



Regular Article

Developmental genetic effects on externalizing behavior and alcohol use: Examination across two longitudinal samples

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Abstract

Externalizing behavior in early adolescence is associated with alcohol use in adolescence and early adulthood and these behaviors often emerge as part of a developmental sequence. This pattern can be the result of heterotypic continuity, in which different behaviors emerge over time based on an underlying shared etiology. In particular, there is largely a shared genetic etiology underlying externalizing and substance use behaviors. We examined whether polygenic risk for alcohol use disorder predicted (1) externalizing behavior in early adolescence and alcohol use in adolescence in the Early Steps Multisite sample and (2) externalizing behavior in adolescence and alcohol use in early adulthood in the Project Alliance 1 (PAL1) sample. We examined associations separately for African Americans and European Americans. When examining European Americans in the Early Steps sample, greater polygenic risk was associated with externalizing behavior in early adolescence. In European Americans in PAL1, we found greater polygenic risk was associated with alcohol use in early adulthood. Effects were largely absent in African Americans in both samples. Results imply that genetic predisposition for alcohol use disorder may increase risk for externalizing and alcohol use as these behaviors emerge developmentally.

Keywords: adolescence; alcohol use; externalizing; longitudinal; polygenic

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Alcohol misuse costs the United States hundreds of billions of dollars annually (Sacks et al., 2015) and it is estimated that 95,000 people die each year from alcohol-related causes (Centers for Disease Control and Prevention, 2019). These rates of mortality make alcohol misuse the third leading preventable cause of death in the US, following tobacco use and poor diet/physical inactivity (Mokdad et al., 2005). Beyond these outcomes, alcohol use is associated with multiple types of cancer, other chronic health conditions (Yoon, 2018), and a range of mental health issues (Burns & Teesson, 2002), including alcohol use disorder (Moos et al., 2004). Developing a better understanding of the etiology of alcohol misuse is key in improving effectiveness of prevention and intervention efforts.

To improve understanding of the etiology of alcohol misuse one must think about risk for alcohol misuse in the context of development. Generally, alcohol use begins in early to mid-adolescence, approximately 14–17 years old (Chen & Jacobson, 2012), becoming more normative in adolescence and early adulthood, approximately 18–20 years old. These general trends of increased alcohol use across adolescence are impacted by early adolescent traits that can forecast propensity for use/misuse during adolescence and into

adulthood. Extant theory and literature have found that externalizing behavior, including aggression, delinquency, and behavioral disinhibition, is a developmental precursor to substance use in adolescence (e.g., Brook et al., 1996; Iacono et al., 2008; Sitnick et al., 2014). Specifically, some individuals may inherit a liability for externalizing behavior, which manifests prior to the onset of alcohol use. Early in life, the expression of this propensity for externalizing behavior is broad and non-specific, but over the course of adolescence it can result in liability for alcohol use as a result of previous externalizing behavior or due to exposure to certain environmental factors (e.g., parents, peers) as a result of this broad liability (Iacono et al., 2008). Further, there is heterotypic continuity in these externalizing facets over time, that is, changing manifestation of individual externalizing behaviors across development based on an underlying shared etiology. In particular, externalizing behaviors such as aggression, delinquency, and behavioral disinhibition are most common in early to mid-adolescence and substance use becomes more common in adolescence into early adulthood as externalizing behaviors normatively subside (Samek et al., 2017; Tielbeek et al., 2018; Zellers et al., 2020). Thus, externalizing behavior in early adolescence is predictive of alcohol use in adolescence once drinking becomes more normative and both behaviors may emerge due to underlying etiological factors. One factor that may underlie both externalizing behavior in adolescence and later alcohol use is genetic predisposition.

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Liability for both externalizing behavior and alcohol use can be due to genetic predisposition. There is a robust literature indicating a largely shared genetic etiology underlying alcohol use, substance use, aggression, antisocial behavior, and disinhibition (Barr et al., 2020; Derringer et al., 2015; Gizer et al., 2016; Kendler et al., 2003; Krueger et al., 2002; McGue et al., 2013; Vrieze et al., 2013; Waldman et al., 2018; Young et al., 2009). This broad “externalizing” factor has been found to have a large heritable component (e.g., heritability = .80–.85; Hicks et al., 2011; Krueger et al., 2002). The high heritability of the broad externalizing factor, on which each of the individual behaviors loads, has led many to conceptualize these lower order factors as “facets” of this broader construct. Further, both broad and specific genetic predisposition for externalizing behaviors increases risk for developing externalizing behaviors. For instance, one study found general genetic liability across conduct disorder, adult antisocial behavior, alcohol dependence, and drug dependence increased one’s risk for developing any/all of these externalizing phenotypes in parent-to-child transmission (Hicks et al., 2004). Conversely, specific liability for individual disorders, such as alcohol use disorder, increased transmission of distinct behaviors in siblings. Moreover, these genetic effects can vary by age.

