, but only among males. There was no evidence of interaction between PRS and close friend substance use on heavy episodic drinking outcomes.

Peer influences are central to developmental models of substance use. The findings suggest that close friends who use substances may have a particularly strong influence on heavy episodic drinking behaviors during adolescence and young adulthood, even after controlling for the perception of substance use among the larger peer group and self-rated parental knowledge. The increased autonomy this developmental period may afford greater opportunity to engage in drinking behaviors, especially when close friends model and reciprocate such behaviors via socialization effects (Shanahan and Hofer, 2005). Proximal social structures may also be more salient predictors of heavy episodic drinking than distal ones, as individuals are more pressured to support, provide, and appease in closer relationships (Brown et al., 1997). Other studies found that different peer contexts (i.e., close friends, peer groups, and social crowds) demonstrate separable effects on adolescent substance use and that the association between substance use among close friends and the adolescents' own substance use was moderated by their peer group status (Hussong, 2002), although our own data did not reveal 3-way interactive effects.¹ The absence of a main effect for close friend substance use on the later-stage heavy episodic drinking trajectories during young adulthood (i.e., slope 2) may reflect the attenuated influence that high-school peers have on the later young adult years in terms of heavy episodic drinking. However, it is possible that substance use among current (i.e., adult) peers also play an influential role on drinking behaviors during the later young adult years (Mrug and Windle, 2014); these data were not available for the current study, unfortunately. It is noted that an important limitation was that peer influences were modeled as unidirectional effects, in which close friends were assumed to predict adolescent heavy episodic drinking and not conversely. Adolescents at high genetic risk for alcohol use

problems are perhaps even more influential to the peers around them, as early substance use is often associated with greater popularity and social influence (Brechtwald and Prinstein, 2011). Future studies of adolescent peer influences should feature more rigorous investigations of peer influences (e.g., direct observations, prospective data from a young age) to better characterize bidirectional peer effects.

PRS predicted a higher initial status and a greater rate of change in heavy episodic drinking during the transition from adolescence to young adulthood (age 15.5 to 21.5) for males, but not for females. Furthermore, there was no main effect for PRS on heavy episodic drinking trajectories from young adulthood to later young adulthood (age 23.5 to 27.5). First, research on sex differences in genetic influences for alcohol-related phenotypes has been mixed, as some studies have reported no differences in the degree of genetic influences (Agrawal et al., 2008; Prescott et al., 1999) or stronger genetic effects for one sex over the other (Dick et al., 2007; Perry et al., 2013). Crucially, earlier patterns of drinking (i.e., age of onset) are not typically accounted for in these studies, and some evidence suggests that genetic influences are stronger among earlier onset male drinkers than female drinkers (McGue et al., 1992; although for an exception, see Dick et al., 2007). It is speculated that the more robust association between PRS for alcohol dependence and early patterns of heavy episodic drinking in males may be developmentally driven and that discrepancies in the literature regarding sex differences in genetic influences for alcohol-related phenotypes may be addressed by controlling for age of onset in cross-sectional designs, or by adopting a more developmental approach that accounts for the transition from adolescence into adulthood.

Regarding $G \times E$, previous studies reported interactive effects between genetic and peer influences on the development of alcohol use behaviors in adolescents (Mrug and Windle, 2014; Salvatore et al., 2014b). The current study found no evidence of interaction between close friend substance use and PRS in predicting either initial levels of heavy episodic drinking (intercepts) or the rate of change of heavy episodic drinking from adolescence to early adulthood (slope 1) and from early adulthood to later adulthood (slope 2). It is possible that study-related differences between the current study and others may partially account for the absence of $G \times E$ effect in the current study. For instance, Mrug and Windle (2014) used a candidate gene approach to testing $G \times E$ and focused on a single (albeit well-characterized) *DRD4* polymorphism in relation to peer substance use effects on trajectories of alcohol use. Salvatore and colleagues (2014b) found a significant $G \times E$ effect involving PRS and low parental knowledge and high peer deviance on age 14 alcohol problems, but they used cross-sectional moderation analyses on a twin sample (FinnTwin12). The failure to replicate previous findings does not necessarily indicate the absence of a $G \times E$ effect, but reflects the well-known challenges of uncovering small $G \times E$ effects within a limited study sample size for complex phenotypes (for relevant

¹Results available upon request.

review on this topic, see Manuck and McCaffery, 2014). Studies should continue to prioritize analytic rigor (e.g., longitudinal modeling, multiple measures of the environment) and cutting edge genotyping assays to more precisely characterize the extent to which genes and environments interact as they relate to complex phenotypes.

The absence of interactive effects between PRS and close friend substance use on heavy episodic drinking outcomes may also be due to the stringent test of $G \times E$ that was conducted in the current study, where parental knowledge and school substance use effects were statistically controlled within a rigorous development framework. Few studies have accounted for concomitant social processes (i.e., familial, school, and peer influences) in the study of $G \times E$, and it is speculated that the effects of specific environmental influences on adolescent behavior may be overestimated without considering multiple social influences simultaneously (Jaccard et al., 2005), particularly in the context of $G \times E$. Furthermore, the presence of gene–environment correlations may confound the study of $G \times E$ effects (Knafo and Jaffee, 2013). For instance, adolescents with a genetic propensity for alcohol use problems and behaviors may select (or attract) peers who also engage in substance use behaviors, suggesting that the same genes responsible for conferring risk for alcohol use problems may be simultaneously influencing environmental exposure as well. One safeguard against confounds driven by multiple social influences involved in $G \times E$ and gene–environment correlations are studies of experimentally manipulated environmental exposures, such as those involving randomized clinical trials or laboratory experiments (Manuck and McCaffery, 2014), but these studies have only recently emerged (e.g., see van IJzendoorn et al., 2011).

