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The Associations Between Polygenic Risk, Sensation Seeking, Social Support, and Alcohol Use in Adulthood

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Genetic predispositions play an important role in alcohol use. Understanding the psychosocial mechanisms through which genetic risk unfolds to influence alcohol use outcomes is critical for identifying modifiable targets and developing prevention and intervention efforts. In this study, we examined the role of sensation seeking and social support from family and friends in linking genetic risk to alcohol use. We also examined the role of social support in moderating the associations between genetic risk and sensation seeking and alcohol use. Data were drawn from a sample of 2,836 European American adults from the Collaborative Study on the Genetics of Alcoholism (46% male, mean age = 35.65, standard deviation [*SD*] = 10.78). Results from path analysis indicated that genome-wide polygenic scores for alcohol consumption (alc-GPS) were associated with higher sensation seeking, which in turn was associated with higher levels of alcohol use. alc-GPS was also associated with higher alcohol use indirectly via lower levels of family support. In addition, high friend support attenuated the association between alc-GPS and sensation seeking and alcohol use. The pattern of associations was similar for males and females, with some differences in the associations between social support and alcohol use observed across age. Our findings highlight the important role of intermediate phenotypes and gene–environment interplay in the pathways of risk from genetic predispositions to complex alcohol use outcomes.

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General Scientific Summary
This study suggests that higher sensation seeking is an important pathway linking genetic risk to alcohol use across emerging to middle adulthood. Social support is important in buffering individuals' risk predispositions in relation to alcohol use, although effects depend on the source of social support and age.

Keywords: polygenic scores, sensation seeking, social support, alcohol use, gene–environment interplay

Supplemental materials: https://doi.org/10.1037/abn0000568.supp

Alcohol use and misuse are prevalent and represent a significant public health concern in the United States and worldwide (Grant et al., 2015; World Health Organization, 2018). Genes play an important role in alcohol use outcomes, accounting for approximately 50% of the variance in alcohol use disorder (Verhulst et al., 2015). Very little is known, however, about *how* genetic factors influence complex behavioral outcomes such as alcohol use (Li et al., 2017). Understanding the psychosocial mechanisms through which genetic risk unfolds to influence alcohol use outcomes is critical for identifying modifiable targets and developing prevention and intervention efforts. Genetic factors may influence alcohol use outcomes through multiple mechanisms at different levels (e.g., individual, interpersonal). Two plausible mechanisms involve intermediate phenotypes (i.e., personality characteristics such as sensation seeking) and gene–environment interplay (i.e., social support from friends and family), both of which have been shown to be genetically influenced (Kendler, 1997; Koopmans et al., 1995) and associated with alcohol use outcomes (Hittner & Swickert, 2006; Peirce et al., 2000). In this study, we examined the role of sensation seeking and perceived social support from family and friends in linking genetic risk to alcohol use in a sample of adults.

Sensation Seeking as Intermediate Phenotype Linking Genetic Influences to Alcohol Use

Complex behavioral outcomes such as alcohol use are quite distal from the level of genetic function. Thus, studying the role of intermediate phenotypes may help to unpack the pathways through which genetic risk unfolds to influence psychiatric and behavioral outcomes (Gottesman & Gould, 2003; Lenzenweger, 2013). Sensation seeking, or a tendency to seek out novel sensations and experiences (Zuckerman, 1984), is an especially compelling intermediate phenotype in molecular genetic studies of alcohol phenotypes. First, sensation seeking is a personality trait that cosegregates with alcohol use disorder (AUD). For example, individuals with a family history of AUD tend to report higher levels of sensation seeking than those without a family history of AUD (Grucza et al., 2006; Sher et al., 1991). Second, sensation seeking is moderately heritable, with an estimated heritability of 40–80% (Harden et al., 2012). In addition, twin studies showed substantial overlap in the genetic etiology between sensation seeking and alcohol use outcomes (Mustanski et al., 2003; Slutske et al., 2002). Finally, high sensation seeking is robustly associated with alcohol use among adolescents and adults (Hittner & Swickert, 2006), with some longitudinal studies suggesting that sensation seeking may be a predictor of increased alcohol use. For example, using longitudinal data from the National Longitudinal Survey of Youth, Quinn and Harden (2013) found that a slower decline in sensation seeking was associated with a more rapid increase in alcohol use from ages 15 to 26.

However, very few studies have explicitly investigated the role of sensation seeking in mediating the association between genetic factors and alcohol use. Using data from the Finnish Twin Cohort, Li et al. (2017) showed that sensation seeking partially mediated the association between genetic risk for alcohol dependence, measured as a genome-wide polygenic score (GPS), and alcohol use problems at age 16. In a sample of college students, sensation seeking also partially mediated the association between genetic predispositions toward risky behaviors and alcohol consumption (Ksinan et al., 2019). Notably, previous studies on the mediating role of sensation seeking have primarily focused on adolescents or emerging adults. Limited research has examined whether the role of sensation seeking in alcohol use varies across a broader range of ages across adulthood. However, there is some evidence of a general decline in levels of sensation seeking beyond adolescence (Evans-Polce et al., 2018) and between emerging adulthood and middle adulthood (Zuckerman et al., 1978). The association between sensation seeking and binge drinking has also been found to decline across ages 18–30 (Evans-Polce et al., 2018). It remains unknown whether the associations between sensation seeking and alcohol use outcomes continue to decline beyond emerging adulthood or are similar between emerging adults and middle-aged adults.