Twin and polygenic studies indicate that genetic effects on facets of externalizing behavior and alcohol use can vary with age (Elam et al., 2019, 2021; Kendler et al., 2011; van der Laan et al., 2021). Collectively, this work illustrates that genetic influences on externalizing behavior peak in early to mid-adolescence then decline over time, whereas genetic influences on alcohol use increase to a peak in early adulthood and attenuate thereafter. Further, recent findings indicate that polygenic scores explain greater variance in alcohol use in early adulthood compared to adolescence as incidence of alcohol use increases (Elam et al., 2021; Kandaswamy et al., 2021). However, it is unclear whether this is due to increases in genetic effects or increased prevalence of alcohol use due to greater exposure and access to alcohol across adolescence so genetic effects are more easily detected, or both. What is apparent is that genetic effects over time mirror normative patterns of externalizing behavior and alcohol use when examined within construct. Less research has examined associations across these constructs over time, that is, whether genetic predisposition for externalizing behaviors is associated with substance use, and vice versa, but associations are plausible given overlap in liability for these behaviors.

Early genetics research has demonstrated the GABRA2 gene is associated with alcohol use in adulthood (e.g., Agrawal & Bierut, 2012). Extending this finding to younger ages and different externalizing constructs, GABAergic genes and related polymorphisms have been found to be associated with lower behavioral control in late childhood and greater rule breaking from mid- to late-adolescence, which both mediated effects on later substance use in adolescence (Trucco, Villafuerte, et al., 2014; Trucco et al., 2016). Using a twin design, common genetic influences contributed to externalizing behavior in adolescence and substance use disorder in early adulthood (Samek et al., 2017). When examining polygenic scores, genetic predisposition for smoking has been associated with externalizing at ages 11, 14, and 17 (Hicks et al., 2021). In a related study, polygenic scores for alcohol, cannabis, and smoking were broadly associated with alcohol use, cannabis use, nicotine use, and a broader substance use factor, cumulatively measured from ages 14 to 24 (Schaefer et al., 2021). When examining this issue in a longitudinal model, cannabis use disorder and regular smoking polygenic scores were associated with behavioral

disinhibition at age 11, which predicted latent substance use across age 14 to 24. Problematic alcohol use and regular smoking polygenic scores directly predicted latent substance use. Finally, using polygenic scores for risky behavior, associations were found with alcohol and cannabis use in early adulthood, but not with antisocial behaviors (Ksinan et al., 2022).

It is important to note that little genetic research has examined associations with externalizing behavior and alcohol use in diverse populations. Twin and molecular genetic research have found converging and unique influences on externalizing behavior and alcohol use in African Americans and European Americans (Brick et al., 2019; Sartor et al., 2013; Webb et al., 2017). Most recently, different time-varying patterns of polygenic influence on alcohol use were found for African Americans and European Americans from adolescence to adulthood (Elam et al., 2021). Specifically, effects emerged earlier in adulthood and declined more sharply for African Americans, whereas effects in European Americans emerged slightly later and remained elevated. This is supported by evidence that there is variation in genetic effects across genetic ancestry (Martin et al., 2017, 2019). Thus, it is important to examine genetic effects on externalizing behavior and alcohol use separately in African Americans and European Americans.

Collectively, accumulating evidence appears to indicate that genetic predisposition for externalizing behavior and substance use are primarily associated with externalizing behaviors in early- to mid-adolescence and substance use in adolescence and early adulthood. We add to this literature by examining polygenic predisposition for alcohol use disorder as a predictor of (1) externalizing behavior in early adolescence and alcohol use in adolescence, and (2) externalizing behavior in adolescence and alcohol use in early adulthood.

In the current study, we created polygenic scores for alcohol use disorder (AUD-PGS) using summary statistics from two large genome-wide association studies (GWAS) on alcohol use disorder in African Americans (AAs) and European Americans (EAs) (Kranzler et al., 2019), allowing for investigation of developmental associations in distinct ethnic subgroups. We chose to examine polygenic scores for alcohol use disorder given previous evidence that polygenic scores for various substance use disorders and problematic substance use predict subclinical substance use, externalizing and impulsive behavior, and sensation seeking in adolescence and early adulthood, possibly because they better capture genetic signals across constructs and developmental periods (Johnson et al., 2021; Li et al., 2017; Salvatore et al., 2015; Schaefer et al., 2021).

