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RESEARCH ARTICLE

Association of parental divorce, discord, and polygenic risk with children's alcohol initiation and lifetime risk for alcohol use disorder

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Abstract

Background: Parental divorce and discord are associated with poorer alcohol-related outcomes for offspring. However, not all children exposed to these stressors develop alcohol problems. Our objective was to test gene-by-environment interaction effects whereby children's genetic risk for alcohol problems modifies the effects of parental divorce and discord to predict alcohol outcomes.

Methods: The sample included European (EA; $N = 5608$, 47% male, $M_{age} \sim 36$ years) and African (AA; $N = 1714$, 46% female, $M_{age} \sim 33$ years) ancestry participants from the Collaborative Study on the Genetics of Alcoholism. Outcomes included age at initiation of regular drinking and lifetime DSM-5 alcohol use disorder (AUD). Predictors included parental divorce, parental relationship discord, and offspring alcohol problems polygenic risk scores (PRS_{ALC}). Mixed effects Cox proportional hazard models were used to examine alcohol initiation and generalized linear mixed effects models were used to examine lifetime AUD. Tests of PRS moderation of the effects of parental divorce/relationship discord on alcohol outcomes were examined on multiplicative and additive scales.

Results: Among EA participants, parental divorce, parental discord, and higher PRS_{ALC} were associated with earlier alcohol initiation and greater lifetime AUD risk. Among AA participants, parental divorce was associated with earlier alcohol initiation and discord was associated with earlier initiation and AUD. PRS_{ALC} was not associated with either. Parental divorce/discord and PRS_{ALC} interacted on an additive scale in the EA sample, but no interactions were found in AA participants.

Conclusions: Children's genetic risk for alcohol problems modifies the impact of parental divorce/discord, consistent with an additive model of diathesis–stress interaction, with some differences across ancestry.

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KEYWORDS
alcohol use disorder, divorce, gene–environment, parental conflict, polygenic scores

INTRODUCTION

Parental divorce and relationship discord are common adverse childhood experiences and are associated with offspring alcohol misuse (Arkes, 2013; Jackson et al., 2016; Thompson et al., 2008). In the United States, more than 1 million children and adolescents go through the process of parental divorce each year (Bing et al., 2009), and 28.2% of American adults experience parental separation/divorce prior to age 18 (Giano et al., 2020). Additionally, exposure to parental marital conflict is common among children, even in the absence of parental divorce/separation (Amato et al., 1995; Amato & Sobolewski, 2001). Parental divorce and parental discord are, on average, associated with a range of poorer outcomes among offspring (Amato & Keith, 1991; Auersperg et al., 2019). Because a large number of people are exposed to parental divorce and parental discord while growing up, the issue of how exposure to parental divorce and parental discord might influence children's development is of long-standing interest to families, clinicians, researchers, and policymakers. In the case of alcohol outcomes, exposure to parental divorce and parental relationship discord is associated with offspring alcohol use behaviors, including earlier initiation of drinking (Jackson et al., 2016; Sartor et al., 2007) and the development of alcohol use disorder (AUD; Grant et al., 2015; Thompson et al., 2008).

However, not all offspring exposed to parental divorce and parental relationship discord go on to experience alcohol-related problems (Amato, 2001). Accordingly, it is important to better understand variability in offspring's response to parental divorce and parental relationship discord. Offspring genetic factors are one plausible contributor to variability in offspring responses to parental divorce and discord. For example, there is evidence that the effects of parental divorce on offspring risk for early alcohol initiation and risk for AUD are the strongest among those with a parental history of AUD (Thompson et al., 2008; Waldron et al., 2014). This pattern of effects could be consistent with the diathesis–stress mechanisms of gene-by-environment interaction (GxE; Shanahan & Hofer, 2005), whereby individuals respond differently to stressor (e.g., family adversity) based on a vulnerability factor (i.e., familial risk for AUD, which is a mixture of both genetic and environmental influences; Kendler et al., 2015). These findings suggest that variability in responses to parental divorce and parental discord may be attributable, in part, to offspring's own genetic predisposition for AUD (Pilowsky et al., 2009). This possibility was previously explored in one molecular genetic study, and results showed that the effects of parental divorce on Dutch adolescents' externalizing behavioral problems differed as a function of offspring's dopamine receptor D4 (*DRD4*) genotype (Nederhof et al., 2012). Although the results of this candidate G×E study provide initial evidence, the candidate gene approach no longer represents the state of the science because complex behaviors, including alcohol outcomes, have a polygenic architecture that includes the effects of many variants across the genome (Kranzler et al., 2019; Plomin, 2019). Moreover, candidate G×E studies often fail to replicate and are subject to publication bias (Dick et al., 2015; Duncan & Keller, 2011).

The present study addresses limitations of prior studies to examine whether offspring genetic predispositions for alcohol problems, as characterized by the polygenic scoring approach, moderate the effects of parental divorce and parental relationship discord on offspring alcohol outcomes in a high-risk, ancestrally diverse Collaborative Study on the Genetics of Alcoholism (COGA) sample. Genome-wide polygenic scores (PRS) represent an individual's overall genetic liability for a given behavior/trait. This approach involves summing the number of alleles for each common genetic variants (single-nucleotide polymorphisms; SNPs), weighted by the effect size drawn from the results from genome-wide association study (GWAS) in a large-scale discovery sample (Bogdan et al., 2018). We tested two preregistered hypotheses (osf.io/nambu):

1. Parental divorce, parental relationship discord, and higher offspring alcohol problems polygenic scores will be associated with (a) earlier age at first regular drinking and (b) higher risk of developing an alcohol use disorder.
2. The associations of parental divorce and parental relationship discord with (a) earlier age at first regular drinking and (b) higher risk of developing an alcohol use disorder (AUD) will be stronger among offspring with higher alcohol problems polygenic scores.