Gene–Environment Interplay: The Role of Social Support

Social support, defined as the perception of having support from and access to social connections (Lin et al., 1979), is considered a robust environmental factor associated with alcohol use outcomes. Higher social support is associated with lower alcohol consumption and problems (Groh et al., 2007; Peirce et al., 2000), particularly during stressful periods (Steptoe et al., 1996). Social support is thought to be protective against alcohol use and problematic drinking by providing greater social control and/or buffering the effects of stressful events, and it is also thought to reduce individuals' likelihood of drinking to cope (Brick et al., 2018; Humphreys et al., 1999). High social support from family, romantic partners, and friends has been shown to be negatively associated with alcohol use problems (Jarnecke & South, 2014). However, the role of social support may vary depending on the source of support. For example, in a sample of adult twins, social support from romantic partners was associated with fewer alcohol problems, but support from friends was not (Salvatore et al., 2015).

In addition, the nature and functioning of social support change across the life course (Ertel et al., 2009). Although different age groups do not have unique desires for social support, research documents that the role of social support from family and friends varies over the life span (Segrin, 2003). For example, younger adults have larger support networks and greater perceptions of support from friends (Levitt et al., 1993; Vaux, 1985), whereas older adults have greater perceptions of support from emotionally close family relationships (Antonucci et al., 2004; Levitt et al., 1993). Because the health benefits of social support, including lower levels of drinking, depend on receivers' preferences (Cohen & Wills, 1985), evidence indeed suggests that support from friends may benefit younger adults more and that support from family may benefit older adults more (Walen & Lachman, 2000).

Theory and research suggest that individuals shape their social environments through gene–environment correlation (rGE) processes (Plomin et al., 1977; Scarr & McCartney, 1983). Prior evidence suggests that social support is genetically influenced: Some studies found that between 40% and 80% of the variance in dimensions of social support can be attributed to genetic differences between individuals (Bergeman et al., 1990; Kendler, 1997; Wang et al., 2017). Others found a moderate degree of heritability for social support from spouse and parents (ranged from 15% to 30%) but small to no genetic influence on social support from friends (Kutschke et al., 2018). Twin research also showed overlap in genetic influences between social support and AUD (Salvatore et al., 2015). Taken together, it is plausible that rGE processes related to social support may serve as a pathway linking genetic factors to alcohol use outcomes. That is, a higher genetic risk may lead to lower social support, which in turn can result in an elevated risk for alcohol use and related problems, although the effects may vary across sources of social support.

Gene–environment interplay can also occur in the form of gene–environment interaction (GxE). That is, environmental factors may buffer or exacerbate the association between genetic factors and developmental outcomes (Plomin et al., 1977). There is evidence that social support moderates genetic influences on alcohol use outcomes. For example, using a sample of young adults in the Finnish Twin Study, Barr et al. (2017) found that higher levels of social support were associated with increased genetic influence on alcohol misuse for females and reduced genetic influence for males. Support from parents was found to mitigate the genetic risk effect of the serotonin transporter gene (*5-HTTLPR*) on developmental trajectories of alcohol use from adolescence to young adulthood in a nationally representative sample (Su et al., 2019). Together, these studies indicate that social support buffers genetic risk in relation to alcohol use and also suggest the need to examine potential sex differences in the role of social support. Given that sensation seeking is a genetically influenced trait related to increased risk for alcohol use, it is also possible that social support also buffers the relation between sensation seeking and alcohol use; however, to our knowledge, no study has tested this hypothesis.

The Present Study

The goal of this study was to examine the role of sensation seeking and social support in linking genetic risk to alcohol use. We examined two alternative models, one in which both sensation seeking and social support serve as indirect pathways linking genetic risk to alcohol use (Figure 1, Panel A) and another in which sensation seeking serves as an indirect pathway linking genetic risk to alcohol use, and social support moderates the association between genetic risk and sensation seeking and alcohol use (Figure 1, Panel B). Complex behavioral outcomes, such as alcohol use, are polygenic, such that many common genetic variants contribute to risk. In this study, we indexed individuals' genetic predispositions by using a genome-wide polygenic score (GPS) approach that aggregates the effects of common genetic variants across the genome. The calculation of a reliable GPS requires a discovery genome-wide association study (GWAS) with a large sample size to estimate the effects of common genetic variants across the genome (Dudbridge, 2013). We focused on alcohol consumption genome-wide polygenic scores (alc-GPSs) because the largest GWAS on alcohol-related phenotype to date was on alcohol consumption (drinks per week), conducted by the GWAS & Sequencing Consortium of Alcohol and Nicotine Use with about 1 million individuals (Liu et al., 2019), allowing us to calculate relatively reliable alc-GPSs in our sample.