We examined this research question using two mediation models in which the AUD-PGS predicted externalizing behavior (“a” path) and alcohol use (“c” path), and externalizing behavior predicted alcohol use (“b” path). This conceptual framework is in-line with past research examining polygenic prediction of substance use via earlier behavior and allows us to examine genetic prediction of both externalizing behavior and alcohol use while examining for genetically mediated effects (e.g., Li et al., 2017; Schaefer et al., 2021; Trucco, Villafuerte, et al., 2014, Trucco et al., 2016). In Model 1, the AUD-PGS was considered a predictor of externalizing behavior in early adolescence and alcohol use in adolescence, and externalizing behavior a predictor of alcohol use. We examined this in the Early Steps Multisite sample (referred to as Early Steps hereafter) which is a randomized control trial of a family centered intervention, the Family Check-Up (FCU), that has assessed individuals from age 2 to 16. In Model 2, the AUD-PGS was considered a predictor of externalizing behavior in adolescence and alcohol use in

early adulthood, and externalizing behavior a predictor of alcohol use. We examined this in the Project Alliance 1 (PAL1) sample which is a randomized control trial of the same FCU intervention and has assessed individuals from ages 12 to 31. We examined both models separately in AA and EA participants. Intervention condition did not have direct effects on externalizing behavior or alcohol use, thus, intervention effects were controlled for but not a focus of the study based on the relatively small sample sizes.

We hypothesized that the AUD-PGS would predict externalizing behavior in early adolescence with attenuated or absent associations with alcohol in adolescence, and that externalizing behavior would predict alcohol use. We also hypothesized that the AUD-PGS would predict alcohol use in early adulthood, but associations with externalizing behavior in adolescence would be attenuated or absent, and that externalizing behavior would predict alcohol use.

Method

Participants and procedures

Early Steps sample

The Early Steps sample is a longitudinal randomized trial of 731 ethnically and racially diverse, low-income families with 2-year-old children. Families were recruited between 2002 and 2003 from Women, Infants, and Children Nutritional Supplement Programs at three sites in metropolitan Pittsburgh, Pennsylvania (urban), Eugene, Oregon (suburban), and within and outside Charlottesville, Virginia (rural). Given this recruitment strategy this sample is considered at-risk. Screening procedures were used to recruit families of toddlers at high risk for conduct problems, based on socio-demographic risk, primary caregiver risk, and toddler behavior problems. Participation rates of those families invited to participate who qualified by risk status were high across the three sites [83.2% total (49% female); 84% in Eugene ($n = 271$), 76% in Charlottesville ($n = 188$), and 88% in Pittsburgh ($n = 272$)]. Primary caregivers (96% mothers) self-identified as belonging to the following ethnic groups: 11% Latino, 28% African American, 54% European American, 4% biracial, and 3% other groups (e.g., Native American, Asian American, Pacific Islander). For more information about sample characteristics see Dishion *et al.* (2008).

Similar to the PAL1 sample, families were randomly assigned to control or intervention conditions of the FCU after the baseline assessment at child age 2. All families were re-contacted at child ages 3, 4, 5, 7.5, 8.5, 9.5, 10.5, 14, and 16 years (81% of the sample participated at age 16) for home-based assessments with primary caregivers (96% biological mothers at age 2) and children. Primary caregivers completed questionnaires regarding the physical and socio-cultural environment and children's behavior. Of the adolescents who participated at 14 years, 515 were genotyped (86.7% of the sample who participated in home visits at age 14) and were used in the present study. The final analytic sample consisted of 477 individuals after accounting for missing demographic covariates and within this sample there were 223 EA participants and 138 AA participants available. Selective attrition analyses revealed no significant differences between members of the initial sample and those who were genotyped with respect to ethnicity, gender, age, study site, aggressive/disinhibited behavior, or alcohol use.

PAL1 sample

The PAL1 sample is a longitudinal randomized trial of 999 adolescents and their families recruited in 1996-1997 in Portland,

Oregon. Participants were randomized to intervention and control conditions of the FCU which is designed to reduce adolescent problem behavior by improving parenting and family functioning. All adolescents in 6th grade at three middle schools were invited to participate (of which 90% consented). Children were initially assessed at 11-12 years old, after which the intervention was administered, followed by four annual assessments (waves 1-5). Additional assessments were administered at 16-17, 18-19, 23-24, 24-25, 26-27, 28-30 years old (referred to as waves 6-11). At waves 1-5 a stratified sampling technique based on teacher assessments of risk status on externalizing behavior and substance use was used to classify participants as either no risk, at-risk, or high risk, and only those at high risk were subsequently assessed on externalizing measures. All individuals were assessed on all measures in waves 6-11. Retention at the last completed wave of data collection was excellent (83%). The sample was later genotyped as part of an age 26-27 assessment. Participants self-reported as 51% male, 44% European American, 30% African American, 13% multiracial, 6% Latino, 4% Asian American, and 4% other groups (Native American, Pacific Islander). A representative subsample of the genotyped individuals with data available on externalizing behavior and alcohol use comprise the sample for the current study ($n = 631$). For more information see Dishion & Kavanagh (2003).

All PAL1 participants were assessed at ages 17 and 19 (waves 6 and 7) so the adolescent-early adult model (Model 2) represented the full continuum of risk. The final analytic sample for the adolescent-early adult model consisted of 551 individuals after accounting for missing demographic covariates and within this sample there were 240 EA participants and 169 AA participants available.