MATERIALS AND METHODS

COGA is a diverse family-based study whose objective is to identify genetic and environmental factors implicated in the development of AUD and related psychiatric disorders (Begleiter et al., 1995; Bucholz et al., 2017; Reich et al., 1998). Probands were identified through alcohol treatment centers across seven sites in the United States. Probands along with their families were invited to participate if the family was sufficiently large (usually sibships >3 with parents available), with two or more members living in the COGA site's catchment area. Comparison families were recruited from the same communities. The Institutional Review Board at all data collection sites approved the study, and written consent (and assent for adolescents) was obtained from all participants. The present study made use of data from participants of European or African ancestry, the two largest ancestry groups in COGA, as determined by genetic ancestry principal component analysis. Analytic sample sizes differed across the outcome measures of interest and ranged from 4638 to 5608 in the European ancestry sample (47% male; M_{age} = 36.26 years,

SD = 14.05) and 1215 to 1714 in the African ancestry sample (46% male; M_{age} = 33.46 years, SD = 11.89).

Measures

Alcohol outcomes

Measures of alcohol initiation and lifetime alcohol use disorders were coded from the Semi-Structured Assessment for the Genetics of Alcoholism Interview (Bucholz et al., 1994; Hesselbrock et al., 1999). Age of initiating regular drinking was coded from participants' response to the question, "At what age did you begin to drink regularly; that is, drinking at least once a month for 6 months or more," measured in years. Lifetime diagnoses (binary) of alcohol use disorder were made based on Diagnostic and Statistical Manual of Mental Disorder (DSM-5) criteria (American Psychiatric Association, 2013). To ensure that participants had passed through the period of highest risk for onset of AUD before being classified as unaffected, those <23 years of age at their assessment who were without an AUD diagnosis were set to missing.

Parental divorce and perceptions of parental relationship discord

Participants' retrospective reports of whether their parents were divorced/separated while growing up between the ages of 6 and 13 were coded from questions concerning parental absence due to divorce and shared custody living arrangements from the Home Environment Interview section of the SSAGA (Bucholz et al., 1994; Holmes & Robins, 1988). Participants also retrospectively reported on their perceptions of parental relationship discord using five questions. These items asked participants about the quality of their parents' marriage/relationship (rated on a 4-point scale, from *poor* to *excellent*) and how much conflict or tension there was in the household (rated on a 4-point scale, from *none* to *a lot*); and three yes/no questions: whether their parents usually seemed to enjoy each other; whether their parents often argued or fought in front of them; and whether either of their parents ever hit the other. A composite measure was calculated by taking the prorated sum of the items for participants who responded to at least three items. Response options were 0 (*no*) and 1 (*yes*) for binary items. For other questions, the response was made using a 4-point ordinal scale. Items were rescaled to range between 0 and 1 (0, 0.33, 0.66, 1) so that ordinal and binary items were weighted similarly into the prorated sum. A full description of the development of parental relationship discord composite is detailed in Thomas et al. (2022).

Genotyping and alcohol problems polygenic scores

Participants' DNA samples were genotyped using the Illumina Human1M array (Illumina), the Illumina Human OmniExpress 12V1 array (Illumina), the Illumina 2.5 M array (Illumina), or the Smokescreen genotyping array (Biorealm LLC). A full description of data processing, quality control, and imputation is available in Lai et al. (2019). Data were imputed to 1000 Genome Phase 3, and single-nucleotide polymorphisms (SNPs) with a genotyping rate <0.95, that violated Hardy–Weinberg equilibrium ($p < 10^{-6}$), or had minor allele frequency (MAF) <0.01 were excluded from analysis.

To avoid population stratification (Cardon & Palmer, 2003), we conducted our analyses separately by ancestry group. Genetic ancestry principal components were computed from GWAS data using Eigenstrat (Price et al., 2006) and the 1000 Genomes, Phase III reference panel. Individuals were assigned an ancestry classification (European, African, or Other) based on the first two principal components. Our analyses included participants of European (EA) and African (AA) ancestry.

Genetic risk for alcohol problems was indexed by constructing genome-wide polygenic risk scores (PRS), which are aggregate measures of the number of risk alleles individuals carry, weighted by effect sizes from GWAS summary statistics. We used PRS-CSx (Ruan et al., 2022) to construct the polygenic scores. This approach uses ancestry-specific discovery sample GWAS weights, paired with linkage disequilibrium information from an ancestry-matched external reference panel, to estimate the posterior effect size for each SNP. For participants of European ancestry, we used discovery sample GWAS summary statistics for alcohol problems in individuals of European ancestry from a recent meta-analysis of GWAS weights from the Psychiatric Genomics Consortium (PGC) DSM-IV alcohol dependence analyses (COGA sample removed; Walters et al., 2018), the UKBiobank AUDIT-P analyses (Sanchez-Roige et al., 2017), and the Million Veteran Program (MVP) alcohol use disorder analysis (Kranzler et al., 2019; Zhou et al., 2020). For participants of African ancestry, we used GWAS summary statistics from a meta-analysis of the European ancestry in tandem with GWAS summary statistics from the PGC DSM-IV alcohol dependence analyses (COGA sample removed; Walters et al., 2018) and MVP alcohol use disorder analysis (Kranzler et al., 2019) in individuals of African ancestry. Because PRS-CSx improves predictive power for non-European ancestry samples with smaller GWAS (Ruan et al., 2022), we included both the European and African ancestry-derived polygenic scores in the AA sample in COGA, but just the European ancestry-derived polygenic scores in the EA sample in COGA.