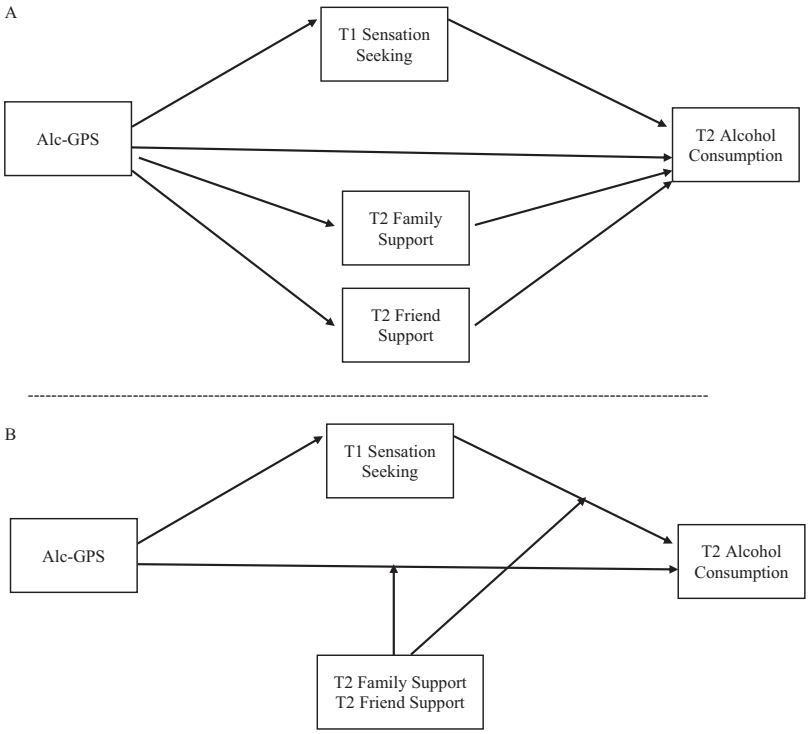
We hypothesized that higher alc-GPSs would be associated with higher levels of alcohol use. Further, we hypothesized that the effect of alc-GPS would, at least in part, manifest indirectly by influencing sensation seeking and social support. We also hypothesized that social support would buffer risks associated with alcohol use, such that the association between alc-GPS and alcohol use, as well as the association between sensation seeking and alcohol use, would be attenuated by high levels of social support. We considered social support from family and friends separately in order to examine whether patterns of associations vary as a function of the source of social support, given prior evidence of differential effects (Salvatore et al., 2015). In addition, we tested sex as a moderator of the hypothesized pathways, given evidence of sex differences in rates of alcohol use and levels of sensation seeking and social support (Cross et al., 2013; Grant et al., 2015). Because sensation seeking and sources of social support tend to change across the adulthood years, we capitalized on the rich data set from the Collaborative Study on the Genetics of Alcoholism (COGA), which includes participants of a wide age range, to explore whether the associations between alc-GPS, sensation seeking, social support, and alcohol use vary across developmental stages (i.e., emerging adulthoods vs. young adulthood vs. middle adulthood).

Method

Sample

Data for this study were drawn from COGA, a multisite, large, multigenerational family study that aims to understand genetic influences on alcoholism (Begleiter et al., 1995). Probands were identified through alcohol treatment programs at six U.S. sites and were invited to participate if they had a sufficiently large family with two or more members in the COGA catchment areas. Population-based comparison families were also recruited. Data collection for COGA started in 1991 (Phase I) when adults in the target extended families were invited to complete the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), a comprehensive interview that assesses demographic factors, alcohol use behaviors, and a variety of psychiatric phenotypes (Bucholz et al., 1994). COGA Phase II data collection occurred around 1996,

Figure 1
Alternative Conceptual Models Linking Polygenic Risk Score, Sensation Seeking, Social Support, and Alcohol Consumption



where participants in COGA Phase I were invited for a follow-up assessment, and eligible family members who did not participate in Phase I were invited to participate as well. Participants also completed questionnaires at each phase. All COGA participants were asked to provide a DNA sample via blood or saliva. Institutional review boards at all sites approved this study, and written consents were obtained from participants.

For the purpose of the present study, we focused on COGA participants of European ancestry (as determined by their genetic information) because the sample for the discovery GWAS we used to calculate GPSs was primarily of European ancestry (Liu et al., 2019), and GPSs derived from GWASs of European-centric samples may be biased in non-European samples (Martin et al., 2017). We included participants who (a) participated in both COGA Phase I (T1) and Phase II (T2), providing longitudinal data; (b) were age 18 of older at T1 and age 65 or younger at T2; (c) had genomic data available for the calculation of GPSs; (d) reported on sensation seeking and social support; and (5) indicated that they have ever used alcohol. The analytic sample included 2,836 adults, 46% male; age ranged from 18 to 61 (mean [*M*] = 35.65, standard deviation [*SD*] = 10.78) at T1 and 22 to 65 (*M* = 41.44, *SD* = 14.30) at T2.

Measures

Alcohol Use

Participants reported the number of drinks of different kinds of alcoholic beverages (beer, wine, liquor, other) they consumed on a typical day (Monday, Tuesday, . . . Sunday) of the week in the past 6 months as part of the SSAGA at T2 (Bucholz et al., 1994). Scores were summed across days and kinds of drinks to derive a composite score that indicated drinks per week. A total of 769 (27.1%) participants indicated that they consumed no alcohol (zero drinks) during the past 6 months.

Sensation Seeking

Participants completed the Sensation Seeking Scale, a 40-item self-report questionnaire designed to measure differences in the degree to which individuals seek out stimulation and arousal (Zuckerman, 1984), at T1. The items are presented as 40 pairs of statements, such as "I like wild, uninhibited parties" and "I prefer quiet parties with good conversation." For each pair, respondents chose the statement that best describes their likes or the way they feel. Scores were summed across items and ranged between 0 and 40, with higher scores indicating higher sensation seeking (α = .86).

Social Support

Participants completed the Perceived Social Support From Family Scale and the Perceived Social Support From Friends Scale (Procidano & Heller, 1983) at T2. These are 20-item self-report measures used to assess social support specifically from family members or friends. Sample items include "My family/friends give me the moral support I need," and "I rely on my family/friends for emotional support." Participants responded to each statement on a 4-point scale ranging from 1 (*generally false*) to 4

(*generally true*). Scores were averaged across items, and higher scores represent higher family support ($\alpha = .95$) or friend support ($\alpha = .91$).