Across both samples, selective attrition analyses revealed no significant differences between members of the initial sample with no genetic data and those who were genotyped with respect to ethnicity, gender, risk indices, or aggressive/disinhibited behaviors. In the PAL1 sample there was evidence of a greater proportion of females ($p < .001$) and some evidence of lower alcohol use on some indices (alcohol use frequency in early adulthood [$p = .007$]), but not quantity or 5 drinks in a row in early adulthood ($ps > .29$). Intervention condition did not have direct effects on externalizing behavior or alcohol use, thus, intervention effects were controlled for but not a focus of the study based on the relatively small sample size.

All study protocols for both the Early Steps and PAL1 samples were approved by the University's Institutional Review board. Parent or guardian consent was obtained for all minors and adolescents provided assent for participation in the study, while adult participants provided their own consent. Families were compensated for their time at each age.

Genotyping procedures

For both Early Steps and PAL1 samples, DNA was collected using the Oragene saliva collection kits and extracted according to Oragene's recommended procedures. Genotyping was performed at Rutgers University Cell and DNA Repository using the Affymetrix BioBank Array. Single nucleotide polymorphisms (SNPs) that are palindromic with ambiguous effect directions (A/T or C/G), SNPs with a genotyping rate of $<.95$, SNPs that did not pass Hardy-Weinberg equilibrium ($p < 10^{-6}$), or SNPs with a minor allele frequency $<.01$ were excluded. Given our relatively small sample sizes, we opted to use these quality control

thresholds to maximize the number of SNPs available for polygenic score formation as the PRS-CSx method (see below) significantly drops the number of SNPs used in the final score through the use of external reference panels.

Measures

AUD-PGS in Early Steps and PAL1 samples

We leveraged discovery GWAS summary statistics for alcohol use disorder from both AA and EA ancestries from Kranzler et al. (2019). From these GWAS, we used information for those of European Ancestry ($n = 202\text{K}$) as well as those of African Ancestry ($n = 57\text{K}$) as the discovery GWAS. To create polygenic scores, we used PRS-CSx (Ruan et al., 2022), a Python based command line tool that integrates GWAS summary statistics and external linkage disequilibrium (LD) reference panels from multiple populations to improve cross-population polygenic prediction. Posterior SNP effect sizes are inferred under coupled continuous shrinkage (CS) priors across populations. PRS-CSx is an extension of the Bayesian polygenic prediction method PRS-CS (Ge et al., 2019) method and uses LD information from 1000 Genomes Project European and African reference panels and estimates the posterior effect sizes for SNPs in a given set of GWAS summary statistics. Empirical tests and simulations have shown improved PRS-CS and PRS-CSx methods improve predictive power beyond traditional methods of polygenic construction (Ge et al., 2019; Ruan et al., 2022). Because PRS-CS uses LD information from an external reference panel, we matched ancestries between the discovery samples and the ancestry reference provided by PRS-CS. Summary statistics for AAs and EAs AUD-PGS were drawn from each respective alcohol use disorder GWAS. AUD-PGS were calculated using joint modeling across GWAS summary statistics via coupled shrinkage priors (Ruan et al., 2022). Final AUD-PGS were based on posterior PRS-CSx weights and created using the *score* procedure in PLINK 1.9 (Chang et al., 2015).

Population stratification and genetic admixture

Principal Components Analysis were conducted to represent population admixture separately in the Early Steps sample, using PLINK (Purcell et al., 2007), and in the PAL1 sample, using *snpgdsPCA* function from R SNPRelate package (Zheng et al., 2012). For both samples, the first 20 principal components (PCs) were extracted and residualized from the AUD-PGS in each respective sample.

Externalizing behavior

Early Steps sample. At age 14 externalizing behavior was assessed using the Child Behavior Checklist (Achenbach et al., 2001). The 10-item attention, 18-item aggression, and 17-item rule breaking subscales were used to index externalizing behavior (0 = Not True to 2 = Often True; “Destroys own things.” “Disobedient at home”; α range .82–.93). An externalizing latent variable was formed using these subscales as indicators.

PAL1 sample. At age 17 externalizing behavior was assessed using adolescent self-report on the Early Adolescent Temperament Questionnaire (Rothbart et al., 2001). 16 items from the activation control, attention, and inhibitory control subscales were conceptualized as a single effortful control index ($\alpha = .72$) and along with the 6-item aggression subscale ($\alpha = .75$) were used as two indicators of externalizing behavior (1 = Almost always untrue to 5 = Almost always true; “When I get angry I throw or break

things,” “When someone tells me to stop doing something, it is easy for me to stop”). Adolescents also reported on their behavioral responses to stressful situations using the life events coping scale inventory (Dise-Lewis, 1988), which assesses behavioral responses to stressful situations and the delinquency/aggression subscale was used in the present study (1 = I would definitely do this to 5 = I would definitely not do this; “When I am stressed I get in a fight with someone,” $\alpha = .87$). An externalizing latent variable was formed using these three scales as indicators.