Another possibility for these divergent results is that utilizing a GWAS approach to characterize genetic risk for alcohol problems may preclude identification of genetic effects that may be contingent upon exposure to environmental conditions (Caspi et al., 2010). For example, rs1229984 (Arg48His) on *ADH1B* has been identified and subsequently replicated in GWAS for its association with alcohol dependence across different populations (Bierut et al., 2012; Gelernter et al., 2014). Despite a robust main effect of rs1229984 on alcohol-related outcomes across samples, $G \times E$ studies involving this variant have so far produced inconsistent results (e.g., Meyers et al., 2015; Olfson et al., 2014; Sartor et al., 2014). Although this is partly attributable to differences in how studies measure the environment, robust genotype-to-phenotype associations detected in GWAS may not guarantee robust $G \times E$ findings. One possible direction for future studies is to characterize genetic variation in phenotypes that are plausibly related to how an individual reacts to environmental factors (e.g., stress sensitivity, social vulnerability) (Caspi et al., 2010).

Some study limitations are noteworthy. First, young adult participants were asked to recall their parenting and peer influences retrospectively, whereas adolescents reported on these effects concurrently. Although participants were

followed longitudinally, they did not contribute to data across the entire age range in the study (age 15 to 28). To characterize the heterogeneity of heavy episodic drinking, a growth mixture model would have been preferred. Limited data precluded this analysis, although data collection in the prospective study is ongoing and we anticipate on having enough data with which to perform more rigorous examinations of growth mixture models that extend beyond age 28 in future investigations. Second, the participants in the prospective study were genetically related to the participants of the original COGA study, which was a case–control designed study (proband status of the relatives was not controlled for in the current analyses). Thus, the derivation of PRS did not involve a completely independent discovery and target dataset. As overlap between these data sets may potentially lead to an overestimation of the prediction accuracy for the PRS (Wray et al., 2013), interpretations regarding the main effect of the PRS on heavy episodic drinking outcomes should be made with some caution. On the other hand, it is possible that this estimation may simply reflect the enrichment of genes for alcohol use in both samples. In other words, given that alcohol use disorders are known to be influenced by many genes of small effect, using genetically related case–control samples that are likely enriched for the same small-effect genes associated with alcohol use may lead to more robust characterizations of risk. Although this is beyond the scope of the current study, future studies should examine whether PRS effects significantly differ between discovery samples with related versus and nonrelated individuals to the target sample. Third, heavy episodic drinking was defined as having 5 or more alcoholic drinks within a 24-hour period, which is a more stringent threshold for females where 4 drinks are considered the typical threshold. Hence, sex differences regarding genetic and environmental influences on trajectories of heavy episodic drinking could not be explicitly tested in the current analyses, although separate analytic models were conducted for males and females. Using sex-specific cutoffs (i.e., according to the standard definitions of binge drinking) may potentially lead to a more consistent pattern of results for males and females. Additionally, given sex differences in heritability estimates for alcohol use problems (King et al., 2005), it is possible that different genes may be involved for alcohol-related phenotypes in males and females. Future studies may consider conducting GWAS separately for males and females, so that PRS are sex-specific. Finally, the findings may not be generalizable as the analyses were limited to European Americans. Recent evidence suggests that the association of alcohol dependence with specific genetic variants may differ between racial and ethnic groups (Gelernter et al., 2014).

The current study is innovative for investigating $G \times E$ effects using a polygenic approach within a developmentally sensitive design. Including those that have already been mentioned, there are several additional implications for future research. Different phenotypic targets for PRS may be warranted for researchers who are primarily interested in $G \times E$

(e.g., stress sensitivity). Alternatively, researchers can focus on testing $G \times E$ using genes that have already been (or will be) identified through GWAS, although having “high-quality” environment measures will be important for these types of studies (Caspi et al., 2010). From a clinical perspective, PRS have the potential to explain a significant amount of the variation in psychiatric disorders as sample sizes increase, but the current findings fall well short of being able to make any clinically meaningful predictions. Investigating environmental influences simultaneously with genetic information may be crucial for enhancing our abilities to make accurate diagnostic predictions down the line.

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SUPPORTING INFORMATION

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

Appendix S1. Additional acknowledgments.

Fig. S1. Manhattan plot of GWAS on alcohol dependence symptoms.

Fig. S2. Q-Q plot of GWAS results.

Table S1. Fit indices for linear, quadratic, and piecewise growth models for heavy episodic drinking.

Table S2. Hierarchical Poisson regression: PRS \times close friend substance use interaction (without covariates) on heavy episodic drinking intercepts and slopes.

Table S3. Hierarchical Poisson regression: PRS \times close friend substance use (IPA) interaction on heavy episodic drinking intercepts and slopes.

Table S4. Hierarchical Poisson regression: PRS \times standard residualized values of close friend substance use interaction on heavy episodic drinking intercepts and slopes.