Genotyping and Genome-Wide Polygenic Scores

Participants' DNA samples were genotyped using the Illumina Human1M array (Illumina, San Diego, CA), the Illumina Human OmniExpress 12V1 array (Illumina), the Illumina 2.5M array (Illumina), or the Smokescreen genotyping array (Biorealm LLC, Walnut, CA; Baurley et al., 2016). Data processing, quality control, and imputation have been described elsewhere (Lai et al., 2019). Briefly, data were imputed to 1000 Genome Phase 3, and single-nucleotide polymorphisms (SNPs) with a genotyping rate $< .95$ or that violated Hardy–Weinberg equilibrium ($p < 10^{-6}$) or with minor allele frequency (MAF) $< .01$ were excluded from the analysis.

We calculated GPSs using estimates from a GWAS of alcohol consumption (drinks per week) with about 1 million individuals (Liu et al., 2019). We used PRS-CS (Ge et al., 2019), which employs a Bayesian approach to correct for GWAS summary statistics for the nonindependence of SNPs in linkage disequilibrium (LD), to calculate alc-GPS. As recommended by the PRS-CS developers, SNPs for alc-GPS creation were limited to HapMap3 SNPs that overlapped between the original GWAS summary statistics and the LD reference panel (1000 Genomes Phase III European ancestry reference panel).

Covariates

We included participants' age at T1 and sex as covariates, given their demonstrated associations with alcohol use. We also included the first three genetic ancestry principal components (PC1–PC3) as covariates to account for potential population stratification. In addition, given the wide range of age in our sample, which offered a great opportunity for us to examine similarities and differences in pathways of risk across developmental periods, we created an age-group variable to classify participants into three groups based on their age at T2: emerging adulthood (ages 18–29, $n = 452$), young adulthood (ages 30–44, $n = 1{,}367$), and middle adulthood (ages 45–65, $n = 1{,}017$). Our grouping of age groups is consistent with studies in the epidemiology literature (e.g., Grant et al., 2015).

Analytic Strategy

We first conducted descriptive statistics and correlations between the study variables. We then conducted path analysis using Mplus Version 8.3 to examine whether sensation seeking and social support serve as indirect pathways linking alc-GPS to alcohol use (Figure 1, Panel A). In the path model, alc-GPS was specified as an exogenous variable associated with alcohol use directly and indirectly through sensation seeking, family support, and friend support. Sensation seeking, family support, and friend support were specified as associated with alcohol use. Family and friend support were also specified to be correlated. Age, sex, and genetic ancestry principal components were specified as covariates for sensation seeking, family and friend support, and alcohol use.

Indirect effects of alc-GPS on alcohol use via sensation seeking, family support, and friend support were tested using the MODEL INDIRECT command in Mplus, which provides a test of specific indirect effects in addition to the total indirect and direct effects of alc-GPS on alcohol use. Indirect effects were evaluated using bias-corrected bootstrapping (1,000 times) with a 95% confidence interval (CI; MacKinnon et al., 2004), with CIs not including zero indicating statistically significant indirect effects. Clustering within families was accounted for using the CLUSTER command in Mplus. Maximum likelihood with robust standard errors (MLR) estimation was used in all analyses to account for nonnormality and nonindependence of the observed data. Missing data were accounted for using full-information maximum likelihood.

Next, we examined an alternative model where social support moderates the associations between alc-GPS and alcohol use, as well as the association between sensation seeking and alcohol use (Figure 1, Panel B). In this model, alc-GPS was specified to be associated with alcohol use directly and indirectly via sensation seeking. Sensation seeking, family support, and friend support were specified to be associated with alcohol use. In addition, product terms between alc-GPS and family/friend support, as well as product terms between sensation seeking and family/friend support, were included as additional independent variables associated with alcohol use; variables were mean-centered before creating the product terms. alc-GPS and family/friend support were specified to be correlated using the "WITH" command in Mplus to account for potential rGE. Follow-up analysis was conducted to check the robustness of significant GxE effects by including Covariates × Genetics and Covariates × Environment interaction terms in the model that further account for potential confounding effects (Keller, 2014).

We also conducted multigroup path analyses to examine whether the patterns of associations differed between males and females and across age groups. Multigroup analyses were conducted by removing sex or age from the path model and then comparing a model with all remaining paths constrained to equality with another model that had all paths freely estimated across the comparison groups (i.e., females vs. males; emerging adulthood vs. young adulthood vs. middle adulthood). A statistically significant Wald chi-square test of parameter equalities would indicate significant differences in path coefficients across groups.

Results

Preliminary Analysis

Descriptive statistics and correlations between variables are presented in Table 1. alc-GPS was positively correlated with sensation seeking ($r = .07$) and alcohol use ($r = .10$) and negatively correlated with family support ($r = -.05$) but was not significantly correlated with friend support ($r = -.03$). Sensation seeking was negatively correlated with family and friend support ($r = -.13$ and $r = -.05$, respectively) and positively correlated with alcohol use ($r = .19$). Family and friend support were modestly correlated ($r = .44$), and both were negatively correlated with alcohol use ($r = -.14$ and $r = -.18$, respectively). Age and sex both showed significant correlations with sensation seeking, social support, and alcohol use, suggesting the importance of including them as covariates in analyses and exploring potential differences in pathways of risk across age and sex. PC1–PC3 were all correlated with alc-GPS; PC1 was also correlated with alcohol use, suggesting the importance of accounting for potential confounding effects due to