Alcohol use

Early Steps sample. At 16 years old alcohol use was assessed by separately asking about quantity and frequency of consumption of alcohol (e.g., “How often did you drink beer in the last 3 months?”; 0 = Never to 7 = 2–3 times a day or more; “How much beer did you drink in the past 3 months?”; 0 = Less than one can to 5 = More than five cans). A separate item assessed the largest ever number of alcoholic drinks a participant had consumed in a 24 hour period in the last 3 months, an indicator of problematic drinking. These three measures, alcohol quantity, frequency, and largest number of drinks, were used as indicators of an alcohol use latent variable. There were low levels of alcohol use at age 16 with 84% reporting “less than one can” for quantity of alcohol use, 88% reporting “never” for frequency of alcohol use, and 86% reporting zero for the largest number of drinks. Means and standard deviations for these scales can be found in Table 1.

PAL1 sample. At 19 years old alcohol use was assessed asking about quantity and frequency of consumption of alcohol (e.g., “How often did you drink beer in the last 3 months?”; 0 = Never to 7 = 2–3 times a day or more; “How much beer did you drink in the past 3 months?”; 0 = Less than one can to 5 = More than five cans). A separate item assessed number of times in the past 3 months the participant had consumed five or more drinks in a row, an indicator of problematic drinking. These three measures, alcohol quantity, frequency, and five in a row, were used as indicators of an alcohol use latent variable. There were moderate levels of alcohol use with no individuals reporting “less than one can” for quantity of alcohol use, 18% reporting “never” for frequency of alcohol use, and 33% reporting zero for having five drinks in a row. Means and standard deviations for these scales can be found in Table 2.

Covariates

Participant gender, age, and intervention group status were included as covariates in all analyses, as was location site in Model 1 with the Early Steps sample. Given both samples participated in the FCU, we also included an AUD-PGS by intervention interaction term to account for possible interaction effects.

Statistical Analyses

Given the recruitment strategy in Early Steps sample, Model 1 constituted tests in high-risk participants. Conversely, Model 2 using PAL1 participants represented those individuals across the continuum of risk. We performed sensitivity analyses by also investigating Model 2 in at-risk and high-risk individuals.

After examining descriptive statistics and bivariate correlations, study variables were examined in a multigroup path model in Mplus. Where indicated by significant AUD-PGS to externalizing behavior and externalizing behavior to alcohol use effects, indirect effects were estimated using Rmediation (Tofighi & MacKinnon,

Table 1. Means, standard deviations, and correlations among primary constructs in the Early Steps sample for African Americans (below the diagonal) and European Americans (above the diagonal)

	1	2	3	4	5	6	7	8	9	10	Mean (SD)
1. AUD-PGS	1	.05	.03	.08	.18*	.08	.06	.06	-.02	.00	-.03 (.94)
2. Aggression	-.04	1	.66***	.81***	.03	.05	.06	-.11 ⁺	-.01	-.06	57.96 (9.36)
3. Inattention	.00	.71***	1	.55**	-.08	-.07	-.06	-.07	-.08	-.01	59.59 (9.60)
4. Rule breaking	.01	.75***	.67***	1	.13*	.21**	.24***	-.10	.07	.01	56.20 (6.50)
5. Alcohol frequency	-.13	.14 ⁺	-.03	.09	1	.79***	.74***	.10	.08	-.04	.89 (1.97)
6. Alcohol quantity	-.15 ⁺	.15 ⁺	.05	.16*	.74***	1	.88***	.00	.15*	-.03	.94 (2.38)
7. Alcohol max drinks	-.11	.21**	.09	.19*	.86***	.66***	1	.00	.26***	-.01	1.94 (5.12)
8. Gender	.11	.00	.06	-.07	.05	.02	.10	1	.03	-.03	4.28 (3.50)
9. Age	.03	-.04	.02	.17*	-.07	-.03	-.05	-.11	1	.04	13.74 (.35)
10. Intervention	.07	-.02	-.05	-.01	.14 ⁺	.14 ⁺	.09	.08	.06	1	.50 (.50)
Mean (SD)	.05 (1.14)	58.28 (1.51)	59.29 (9.89)	56.79 (7.47)	.31 (1.02)	.26 (.95)	.32 (1.10)	4.53 (3.51)	13.74 (.35)	.52 (.50)	

Note. AUD-PGS = Alcohol use disorder polygenic risk score. First 20 ancestry principal components were residualized from the AUD-PGS.

⁺*p* < .10; **p* < .05; ***p* < .01; ****p* < .001.