Covariates

Covariates included age at last assessment, sex, birth cohort, and the first 10 genetic ancestry principal components (PC1-10) in all analyses. Birth cohort was dummy coded using the generational cohort scheme from Bourdon et al. (2020): silent [b. prior to 1945]; baby boomer [b. 1946 to 1964]; generation X [b. 1965

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TABLE 1 Descriptive statistics for key study variables in European and African ancestry participants.

Alcohol phenotype	Sex	Age	ALC[a]	Parental divorce	Parental discord
	N_{male} (%)	M (SD)	M (SD)/*N* (%)	*N* (%)	M (SD)
European ancestry					
Initiation	2645 (47%)	36.26 (14.05)	18.13 (5.21)	735 (14%)	1.56 (1.47)
Valid *N*	5608	5608	5051	5608 (557 censored)[b]	5099 (503 censored)[b]
AUD Dx	2297 (47%)	38.98 (13.21)	2890 (59%)	532 (11%)	1.59 (1.49)
Valid *N*	4834	4834	4834	4834	4638
African ancestry					
Initiation	793 (46%)	33.46 (11.89)	18.88 (4.91)	417 (24%)	1.74 (1.50)
Valid *N*	1714	1714	1419	1714 (295 censored)[b]	1397 (234 censored)[b]
AUD Dx	639 (46%)	36.73 (10.86)	725 (52%)	290 (21%)	1.76 (1.53)
Valid *N*	1383	1383	1383	1383	1215

Abbreviations: ALC, alcohol phenotype; AUD Dx, DSM-5 Alcohol Use Disorder diagnoses; Initiation, age at initiation of regular drinking.

[a]Mean and standard deviation are provided for continuous outcome (age at initiation of regular drinking), and *N* and percentage are provided for dichotomous outcome (AUD Dx).

[b]Participants that did not report initiation of regular drinking were censored at their age at last interview for the Cox proportional hazard models.

to 1980]; and millennial [b. 1981 to 1996], with baby boomer set as reference.

Analytic plan

We conducted analyses to examine the relation between parental divorce, parental relationship discord, offspring alcohol problems polygenic scores (PRS_{ALC}), and alcohol outcomes (i.e., initiation of regular drinking and alcohol use disorder). The parental divorce and parental relationship discord models were run separately in view of prior evidence that both parental marital status and the tenor of their relationship represent separate and unique influences on children's outcomes (Gager et al., 2016), including their alcohol outcomes (Salvatore et al., 2022). Additionally, we note that although a great deal of conflict between parents likely precedes marital dissolution, the potential mechanisms contributing to increased risk for poorer offspring alcohol outcomes associated with parental divorce and parental relationship discord may be different. For example, on average, divorce is associated with reductions in social and economic capital (e.g., income loss; Raley & Sweeney, 2020) and decreases in effective parenting behaviors such as parental monitoring (Amato & Keith, 1991), which is consistently linked with offspring alcohol use behaviors (Jackson & Schulenberg, 2013) likely via increased access to alcohol. In contrast, offspring may use alcohol to cope with distress associated with parental relationship discord (Kuntsche et al., 2005). Thus, because of potential differential mechanisms underlying the associations between parental divorce/relationship discord and offspring alcohol outcomes, separate models were run.

We examined time-to-alcohol initiation in mixed effects Cox regression models using the *coxme* package (Therneau, 2020) for R (R Development Core Team, 2019). We examined the likelihood of alcohol use disorder diagnosis with generalized linear mixed effects models with a logit link using the *lme4* package (Bates et al., 2015). Because COGA included related individuals (i.e., individuals nested in families), these mixed effect models adjusted for familial clustering with a random intercept for family grouping.

We conducted analyses in two stages. We first examined the main effects of parental divorce/parental relationship discord, offspring PRS_{ALC} for the time-to-initiation of regular drinking and likelihood of lifetime AUD. Age and parental relationship discord were mean centered. The alcohol problems PRS and 10 PCs were standardized to have a mean of 0 and standard deviation of 1.

Next, to examine the interaction effects between parental divorce/parental relationship discord and offspring PRS_{ALC} on alcohol outcomes, product terms between mean-centered parental divorce/discord and PRS_{ALC} were calculated (i.e., parental divorce × PRS_{ALC}; parental relationship discord × PRS_{ALC}) and added to the previous main effects models. A statistically significant product term would provide evidence for interaction on a multiplicative scale. For example, when the combined effect of parental divorce/discord and PRS_{ALC} is larger (or smaller) than the *product* of the individual effects, this would indicate an interaction on a multiplicative scale. Alternatively, if the combined effect of parental divorce/discord and PRS_{ALC} is larger (or smaller) than the *sum* of the individual effects of parental divorce/discord and PRS_{ALC}, this would be consistent with interpretation for interaction on an additive scale (Knol et al., 2007; Li & Chambless, 2007). A relative excess risk due to interaction (RERI) of zero would indicate there is no interaction on the additive scale (i.e., perfect additivity). A RERI >0 indicates positive interaction on an additive scale, whereas a RERI <0 indicates negative interaction on an additive scale. For all a priori hypotheses, we used a *p*-value threshold of $p < 0.05$ for inference criteria. All analyses were conducted separately for EA and AA samples to accommodate the inclusion of the polygenic scores.