Table 1
Descriptive Statistics and Bivariate Correlations Between Variables

Variables	*N*	1	2	3	4	5	6	7	8	9	10
1. Age, T1	2,836	—									
2. Sex	2,836	.01	—								
3. PC1	2,836	.03	−.01	—							
4. PC2	2,836	.04*	−.03	.44**	—						
5. PC3	2,836	.04*	−.01	.11**	.45**	—					
6. alc-GPS	2,836	.03	.03	.07**	.07**	.05*	—				
7. Sensation seeking, T1	2,606	−.37**	.38**	.03	−.01	−.01	.07**	—			
8. Family support, T2	2,587	.04	−.14**	−.00	−.03	.01	−.05*	−.13**	—		
9. Friend support, T2	2,589	−.11**	−.29**	−.02	−.03	.01	−.03	−.05*	.44**		
10. Alcohol use, T2	2,835	−.08**	.23**	.05**	.03	−.01	.10**	.19**	−.14**	−.18**	—
M		35.65	.44[a]	−.01	.00	.00	.01	16.14	3.02	3.02	8.49
SD		10.78	—	1.02	1.01	1.03	1.01	7.26	.67	.59	19.38

Note. T1 = Time 1; PC1–PC3 = the first three genetic ancestry principal components; alc-GPS = alcohol consumption genome-wide polygenic scores; T2 = Time 2. Sex was coded 1 = male, 0 = female.
[a] Percentage of male participants.
* $p < .05$. ** $p < .01$.

population stratification, even in our sample with all participants of European ancestry.

Examining Sensation Seeking and Social Support as Indirect Pathways Linking alc-GPS and Alcohol Use

The path model demonstrated excellent fit ($\chi^2 = 24.02$, degrees of freedom [*df*] = 2, $p < .001$; comparative fit index [CFI] = .99, root mean square error of approximation [RMSEA] = .06; standardized root mean square residual [SRMR] = .01). The results from the path model are summarized in Table 2 and illustrated in Figure 2. Consistent with our expectation, alc-GPS was associated with sensation seeking at T1, which in turn was associated with alcohol use at T2. alc-GPS was associated with reduced family support but was not significantly associated with friend support. Friend support, but not family support ($p = .06$), was significantly associated with lower alcohol use at T2. alc-GPS remained significantly associated with alcohol use at T2, above and beyond covariates (age, sex, PC1–PC3), sensation seeking, and social support.

The results indicated that there were significant indirect effects of alc-GPS on alcohol use via sensation seeking and social support. Specifically, alc-GPS was associated with higher levels of alcohol use indirectly via higher sensation seeking (B = .127, 95% CI [.064, .213]). alc-GPS was also associated with more alcohol use indirectly via lower levels of social support from family (B = .042, 95% CI [.005, .118]). There were no significant indirect effects of alc-GPS on alcohol use via social support from friends (B = .034, 95% CI [–.032, .112]).

Examining the Moderating Role of Social Support

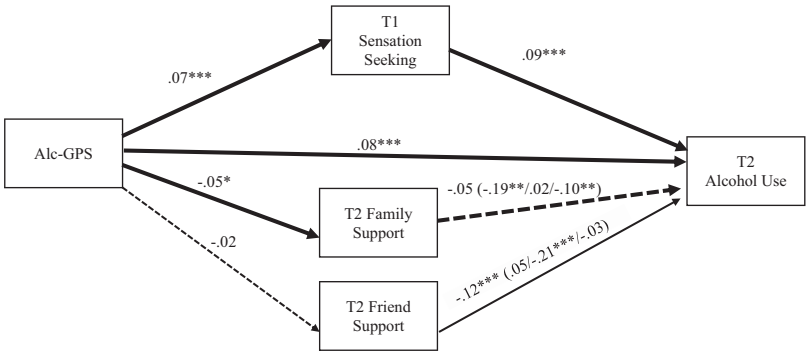
The results from the path model examining the moderating role of social support in the relationships between alc-GPS, sensation seeking, and alcohol use are presented in Table 3. The results indicated a significant interaction between alc-GPS and friend support in relation to alcohol use (B = –2.38, standard error [*SE*] = .93, 95% CI [–4.11, –1.04], β = .07, $p = .01$). This GxE effect was robust, remaining statistically significant after adjusting for interactions

Table 2
Path Coefficients, Direct and Indirect Effects From the Path Model Examining Sensation Seeking and Social Support as Indirect Pathways Linking alc-GPS and Alcohol Use

Paths	B	*SE*	β	*p*
alc-GPS → alcohol use	1.58	.37	.08	<.001
alc-GPS → sensation seeking	.52	.13	.07	<.001
alc-GPS → family support	−.03	.02	−.05	.038
alc-GPS → friend support	−.01	.01	−.02	.435
Sensation seeking → alcohol use	.24	.07	.09	<.001
Family support → alcohol use	−1.38	.75	−.05	.061
Friend support → alcohol use	−3.82	.86	−.12	<.001
Indirect effects	**B**	**95% CI**	**β**	***p***
alc-GPS → sensation seeking → alcohol use	.127	[.064, .213]	.007	.004
alc-GPS → family support → alcohol use	.042	[.005, .118]	.002	.173
alc-GPS → friend support → alcohol use	.34	[−.032, .112]	.002	.444

Note. alc-GPS = alcohol consumption genome-wide polygenic scores. Age at Time 1 (T1), sex, and genetic ancestry principal components were included as covariates for alcohol use, sensation seeking, and family/friend support. Path coefficients for covariates are presented in Table 2 of the online supplemental materials. Analysis accounted for cluster within extended families. *N* = 2,836.