Table 2. Means, standard deviations, and correlations among primary constructs in the PAL1 sample for African Americans (below the diagonal) and European Americans (above the diagonal)

	1	2	3	4	5	6	7	8	9	10	Mean (SD)
1. AUD-PGS	1	-.02	.03	-.04	.12	.20**	.03	-.05	-.06	.05	.00 (.92)
2. Aggression 17yo	-.10	1	.44**	-.42**	.05	.15*	.01	-.12*	.04	-.03	2.03 (.68)
3. Delinquent/aggressive coping 17yo	.04	.47***	1	-.27**	.04	.12 ⁺	.05	-.03	.01	-.01	1.83 (1.25)
4. Effortful control 17yo	.09	-.47***	-.28***	1	-.04	-.18**	-.05	.02	-.01	-.07	3.31 (.48)
5. Alcohol quantity 19yo	-.12	.15	.07	-.02	1	.46**	.55**	-.38**	-.08	.08	3.61 (1.24)
6. Alcohol frequency 19yo	-.09	.15	.16	-.12	.51***	1	.32**	-.26**	-.03	-.01	1.83 (1.28)
7. Alcohol five in a row 19yo	-.05	.13	.14	-.04	.54***	.41**	1	-.21**	.12	-.02	2.02 (1.22)
8. Gender	-.01	.05	-.06	-.02	-.11	-.11	.01	1	-.04	.03	1.46 (.50)
9. Age	.20 ⁺	-.03	.03	.01	-.14	-.07	-.03	-.16 ⁺	1	-.21**	12.75 (.43)
10. Intervention	.06	.13 ⁺	.02	.04	-.03	-.01	.15 ⁺	-.06	.03	1	.51 (.50)
Mean (SD)	.03 (1.09)	2.21 (.73)	1.85 (1.38)	3.40 (.46)	2.71 (1.27)	1.35 (1.37)	.86 (1.13)	1.46 (.50)	12.70 (.43)	.52 (.50)	

Note. AUD-PGS = Alcohol use disorder polygenic risk score. First 20 ancestry principal components were residualized from the AUD-PGS.

⁺*p* < .10; **p* < .05; ***p* < .01; ****p* < .001.

2011) which computes asymmetric confidence limits for the distribution of the product of alpha and beta paths, and has greater statistical power and better adjustment of Type I error when compared to the Sobel test. Model 1 and Model 2 were run in the AA and EA ethnic subgroups within each sample. We refrained from testing for genetic differences across AA and EA ethnic subgroups given known differences in genetic ancestry (e.g., allele frequency and LD patterns).

Full information maximum likelihood was used to handle missing data. Descriptive statistics were conducted in SPSS and all other analyses were conducted in Mplus Version 8.3.

Results

Means, standard deviations, and correlations are presented for the Early Steps sample in Table 1 separately for AAs (below the diagonal) and EAs (above the diagonal), and for the PAL1 sample in Table 2 separately for AAs (below the diagonal) and EAs (above the diagonal). In Early Steps, the AUD-PGS was positively associated with alcohol frequency in adolescence in EAs. In PAL1, the AUD-PGS was positively associated with alcohol frequency in EAs. Broadly, as indicated in Tables 1 and 2, in AAs and EAs in both samples the indices of externalizing and alcohol use were correlated within construct, with some evidence of associations across constructs and over time.

Results for Model 1 in early adolescence to adolescence are presented in Table 3. Model Fit was adequate ($X^2(71) = 144.11$, $p < .001$, RMSEA = .07, CFI = .95, TLI = .93). In the Early Steps sample loadings for the alcohol and externalizing latent factors were significant and adequate in both AA and EA participants (.59–.97). In the EA subgroup, the AUD-PGS was associated with externalizing behavior. In the AA subgroup, externalizing behavior was associated with alcohol use. In neither AAs nor EAs was there evidence of associations from the AUD-PGS to externalizing behavior and externalizing behavior to alcohol use so indirect tests were not conducted. The variance explained in EA externalizing behavior and alcohol use were small ($R^2 = .05$; $R^2 = .05$).

Results for Model 2 in adolescence to early adulthood can be found in Table 3. Model fit was adequate ($X^2(78) = 118.37$, $p = .002$, RMSEA = .04, CFI = .91, TLI = .90). In the PAL1 sample, loadings for the alcohol and externalizing latent factors were significant and adequate in both AA and EA participants (.41–.83). In the EA subgroup, the AUD-PGS was associated with alcohol use. No effects were detected in the AA subgroup. In neither AAs nor EAs was there evidence of associations from AUD-PGS to externalizing behavior and externalizing behavior to alcohol use so indirect tests were not conducted. The variance explained in EA externalizing behavior and alcohol use were small ($R^2 = .18$; $R^2 = .03$).

As a sensitivity test, we ran Model 2 in those designated as at-risk and high risk in the initial wave of the study to mirror the sample in Model 1, results can be found in supplemental Table 1. In the EA subgroup, the AUD-PGS was associated with alcohol use. In neither AAs nor EAs was there evidence of associations from AUD-PGS to externalizing behavior and externalizing behavior to alcohol use so indirect tests were not conducted.

Discussion

The current study sought to examine whether polygenic risk for alcohol use disorder would predict externalizing behavior and alcohol use, and whether externalizing behavior would predict

alcohol use. We tested this in two developmentally different samples capturing externalizing behavior during early adolescence and alcohol use in adolescence, and externalizing behavior in adolescence and alcohol use in early adulthood.