RESULTS

Descriptive statistics

Descriptive statistics for the key study variables are summarized in Table 1, separately for each ancestry group. In the European ancestry sample, age at initiation of regular drinking was 18.13 years and approximately 59% of the sample met lifetime criteria for DSM-5 AUD. Approximately 14% of the sample experienced parental divorce. In the African ancestry sample, age at initiation of regular drinking was 18.88 years, and approximately 52% of the sample met lifetime criteria for DSM-5 AUD. Approximately 24% of the sample experienced parental divorce.

Analyses of time-to-initiation of regular drinking

The results from the main effects Cox models of age at regular drinking as a function of parental divorce/discord and offspring PRS_{ALC} are summarized in Table 2, and the results from the Cox models examining the interactive effects between parental divorce/discord and offspring PRS_{ALC} are summarized in Table 3. Results are presented for each ancestry group separately.

Parental divorce

As shown in Table 2, in the EA sample, exposure to parental divorce and higher PRS_{ALC} significantly increased the hazard of initiating regular alcohol use. In contrast, in the AA sample, only exposure to parental divorce, but not PRS_{ALC}, significantly increased the hazard of initiating regular alcohol use.

As shown in Table 3, in the EA sample, there was no evidence of interaction between exposure to parental divorce and offspring PRS_{ALC} on a multiplicative. However, the combined effect of parental divorce and PRS_{ALC} (i.e., HR = exp (0.30 + 0.14 + 0.01) = 1.57) was not equal to the sum of the individual effects, providing evidence of the presence of interaction on an additive scale (RERI = 1.57 − 1.35 − 1.15 + 1 = 0.07). A RERI of 0.07 indicates the increased hazard due to additive interaction. In the AA sample, there was no evidence of interaction between parental divorce and PRS_{ALC} on a multiplicative or additive scale.

TABLE 2 Hazard ratio of timing at initiation of regular drinking as a function of parental divorce, parental discord, and offspring alcohol problems polygenic score in the European and African ancestry samples.

	European ancestry				African ancestry			
	Parental divorce model (*N* = 5608)		Parental discord model (*N* = 5099)		Parental divorce model (*N* = 1714)		Parental discord model (*N* = 1397)	
Parameter	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Divorce/Discord	**1.35**	**1.23, 1.48**	**1.08**	**1.06, 1.10**	**1.17**	**1.02, 1.35**	**1.07**	**1.03, 1.12**
PRS_{ALC}	**1.15**	**1.11, 1.18**	**1.14**	**1.10, 1.18**	1.00	0.94, 1.07	1.00	0.93, 1.07
Covariates								
Age (years)	**0.97**	**0.96, 0.97**	**0.97**	**0.97, 0.98**	**0.98**	**0.97, 0.99**	**0.99**	**0.98, 1.00**
Sex (male)	**1.50**	**1.41, 1.59**	**1.58**	**1.48, 1.68**	**1.91**	**1.71, 2.14**	**2.07**	**1.82, 2.34**
Silent	1.08	0.94, 1.23	0.99	0.86, 1.14	0.90	0.64, 1.25	0.76	0.53, 1.08
Generation X	1.01	0.91, 1.11	1.00	0.89, 1.11	**0.80**	**0.66, 0.96**	0.84	0.68, 1.04
Millennial	**0.91**	**0.82, 1.01**	0.91	0.81, 1.02	0.83	0.68, 1.02	0.94	0.74, 1.21
PC1	1.00	0.96, 1.03	0.98	0.93, 1.03	1.05	0.96, 1.15	1.03	0.93, 1.13
PC2	**1.05**	**1.02, 1.09**	**1.06**	**1.02, 1.10**	0.99	0.92, 1.07	1.01	0.93, 1.10
PC3	0.98	0.94, 1.01	0.98	0.95, 1.02	1.00	0.91, 1.10	0.98	0.89, 1.09
PC4	1.02	0.97, 1.06	1.01	0.96, 1.05	1.03	0.96, 1.11	1.06	0.97, 1.16
PC5	0.96	0.92, 1.00	**0.94**	**0.90, 0.99**	0.97	0.90, 1.04	0.97	0.90, 1.06
PC6	0.99	0.95, 1.04	1.01	0.97, 1.06	0.97	0.90, 1.05	0.97	0.89, 1.05
PC7	0.97	0.92, 1.02	0.97	0.92, 1.02	0.94	0.81, 1.09	0.93	0.79, 1.09
PC8	0.99	0.93, 1.05	0.99	0.93, 1.05	1.04	0.90, 1.21	1.02	0.87, 1.20
PC9	1.00	0.95, 1.05	1.00	0.95, 1.06	1.00	0.94, 1.06	0.99	0.92, 1.06
PC10	0.96	0.92, 1.00	0.96	0.92, 1.00	1.04	0.96, 1.13	1.01	0.93, 1.11

Note: Birth cohort was dummy-coded indexing generation status, defined as silent [b. prior to 1945]; baby boomer [b. 1946 to 1964]; generation X [b. 1965 to 1980]; and millennial [b. 1981 to 1996], with baby boomer set as reference. Separate models were run for parental divorce and parental relationship discord. Bold type indicates estimate $p < 0.05$.

Abbreviations: CI, confidence interval; HR, hazard ratio; PC, principal component for genetic ancestry; PRS_{ALC}, offspring alcohol problems polygenic score.

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TABLE 3 Hazard ratio of timing at initiation of regular drinking as a function of parental divorce, parental discord, offspring alcohol problems polygenic score, and two-way interactions between parental divorce/discord and polygenic scores in the European and African ancestry samples.