Figure 2
Path Model Examining Sensation Seeking and Social Support as Indirect Pathways Linking alc-GPS and Alcohol Use



Note. alc-GPS = alcohol consumption genome-wide polygenic scores. Standardized path coefficients are presented. Age at Time 1 (T1), sex, and the first three genetic ancestry principal components were included as covariates for alcohol use, sensation seeking, and family/friend support. Family support and friend support were specified to be correlated with each other in the path model (correlation not shown in figure). N = 2,836. Solid paths are statistically significant; dashed paths are not statistically significant; bolded paths indicate statistically significant indirect pathways. For the path coefficients that differed significantly across age groups, group-specific coefficients are presented in parentheses (emerging/young/middle adulthood).
* $p < .05$. ** $p < .01$. *** $p < .001$.

between alc-GPS and covariates (age, sex, PC1–PC3) and interactions between friend support and covariates (p = .010; see Table 2 in the online supplemental materials). As illustrated in Figure 3 (Panel A), simple slope analyses indicated that alc-GPS was associated with higher alcohol use when friend support was low (–1 *SD*, B = 2.91, *SE* = .76, β = .15, $p < .001$) but not when friend support was high (+1 *SD*, B = .12, *SE* = .47, β = .01, p = .799). There was also a significant interaction between sensation seeking and friend support in relation to alcohol use (B = –.27, *SE* = .10, 95% CI [–.43, –.12], β = –.06, p = .006). As shown in Figure 3 (Panel B), sensation seeking was associated with more alcohol use when friend support was low (–1 *SD*, B = .39, *SE* = .10, β = .15, $p < .001$) than when friend support was high (+1 *SD*, B = .09, *SE* = .09, β = .04, p = .296). The indirect effect of alc-GPS on alcohol use via sensation seeking was significant when friend support was low (–1 *SD*; B = .197, 95% CI [.083, .311], β = .010, p = .005) but was not significant when friend support was high (+1 *SD*; B = .048, 95% CI [–.030, .125], β = .002, p = .312).

Examining Differences in Pathways of Risk Across Sex and Age Groups

Sex Differences

Descriptive statistics for males and females are presented in Table 3 of the online supplemental materials. Multigroup analysis was conducted for the path model examining sensation

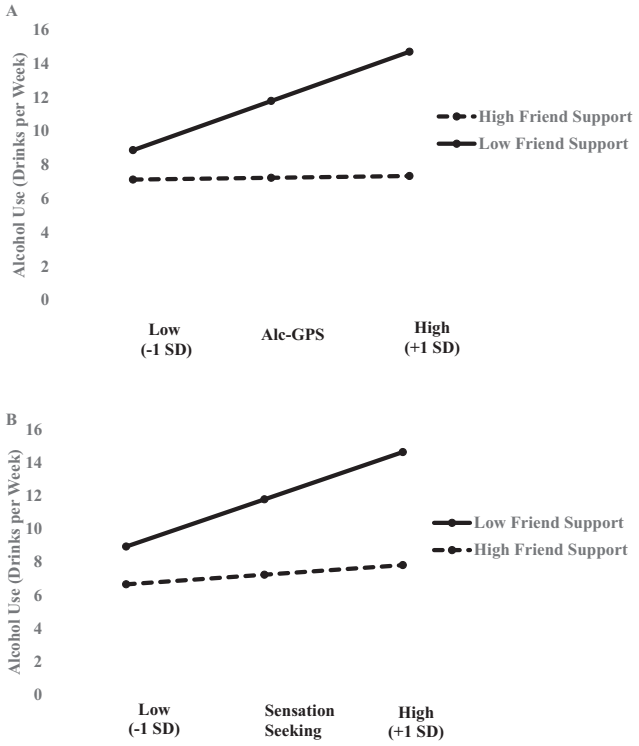
Table 3
Path Coefficients From the Path Model Examining the Moderating Role of Social Support in the Relation Between alc-GPS, Sensation Seeking, and Alcohol Use

Paths	B	*SE*	β	*p*
alc-GPS → alcohol use	1.51	.36	.08	<.001
Sensation seeking → alcohol use	.24	.06	.09	<.001
Family support → alcohol use	−1.18	.74	−.04	.100
Friend support → alcohol use	−3.85	.90	−.12	<.001
alc-GPS × Family Support → alcohol use	−.15	.78	−.01	.849
alc-GPS × Friend Support → alcohol use	−2.38	.93	−.07	.010
Sensation Seeking × Family Support → alcohol use	−.05	.09	−.01	.554
Sensation Seeking × Friend Support → alcohol use	−.27	.10	−.06	.006
alc-GPS → sensation seeking	.52	.14	.07	<.001
Indirect effect	**B**	**95% CI**	**β**	***p***
alc-GPS → sensation seeking → alcohol use	.122	[.061, .211]	.006	.007

Note. alc-GPS = alcohol consumption genome-wide polygenic scores. Age at Time 1 (T1), sex, and genetic ancestry principal components were included as covariates for alcohol use, sensation seeking, and family/friend support. Path coefficients for covariates are presented in Table 2 of the online supplemental materials. Analysis accounted for cluster within extended families. N = 2,836.

Figure 3

Friend Support Moderates the Associations Between alc-GPS/ Sensation Seeking and Alcohol Use



Note. alc-GPS = alcohol consumption genome-wide polygenic scores.

seeking and social support as indirect pathways linking alc-GPS to alcohol use. A Wald test of constraining all of the paths linking alc-GPS, sensation seeking, social support, and alcohol use to be equal across sex was not statistically significant (χ^2 = 11.76, *df* = 7, *p* = .11), suggesting that the patterns of associations between alc-GPS, sensation seeking, social support, and alcohol use were similar for males and females (see Table 4 in the online supplemental materials).

Multigroup analysis to test for sex differences was also conducted for the model examining moderating roles of social support (see Table 5 in the online supplemental materials). A Wald test of constraining the four paths linking interaction terms (i.e., alc-GPS × Family/Friend Support; Sensation Seeking × Family/Friend Support) to alcohol use to be equal between males and females was not statistically significant (χ^2 = 6.63, *df* = 4, *p* = .16), suggesting no sex differences in the moderating role of social support for the associations between alc-GPS, sensation seeking, and alcohol use.