Broadly, findings partially supported our hypotheses. In EA subgroups, we found support for our hypothesis that greater AUD-PGS would predict greater early adolescent externalizing behavior in the Early Steps sample. However, externalizing in early adolescence was only found to predict adolescent alcohol use in AAs. In support of our second hypothesis, we found evidence that the AUD-PGS was associated with alcohol use in early adulthood in the EA subgroup in both the whole PAL1 sample and the at-risk/high-risk subsample.

Contrary to our hypothesis, we only found externalizing behavior associated with alcohol use from early adolescence to adolescence in AAs and therefore no evidence of indirect effects of the AUD-PGS to alcohol use via externalizing behavior. However, in correlations for EAs in the Early Steps sample, rule breaking was positively associated with alcohol frequency, quantity, and maximum number of drinks. In correlations for EAs in the PAL1 sample, alcohol frequency was positively associated with aggression and negatively associated with effortful control. It may be that there are developmentally nuanced associations between facets of externalizing behavior and alcohol use, such that rule breaking in early adolescence is preferentially associated with alcohol use, possibly due to affiliation with deviant peers (Trucco, Colder, et al., 2014). Delinquency and rule breaking may be more transient from adolescence to early adulthood whereas aggression and effortful control are more stable across these periods so more prognostic of alcohol use in early adulthood (Moffitt, 2003). In the current models our use of latent variables for externalizing and alcohol may have masked these nuanced developmental associations. Alternatively, the lack of associations between externalizing and alcohol use could be due to low alcohol use in the Early Steps sample, the collection of measures used to index externalizing in the PAL1 sample, or possibly due to indirect intervention effects on behaviors not captured in the present study. More research is needed to identify whether specific facets of externalizing behavior mediate different aspects of genetic predisposition on alcohol use or other substances across early adolescence, adolescence, and early adulthood.

It is notable that no genetic effects were detected in AA subgroups in either sample. We leveraged distinct GWAS in AA and EA subgroups to create polygenic scores using an advanced Bayesian method to account for our multiethnic sample. This lack of effects may be attributable to the smaller AA sample sizes in both Early Steps and PAL1 samples compared to EAs, the smaller GWAS sample size in AA individuals compared to in EA individuals, or perhaps both. It also may be due to lower levels of alcohol use in AAs versus EAs, which has previously been demonstrated in the PAL1 sample (Elam et al., 2021). In addition, AAs are subject to higher rates of some contextual risk factors including discrimination, residential segregation, and limited access to adequate health resources which can increase risk for externalizing behavior and alcohol use (Scott, 2017). Thus, environmental factors not captured in the current study may be more salient than genetic effects for AAs, especially during these sensitive developmental periods (Dick et al., 2007). This aligns with the limited research finding lower heritability for early alcohol use (age at first drink) in AAs compared to EAs (Sartor et al., 2013). This topic is an important area for future research given the scarcity of genetics research in diverse racial/ethnic samples.

Table 3. Standardized coefficients of polygenic scores for alcohol use disorder predicting externalizing and alcohol use in Early Steps and PAL1 samples

	Model 1 (Early Steps): Early adolescence to adolescence		Model 2 (PAL1): Adolescence to early adult	
	Externalizing	Alcohol use	Externalizing	Alcohol use
	<i>B</i> (95% CI), <i>p</i> value	<i>B</i> (95% CI), <i>p</i> value	<i>B</i> (95% CI), <i>p</i> value	<i>B</i> (95% CI), <i>p</i> value
<i>European Americans</i>				
AUD-PGS	.21 (.01, .42), .045	.04 (–.17, .25), .703	–.13 (–.31, .05), .16	.27 (.04, .51), .026
Externalizing	–	.08 (–.07, .23), .314	–	.04 (–.11, .19), .59
Gender	–.15 (–.28, –.02), .030	–.02 (–.16, .12), .788	–.12 (–.22, –.02), .028	–.41 (–.54, –.28), <.001
Age	.02 (–.12, .15), .783	.19 (.05, .34), .010	.03 (–.07, .14), .569	.01 (–.14, .15), .932
Intervention	–.09 (–.23, .04), .186	–.01 (–.14, .13), .929	–.02 (–.13, .08), .676	–.01 (–.15, .13), .902
AUD-PGS × intervention	–.18 (–.38, .03), .098	.07 (–.14, .28), .538	.16 (–.02, .33), .09	–.15 (–.40, .09), .223
<i>African Americans</i>				
AUD-PGS	.07 (–.19, .33), .577	–.07 (–.18, .05), .265	–.05 (–.25, .14), .595	.21 (–.56, .02), .071
Externalizing	–	.11 (.03, .20), .008	–	–.27 (–.02, .44), .085
Gender	.04 (–.14, .21), .661	.07 (–.01, .14), .091	.05 (–.07, .18), .395	–.12 (–.34, .09), .273
Age	.02 (–.16, .20), .839	.001 (–.08, .08), .975	–.07 (–.20, .05), .254	–.04 (–.28, .21), .784
Intervention	–.02 (–.19, .15), .807	.01 (–.07, .09), .784	.14 (.02, .27), .028	.06 (–.16, .27), .618
AUD-PGS × intervention	–.10 (–.36, .16), .435	.04 (–.08, .15), .520	–.10 (–.29, .10), .335	.27 (–.02, .56), .076