	European ancestry				African ancestry			
	Parental divorce model ($N = 5608$)		Parental discord model ($N = 5099$)		Parental divorce model ($N = 1714$)		Parental discord model ($N = 1397$)	
Parameter	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Divorce/Discord	**1.35**	**1.23, 1.48**	**1.08**	**1.05, 1.10**	**1.17**	**1.01, 1.34**	**1.07**	**1.03, 1.12**
PRS	**1.15**	**1.11, 1.19**	**1.14**	**1.10, 1.18**	1.02	0.95, 1.10	1.00	0.93, 1.07
Divorce/Discord × PRS_{ALC}	1.01	0.93, 1.10	1.02	1.00, 1.04	0.93	0.82, 1.06	1.01	0.97, 1.05
Covariates								
Age (years)	**0.97**	**0.96, 0.97**	**0.97**	**0.97, 0.98**	**0.98**	**0.97, 0.99**	**0.99**	**0.98, 1.00**
Sex (male)	**1.50**	**1.41, 1.59**	**1.58**	**1.49, 1.68**	**1.91**	**1.71, 2.14**	**2.07**	**1.83, 2.34**
Silent	1.08	0.94, 1.23	1.00	0.86, 1.15	0.90	0.65, 1.26	0.75	0.53, 1.07
Generation X	1.01	0.91, 1.11	1.00	0.90, 1.11	**0.79**	**0.66, 0.96**	0.84	0.68, 1.04
Millennial	0.91	0.82, 1.01	0.91	0.81, 1.02	0.83	0.68, 1.02	0.94	0.74, 1.21
PC1	1.00	0.96, 1.03	0.98	0.93, 1.03	1.05	0.96, 1.15	1.03	0.93, 1.13
PC2	**1.05**	**1.02, 1.09**	**1.06**	**1.02, 1.10**	0.99	0.91, 1.07	1.01	0.93, 1.10
PC3	0.98	0.94, 1.01	0.98	0.95, 1.02	1.00	0.91, 1.10	0.99	0.89, 1.09
PC4	1.02	0.97, 1.06	1.01	0.96, 1.05	1.03	0.96, 1.11	1.06	0.97, 1.16
PC5	0.96	0.92, 1.00	**0.94**	**0.90, 0.99**	0.97	0.90, 1.04	0.97	0.90, 1.05
PC6	0.99	0.95, 1.04	1.01	0.97, 1.06	0.97	0.90, 1.05	0.97	0.89, 1.05
PC7	0.97	0.92, 1.02	0.97	0.92, 1.02	0.94	0.81, 1.09	0.93	0.79, 1.09
PC8	0.99	0.93, 1.05	0.99	0.93, 1.05	1.04	0.90, 1.21	1.02	0.87, 1.20
PC9	1.00	0.95, 1.05	1.00	0.95, 1.06	1.00	0.94, 1.06	0.99	0.92, 1.06
PC10	0.96	0.92, 1.00	0.96	0.92, 1.00	1.04	0.96, 1.13	1.02	0.93, 1.11

Note: Birth cohort was dummy-coded indexing generation status, defined as silent [b. prior to 1945]; baby boomer [b. 1946 to 1964]; generation X [b. 1965 to 1980]; and millennial [b. 1981 to 1996], with baby boomer set as reference. Separate models were run for parental divorce and parental relationship discord. Bold type indicates estimate $p < 0.05$.

Abbreviations: CI, confidence interval; HR, hazard ratio; PC, principal component for genetic ancestry; PRS_{ALC}, alcohol problems polygenic score.

Parental relationship discord

As shown in Table 2, in the EA sample, higher parental relationship discord and higher PRS_{ALC} significantly increased the hazard of initiating regular alcohol use. In contrast, in the AA sample, only exposure to parental divorce, but not PRS_{ALC}, significantly increased the hazard of initiating regular alcohol use.

As shown in Table 3, in the EA sample, there was no evidence of interaction between parental relationship discord and offspring PRS_{ALC} on a multiplicative scale. However, the combined effect of parental relationship discord and PRS_{ALC} (i.e., HR = exp (0.07 + 0.13 + 0.02) = 1.25) was not equal to the sum of the individual effects, providing evidence of the presence of interaction on an additive scale (RERI = 1.25 − 1.08 − 1.14 + 1 = 0.03). A RERI of 0.03 indicates the increased hazard due to additive interaction. In the AA sample, there was no evidence of interaction between parental relationship discord and offspring PRS_{ALC} on a multiplicative or additive scale.

Analyses of predicting likelihood of alcohol use disorder diagnoses

The results from generalized linear mixed effects model of alcohol use disorder diagnoses as a function of parental divorce/discord and offspring PRS_{ALC} are summarized in Table 4, and the results from the models examining the interactive effects between parental divorce/discord and offspring PRS_{ALC} are summarized in Table 5. Results are presented for each ancestry group separately.

Parental divorce

As shown in Table 4, in the EA sample, exposure to parental divorce and higher offspring PRS_{ALC} was associated with higher likelihood of lifetime AUD. In the AA sample, exposure to parental divorce and offspring PRS_{ALC} was not associated with lifetime AUD.

TABLE 4 Likelihood of alcohol use disorder as a function of parental divorce, parental discord, and offspring alcohol problems polygenic score in the European and African ancestry samples.