Age-Group Differences

Descriptive statistics across age groups are presented in Table 6 of the online supplemental materials. Multigroup analysis across age groups was conducted for the path model examining sensation seeking and social support as indirect pathways linking alc-GPS to alcohol use. A Wald test of constraining all paths linking alc-GPS, sensation seeking, social support, and alcohol use to be equal across age groups (emerging versus young vs. middle adulthood) was statistically significant (χ^2 = 30.89, *df* = 14, *p* = .006), indicating age differences in the associations between alc-GPS, sensation seeking, social support, and alcohol use. Follow-up analysis testing the paths one by one across age groups indicated that the association between family support and alcohol use significantly varied across age groups (χ^2 = 7.81, *df* = 2, *p* = .020); higher family support was associated with lower alcohol use among emerging (B = –3.97, *SE* = 1.49, β = –.19, *p* = .008) and middle adults (B = –2.78, *SE* = 1.00, β = –.10, *p* = .005) but not among young adults (B = .71, *SE* = 1.18, β = .02, *p* = .550). The association between friend support and alcohol use also significantly differed across age groups (χ^2 = 19.43, *df* = 2, *p* = < .001): Higher friend support was associated with lower alcohol use among young adults (B = –7.57, *SE* = 1.64, β = –.21, *p* < .001) but not among emerging adults (B = 1.23, *SE* = 1.22, β = .05, *p* = .314) and middle adults (B = –.96, *SE* = .81, β = –.03, *p* = .232). There were no significant age differences in the associations between alc-GPS and sensation seeking or social support. The association between sensation seeking and alcohol use also did not significantly differ across age groups (see Table 7 in the online supplemental materials).

Multigroup analysis across age groups was also conducted for the model examining the moderating roles of social support. A Wald test of constraining the four paths linking interaction terms (i.e., alc-GPS × Family/Friend Support; Sensation Seeking × Family/Friend Support) to alcohol use to be equal across age groups was not statistically significant (χ^2 = 15.02, *df* = 8, *p* = .06), suggesting no differences in the moderating role of social support for the associations between alc-GPS, sensation seeking, and alcohol use across age groups (Table 8 in the online supplemental materials).

Discussion

The overarching goal of this study was to examine the role of sensation seeking and social support in linking genetic risk to alcohol use in adulthood. Using data from a large sample of adults from extended families enriched for AUD, our findings indicated that individuals' alc-GPSs were associated with higher sensation seeking, which in turn was associated with higher levels of alcohol use. In addition, alc-GPS was associated with reduced social support from family (but not friends), which in turn was associated with more alcohol use. Furthermore, social support from friends (but not family) moderated the association between individuals' risk predispositions and alcohol use, such that the association between alc-GPS and alcohol use, as well as the association between sensation seeking and alcohol use, was attenuated by high levels of friend support. The findings revealed that the pattern of associations was similar between males and females; however, there were some differences in associations between social support and alcohol use across age groups.

Consistent with our hypothesis and prior work, we found a significant indirect effect of alc-GPS on alcohol use via sensation seeking, suggesting sensation seeking as a promising intermediate phenotype for understanding the mechanisms of genetic influences on alcohol use outcomes. Prior research on the role of sensation seeking in mediating genetic risk has focused on adolescents and emerging adults (Li et al., 2017; Ksinan et al., 2019). Our findings extend the literature to show that this pathway of risk and the role of sensation seeking are similar in adulthood, spanning across

emerging adulthood to middle adulthood, despite the decline in levels of sensation seeking across adulthood. This supports the promise of using sensation seeking to identify at-risk individuals across developmental stages for alcohol use intervention programs (Sargent et al., 2010).

Consistent with our hypothesis, we found evidence for two forms of gene–environment interplay involving the role of social support: rGE and GxE. Supporting the notion that rGE is an important pathway linking genetic risk to developmental outcomes, we found that alc-GPS was associated with lower levels of family support, which in turn were associated with greater levels of alcohol use. This finding of gene–environment correlation can reflect evocative (or reactive) rGE, whereby individuals' predispositions and related traits influence how others respond to them (e.g., the degree of support they provide). Further, because our sample included adults spanning multiple developmental stages, it is also possible that this gene–environment correlation reflects active rGE processes as well, such that individuals' alc-GPSs and related traits contribute to their choices and selections of environments (e.g., family). Generally, our finding is consistent with prior research demonstrating rGE in the family context as an important pathway of risk to alcohol use outcomes. For example, Elam et al. (2018) showed that polygenic risk for aggression was associated with lower levels of family cohesion in adolescence, which in turn was associated with alcohol use in young adulthood. We did not find significant associations between alc-GPS and friend support. This is inconsistent with previous research that provided evidence of rGE in the peer/friend context. For example, the polygenic risk for behavioral disinhibition was associated with affiliation with substance-using peers, in part via higher impulsivity and lower parental monitoring (Elam et al., 2017). It is possible that genetic predispositions toward alcohol use influence individuals' choice and selection of friends who share predispositions and behaviors similar to themselves but do not influence the perception of the amount and quality of support they receive from friends. Future research is needed to replicate our findings and also consider the role of other peer contextual factors, such as peer substance use, in linking genetic predispositions to alcohol use outcomes.

We also found evidence of GxE involving social support. Specifically, we found a significant interaction between alc-GPS and friend support in relation to alcohol use, such that high friend support buffered the association between alc-GPS and alcohol use. Similarly, high friend support also buffered the association between sensation seeking, a genetically influenced trait, and alcohol use. These findings are consistent with prior research suggesting the moderating role of social support on genetic influences (Barr et al., 2017; Su et al., 2019) and the broader literature suggesting the protective role of social support in alcohol use outcomes (Humphreys et al., 1999; Peirce et al., 2000). To our knowledge, this study is among the first to show that high social support buffers the risk associated with sensation seeking in relation to alcohol use. Prior research has largely documented the buffering role of social support for environmental risk factors, such as stress and negative life events (Mulia et al., 2008). Consistent with the social support buffering hypothesis (Cohen & Wills, 1985), our findings extend the literature to suggest that the relations between individuals' risk predispositions, indexed by both genetic risk and genetically influenced traits such as sensation seeking and alcohol use, are stronger for adults with lower levels of perceived social support.

Although both social support from family and social support from friends were associated with lower levels of alcohol consumption, our findings indicated some age differences in these associations. Higher support from family was associated with lower levels of drinking among emerging adults and middle-aged adults but not young adults. In contrast, higher support from friends was associated with lower alcohol use only among young adults (ages 30–44). It is interesting that although younger adults may have greater levels of perception of social support from friends, we did not find an association between friend support and alcohol use among emerging adults. This lack of association may in part reflect that alcohol use often occurs in social contexts among younger individuals (LaBrie et al., 2007). Thus, it is possible that support from friends in the younger adulthood years may not provide increased social control in limiting risky behaviors, including alcohol use. Because older adults' social networks tend to be smaller and include mostly emotionally close relationships, such as close family members, it is unsurprising that we found a link between support from family and alcohol use among middle-aged adults (Antonucci et al., 2004; Levitt et al., 1993). Finally, among the young adults in our sample, only friend support, but not family support, was associated with alcohol use. Young adulthood is characterized by changes in responsibilities associated with adult social roles, such as marriages and parenthood (McCormick et al., 2011). It is possible that family support is already reflected in these adult roles. For example, prior research has shown that new adult social roles are inversely associated with drinking because of the increased social control that these new roles/responsibilities offer (e.g., Barr et al., 2017; Christie-Mizell & Peralta, 2009). Our analyses of age differences based on broad age categories revealed interesting age differences in the pattern of associations between social support and alcohol use. An important next step would be to examine the within-person pattern of change in these relations across the adulthood years.

This study has a number of strengths. First, we used a genetically informative design to understand the mechanisms through which genetic risk unfolds to influence alcohol use. Notably, our results showed that alcohol consumption polygenic scores remained significantly associated with phenotypic alcohol use, above and beyond the effects of important covariates (e.g., age, sex); sensation seeking; and social support from family and friends. This highlights the robustness of genetic effects and the need to examine other biological and psychosocial mechanisms underlying the genetic risk for alcohol use outcomes. Second, we conducted simultaneous tests of sensation seeking and social support as indirect pathways to delineate the pathways by which genetic influences affect alcohol use. Considering multiple mediating pathways simultaneously allowed for an examination of the unique effects of each specific pathway. In addition, we considered alternative conceptual models to examine both rGE and GxE, allowing for a more comprehensive examination of the varying roles that social support could play in the relation between alc-GPS and alcohol use. We also considered social support from family and friends, allowing us to understand whether pathways of associations vary across sources of social support. Furthermore, we used the state-of-the-science GPS approach to characterize individuals' genetic predispositions using results from a large

GWAS study to capture the polygenic nature of the alcohol use phenotype. Finally, we used a large sample of adults with a wide age range, allowing us to examine potential age differences in the associations across emerging to middle adulthood.

Several limitations of this study need to be considered in interpreting the findings. First, we only focused on participants of European ancestry in COGA because the discovery samples in the GWAS study were primarily of European descent, and a mismatch in ancestry between discovery and target samples can result in bias in GPS prediction (Martin et al., 2017). Thus, it is not clear whether our findings are generalizable to non-European populations. Second, social support and alcohol use were both measured at T2, and these measures lack time precedence. Thus, inferences about causal relations need to be made cautiously, and it is possible that the association between social support and alcohol use is bidirectional. Third, we examined sensation seeking as an intermediate phenotype that links alc-GPS to alcohol use. However, there are alternative models that could also explain the association between alc-GPS, sensation seeking, and alcohol use, whereby sensation seeking and alcohol use are indicators of a common underlying factor (e.g., externalizing; Krueger et al., 2002) that is influenced by genetic factors (e.g., alc-GPS). Future research is warranted to test these alternative models to better characterize the relations between sensation seeking and alcohol use and their underlying genetic etiology. Fourth, we examined a conceptual model that considers rGE, with social support serving as an indirect pathway between genetic influences and alcohol use. However, we acknowledge that there can be other alternative explanations for the association between genetic risk, social support, and alcohol use, such as epiphenomenon. Finally, COGA is a high-risk sample with participants from extended families enriched for AUD, and the findings from this study may not be generalizable to other samples with different recruitment strategies (Savage et al., 2018). Future research is needed to replicate our findings in community- and population-based samples.

In conclusion, our results show that sensation seeking serves as an important indirect pathway linking genetic influences to alcohol use. Social support plays an important role in linking genetic risk to alcohol use, as well as buffering individuals' risk predispositions in relation to alcohol use. Our findings emphasize the important role of intermediate phenotypes and gene–environment interplay, including both rGE and GxE processes, in the pathways of risk from genetic predispositions to complex alcohol use outcomes. Our results highlight the potential roles of sensation seeking and social support as targets for prevention and intervention efforts aimed at mitigating the risk for alcohol use outcomes in adulthood.

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