	European ancestry				African ancestry			
	Parental divorce model ($N = 4834$)		Parental discord model ($N = 4638$)		Parental divorce model ($N = 1383$)		Parental discord model ($N = 1215$)	
Parameter	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Divorce/Discord	**1.41**	**1.11, 1.79**	**1.23**	**1.17, 1.29**	1.23	0.90, 1.68	**1.15**	**1.05, 1.25**
PRS_{ALC}	**1.34**	**1.25, 1.44**	**1.31**	**1.21, 1.40**	0.95	0.84, 1.09	0.95	0.83, 1.10
Covariates								
Age (years)	**0.94**	**0.92, 0.95**	**0.94**	**0.93, 0.95**	**0.97**	**0.95, 1.00**	0.98	0.96, 1.01
Sex (male)	**3.56**	**3.11, 4.07**	**3.91**	**3.41, 4.50**	**3.48**	**2.76, 4.39**	**3.70**	**2.88, 4.76**
Silent	**1.44**	**1.05, 1.97**	**1.43**	**1.04, 1.97**	1.31	0.66, 2.62	1.27	0.62, 2.60
Generation X	**0.54**	**0.42, 0.70**	**0.59**	**0.46, 0.75**	**0.38**	**0.24, 0.59**	**0.44**	**0.28, 0.70**
Millennial	**0.52**	**0.40, 0.69**	**0.62**	**0.47, 0.82**	**0.52**	**0.32, 0.87**	0.77	0.44, 1.35
PC1	1.04	0.96, 1.12	1.03	0.95, 1.13	0.94	0.79, 1.12	0.90	0.75, 1.09
PC2	1.06	0.98, 1.16	1.07	0.98, 1.18	1.06	0.89, 1.25	1.08	0.90, 1.30
PC3	0.97	0.89, 1.05	0.98	0.90, 1.06	0.81	0.66, 1.00	0.82	0.66, 1.01
PC4	1.01	0.92, 1.11	1.00	0.91, 1.10	1.15	0.96, 1.38	1.14	0.92, 1.40
PC5	**0.91**	**0.83, 1.00**	**0.91**	**0.83, 1.00**	0.88	0.75, 1.03	0.88	0.75, 1.04
PC6	**1.18**	**1.07, 1.30**	**1.19**	**1.08, 1.32**	1.07	0.91, 1.26	1.08	0.90, 1.28
PC7	0.95	0.85, 1.06	0.93	0.83, 1.04	0.75	0.56, 0.99	**0.72**	**0.53, 0.97**
PC8	1.01	0.89, 1.13	1.01	0.90, 1.15	0.91	0.68, 1.21	0.90	0.66, 1.23
PC9	1.08	0.97, 1.21	1.08	0.97, 1.20	0.97	0.85, 1.10	0.98	0.85, 1.12
PC10	0.94	0.86, 1.03	0.94	0.86, 1.03	1.03	0.88, 1.21	1.08	0.91, 1.29

Note: Birth cohort was dummy-coded indexing generation status, defined as silent [b. prior to 1945]; baby boomer [b. 1946 to 1964]; generation X [b. 1965 to 1980]; and millennial [b. 1981 to 1996], with baby boomer set as reference. Separate models were run for parental divorce and parental relationship discord. Bold type indicates estimate $p < 0.05$.

Abbreviations: CI, confidence interval; OR, odds ratio; PC, principal component for genetic ancestry; PRS_{ALC}, offspring alcohol problems polygenic score.

As shown in Table 5 and visually summarized in Figure S1, in the EA sample, there was no evidence of interaction between parental divorce and offspring PRS_{ALC} on a multiplicative scale. However, the combined effect of parental divorce and PRS_{ALC} (i.e., OR = exp (0.34 + 0.29 + 0.07) = 2.01) was not equal to the sum of the individual effects, providing evidence of the presence of interaction on an additive scale (RERI = 2.01 − 1.41 − 1.33 + 1 = 0.27). A RERI of 0.27 indicates that the risk of developing AUD among individual exposed to parental divorce is 0.27 more with every unit increase in PRS_{ALC} than if there were no interaction between parental divorce and PRS. In the AA sample, there was no evidence of interaction between parental divorce and offspring PRS_{ALC} on a multiplicative or additive scale.

Parental relationship discord

As shown in Table 4, in the EA sample, parental relationship discord and higher PRS_{ALC} were associated with higher likelihood of lifetime AUD. In the AA sample, parental relationship discord, but not PRS_{ALC}, was associated with higher likelihood of AUD.

As shown in Table 5 and as visually summarized in Figure S2, in the EA sample there was no evidence of interaction between parental relationship discord and offspring PRS_{ALC} on a multiplicative scale. However, the combined effect of parental relationship discord and PRS_{ALC} (i.e., OR = exp (0.21 + 0.27 + 0.04) = 1.68) was not equal to the sum of the individual effects, providing evidence of the presence of interaction on an additive scale (RERI = 1.68 − 1.23 − 1.31 + 1 = 0.14). A RERI of 0.14 indicates that for every unit increase in parental relationship discord and every unit increase in PRS_{ALC}, the relative risk of developing AUD is 0.14 more than if there were no interaction. In the AA sample, there was no evidence of interaction between parental relationship discord and offspring PRS_{ALC} on a multiplicative or additive scale.

DISCUSSION

Although parental divorce and parental discord are associated with offspring alcohol use behaviors, not all offspring exposed to these familial stressors go on to experience alcohol-related problems. In this study, informed by the diathesis–stress gene-by-environment

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TABLE 5 Likelihood of alcohol use disorder as a function of parental divorce, parental discord, offspring alcohol problems polygenic score, and two-way interaction terms between parental divorce/discord and polygenic scores in the European and African ancestry samples.

	European ancestry				African ancestry			
	Parental divorce model ($N = 4834$)		Parental discord model ($N = 4638$)		Parental divorce model ($N = 1383$)		Parental discord model ($N = 1215$)	
Parameter	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Divorce/Discord	**1.41**	**1.11, 1.79**	**1.23**	**1.17, 1.29**	1.22	0.90, 1.67	**1.15**	**1.05, 1.25**
PRS	**1.33**	**1.24, 1.44**	**1.31**	**1.21, 1.40**	0.98	0.85, 1.14	0.95	0.83, 1.10
Divorce/Discord × PRS_{ALC}	1.08	0.85, 1.36	1.04	0.99, 1.09	0.88	0.67, 1.17	1.02	0.94, 1.10
Covariates								
Age (years)	**0.94**	**0.92, 0.95**	**0.94**	**0.93, 0.95**	**0.97**	**0.95, 1.00**	0.98	0.96, 1.01
Sex (male)	**3.56**	**3.12, 4.08**	**3.91**	**3.40, 4.50**	**3.48**	**2.76, 4.39**	**3.71**	**2.88, 4.77**
Silent	**1.43**	**1.05, 1.97**	**1.45**	**1.05, 1.99**	1.33	0.67, 2.65	1.27	0.62, 2.60
Generation X	**0.54**	**0.43, 0.70**	**0.59**	**0.46, 0.75**	**0.37**	**0.24, 0.58**	**0.44**	**0.28, 0.70**
Millennial	**0.52**	**0.40, 0.69**	**0.62**	**0.47, 0.82**	**0.52**	**0.31, 0.86**	0.78	0.44, 1.36
PC1	1.04	0.96, 1.12	1.03	0.95, 1.13	0.94	0.79, 1.12	0.90	0.75, 1.09
PC2	1.06	0.98, 1.16	1.08	0.98, 1.18	1.05	0.89, 1.25	1.08	0.90, 1.30
PC3	0.96	0.89, 1.05	0.98	0.90, 1.06	0.82	0.67, 1.00	0.82	0.66, 1.01
PC4	1.01	0.91, 1.11	1.00	0.91, 1.10	1.15	0.96, 1.38	1.14	0.92, 1.41
PC5	**0.91**	**0.83, 1.00**	**0.91**	**0.83, 0.99**	0.88	0.75, 1.03	0.88	0.75, 1.04
PC6	**1.18**	**1.07, 1.30**	**1.19**	**1.08, 1.32**	1.07	0.91, 1.26	1.08	0.90, 1.28
PC7	0.95	0.85, 1.06	0.93	0.83, 1.04	**0.74**	**0.56, 0.99**	**0.72**	**0.53, 0.97**
PC8	1.01	0.89, 1.13	1.02	0.90, 1.15	0.90	0.67, 1.20	0.90	0.66, 1.23
PC9	1.08	0.97, 1.21	1.08	0.97, 1.20	0.97	0.86, 1.11	0.98	0.85, 1.13
PC10	0.94	0.86, 1.03	0.94	0.86, 1.03	1.03	0.87, 1.21	1.08	0.91, 1.29

Note: Birth cohort was dummy-coded indexing generation status, defined as silent [b. prior to 1945]; baby boomer [b. 1946 to 1964]; generation X [b. 1965 to 1980]; and millennial [b. 1981 to 1996], with baby boomer set as reference. Separate models were run for parental divorce and parental relationship discord. Bold type indicates estimate $p < 0.05$.

Abbreviations: CI, confidence interval; OR, odds ratio; PC, principal component for genetic ancestry; PRS_{ALC}, offspring alcohol problems polygenic score.

interaction model (Shanahan & Hofer, 2005), we sought to understand variability in offspring responses to these common familial adversities. We examined whether children's polygenic loading for alcohol problems modified the associations between parental divorce, parental discord, and regular drinking initiation and risk for developing alcohol use disorder in a high-risk, diverse sample of European and African ancestry participants.

In the EA sample, we found a pattern of results consistent with prior literature (Grant et al., 2015; Jackson et al., 2016; Sartor et al., 2007; Thompson et al., 2008) and our hypotheses that parental divorce and parental relationship discord were associated with earlier age at first regular drinking and higher likelihood of developing AUD. In the main effects models, higher polygenic loading for alcohol problems was also associated with earlier age at first regular drinking and higher risk for developing AUD. Most previous studies in this area focus on parental marital status rather than features of parental relationships, and it is notable that the pattern of results observed in the present study was generally consistent across parental divorce and relationship discord. This suggests that exposure to parental relationship discord (i.e., a potentially more common familial adversity, even in the absence of parental divorce) appears to have similar effects as compared to those of parental divorce. Our results highlight the need to consider the influence of parental relationship discord leading up to separation/divorce, as both parental relationship dissolution (e.g., divorce) and conflict between parents are associated with long-term offspring outcomes (Gager et al., 2016; Salvatore et al., 2022; Strohschein, 2012). Investigating whether the influence of parental relationship discord on children's alcohol outcomes is attenuated when parents dissolve their relationships is an important future direction.

We also found evidence of joint effects between parental divorce/discord and offspring genetic risk for alcohol problems in predicting alcohol outcomes. There was evidence of gene–environment interaction on an additive, but not on a multiplicative scale. The lack of evidence for interaction on a multiplicative scale indicates that the magnitude of associations between parental divorce/relationship discord on offspring alcohol outcomes did not differ based on offspring polygenic loading. Said another way, the pathogenic influence

of these forms of family stress on offspring alcohol outcomes was not limited to, for example, offspring with high PRS. Instead, the evidence for interaction on an additive scale suggests that the joint effects of parental divorce/discord and children's genetic risk for alcohol problems exceed the sum of their individual effects. In other words, the risk associated with familial adversity is compounded by offspring's polygenic loading for alcohol problems. This suggests that individuals with a higher genetic loading may need only minimal familial stress to experience an increased risk for alcohol problems. In contrast, individuals with a lower genetic loading may need higher levels of familial stress to develop alcohol problems. This pattern of effects is consistent with the additive model of gene–environment interaction diathesis–stress perspective (Karg & Sen, 2011; Monroe & Simons, 1991). Although prior studies of gene–environment interactions have typically focused on multiplicative gene–environment interactions (Nederhof et al., 2012; Thompson et al., 2008; Waldron et al., 2014), our findings highlight the importance of also considering additive gene–environment interactive effects. This is especially true from a public health perspective, as our findings indicate that the relative risk of developing AUD increases as a function of both children's polygenic predispositions, as well as their exposure to familial stressors.

In the AA sample, we found a pattern of effects consistent with our hypothesis that family relationship adversities are associated with poorer offspring alcohol outcomes. Parental divorce was associated with earlier age of initiating regular drinking but not with likelihood of developing AUD, though the effect was in the same direction as in the EA sample. In contrast, parental relationship discord was associated with both earlier age of initiating regular drinking and greater risk for developing AUD. We note that this pattern of findings is slightly different from what was found in the EA sample. Although the reasons why parental discord predicts both initiation of regular drinking and AUD but parental divorce only predicts initiation in the AA sample are unknown, it is consistent with some prior evidence that there are racial/ethnic differences in the effects of parental divorce on children's outcomes, which have shown that the adverse effects tend to be weaker for African American/Black children than European American/White children (Amato & Keith, 1991). The racial/ethnic disparities in how adverse family experiences influence alcohol use outcomes (Waldron et al., 2018) may, in part, be attributable to differences in how children react to family stressors across diverse populations (Cichy et al., 2012).

In addition, and contrary to our expectation, in the AA sample children's genetic risk for alcohol problems, as indexed with genome-wide polygenic scores, was not associated with initiation of regular drinking and AUD. Furthermore, we did not find evidence for an interaction between parental divorce/discord and PRS on either a multiplicative or additive scale in the African ancestry sample. These null findings are likely attributable to the limited predictive power of polygenic scores in individuals of African ancestry. Predictive power of polygenic scores is largely dependent on matching ancestry between the discovery sample and the independent target sample as well as the sample size of discovery GWAS (Martin et al., 2017). However, populations of non-European ancestry, particularly those of African ancestry, have been historically underrepresented in genome-wide association studies across the field (Popejoy & Fullerton, 2016) and limiting our ability to create well-powered polygenic scores in this ancestral population. Although we attempted to mitigate this issue with the PRS-CSx (Ruan et al., 2022) method, which integrates GWAS summary statistics of European ancestry and African ancestry populations to improve the performance of PRS, the predictive power of PRS in the AA sample was still attenuated. Accordingly, our findings should be viewed as initial evidence, and the question of whether and how genetic factors predict variability in individuals' response to common family stressors in non-European populations merits further investigation.

Our findings have several implications. First, our results underscore both parental divorce and parental discord as stressful family events that are linked to a child's future alcohol outcomes, including earlier alcohol initiation and risk for experiencing clinically significant alcohol problems. Second, in European ancestry families, our results show that family adverse events and children's genetic risk for alcohol problems interact on an additive, but not multiplicative, scale to influence children's key drinking milestones. This demonstrates that the effect of family adverse events and effect of children's genetic predisposition operate jointly in influencing their alcohol outcomes. The combined effect of family adverse events and children's genetic risk is greater than the sum of the individual effects of family adverse events and children's genetic risk. Individuals who are genetically predisposed to alcohol problems and exposed to parental divorce and discord may be an especially important group to target to reduce risk of developing alcohol problems. This highlights the importance of intervention efforts aimed toward reducing family relationship distress as well as strategies for helping families and children effectively cope with divorce and promoting adjustment (McClain et al., 2010; Wolchik et al., 2013). These gene–environment interaction results further imply that these intervention efforts may be especially beneficial for children at high genetic risk for alcohol problems.

Limitations

Our results should be interpreted within the context of the following limitations. First, COGA is a high-risk sample with participants from extended families enriched for alcohol use disorders. Our findings may not generalize to samples with different risk profiles. Second, our measure of parental relationship discord was derived from retrospectively reports from the child's perspective. Consequently, this measure may be subject to recall bias. It also may not objectively reflect the quality of parental marital relationships, as other studies report modest correlations between children's and parents' perceptions of parental relationship discord (Grych et al., 1992). Third, the timing of parental divorce and parental relationship discord while growing up were not assessed. Timing of these exposures may be important in view of evidence that younger children experience

more problems after the divorce of their parents than do children who are older (Lansford, 2009). Fourth, although we treated parental divorce and parental discord as predictors of alcohol outcomes, it is important to note that timing of parental divorce and parental discord was not modeled in relation to offspring alcohol outcomes. Thus, our results are not meant to be interpreted causally. Finally, we used genome-wide polygenic risk scores to index offspring genetic risk for alcohol problems and to examine gene–environment effects. At present, polygenic risk scores for alcohol outcomes have limited predictive ability, accounting for approximately <2% of the variation (Kranzler et al., 2019; Sanchez-Roige et al., 2017; Walters et al., 2018; Zhou et al., 2020).

CONCLUSIONS

In a sample selected for high familial risk for alcohol use disorder, parental divorce and children's polygenic loading for alcohol problems were independently and jointly associated with earlier age at initiation and the likelihood of developing clinically significant alcohol problems, with some evidence for differences across ancestral populations. A similar pattern of finding was also observed for parental relationship discord. Our results are consistent with the additive model of diathesis–stress perspective and underscore the need to consider how genetic risk may shape offspring's response to common family advertises to influence their alcohol use behaviors.

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CONFLICT OF INTEREST STATEMENT

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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