Note. AUD-PGS = Alcohol use disorder polygenic risk score. First 20 ancestry principal components were residualized from the AUD-PGS. Associations with significance at $p < .05$ are bolded.

Findings in the EA subgroups were consistent with the larger literature finding shared genetic effects on externalizing behavior and substance use (Barr et al., 2020; Derringer et al., 2015; Gizer et al., 2016; Kendler et al., 2003; Krueger et al., 2002; McGue et al., 2013; Vrieze et al., 2013; Waldman et al., 2018; Young et al., 2009). This also aligns with past research finding polygenic scores for various substance use disorders and problematic substance use to predict subclinical substance use and various externalizing behaviors in adolescence and early adulthood (Johnson et al., 2021; Li et al., 2017; Salvatore et al., 2015; Schaefer et al., 2021).

Findings are also supported by the limited developmental genetic literature indicating that genetic predisposition for externalizing behavior and/or substance use is primarily associated with externalizing behavior in early- to mid-adolescence and alcohol use in adolescence and early adulthood (Hicks et al., 2021; Ksinan et al., 2022; Samek et al., 2017; Schaefer et al., 2021). Specifically, genetic liability for externalizing behavior and alcohol use overlap, and this liability may increase risk for externalizing behavior in early adolescence prior to regular alcohol use, whereas associations with alcohol use emerge in adolescence and early adulthood when these behaviors become more normative (Kendler et al., 2011). It may be that we are detecting developmentally specific genetic signals emerging from broad liability for externalizing behavior and/or substance use. Alternatively, it may be that these developmental genetic effects emerge for these normative behaviors due to increased power to detect these effects, given greater externalizing behavior in early adolescence and greater alcohol use in early adulthood. Broadly, the extant literature demonstrates that genetic effects over time mirror normative patterns of externalizing behavior and alcohol use when examined within and across externalizing and substance use constructs. Future research is needed to examine developmental genetic effects

on specific indices of externalizing behavior and substance use during these sensitive periods.

Strengths, limitations, and conclusions

This study has limitations that should be acknowledged. First, although the measures of alcohol use between the two studies are nearly identical, the two measures of externalizing behavior in the Early Steps and PAL1 samples were different. It should also be noted that the measure of adolescent externalizing in the PAL1 sample was captured using scales from temperament and coping measures which possibly affected the current results. However, items from these measures were very similar to our other measure of externalizing behavior and their operationalization in a latent variable helped to capture shared variance. Second, the composition of the two samples included in these analyses were a bit different. In particular, the Early Steps sample is a high-risk sample whereas the PAL1 sample was a community-based sample which may affect results. We were able to partially address this by examining effects in Model 2 in the whole sample as well as in at-risk/high-risk groups. Also, given the nature of these samples and low variation in SES, we did not control for SES. Finally, both samples participated in the FCU, which may have buffered genetic expression and altered patterns of externalizing and substance use. To address this concern, we did covary for intervention condition and the interaction of genetic predisposition for alcohol use disorder and intervention condition; however, results may not generalize to other high-risk samples.

Despite these limitations, this study has several important strengths. First, we were able to utilize two prospective, longitudinal studies to examine our primary findings, which gives us confidence that the results are not due to chance. We were able to assess externalizing behavior during two key developmental

periods – early adolescence and adolescence – and thus were able to test our developmentally nuanced question about the timing of the relation between genetic risk, externalizing behavior, and alcohol use. We were also able to control for the key covariates of age, sex, intervention, and ancestry principal components. Additionally, our polygenic scores were based on ethnically aligned GWAS (Kranzler et al., 2019) and created using a method demonstrated to boost predictive accuracy in diverse samples (Ge et al., 2019; Ruan et al., 2022), increasing the power of our AUD-PGS to detect effects if they exist.

The current study joins the larger literature in demonstrating the utility, to some extent, of polygenic scores in predicting a range of phenotypes across populations (Khera et al., 2018; Lewis & Vassos, 2020; Maher, 2015; Mavaddat et al., 2019). This strength should be considered in the context of polygenic limitations including the small variance typically explained in outcomes and issues with portability across races/ethnicities, as demonstrated by the current results. It is also important to note that alcohol consumption itself has a public health impact, and is associated with alcohol use disorder, so is an informative measure of risk (Moos et al., 2004). These findings add to this literature by suggesting that genetic predisposition may confer additional insight in identifying those at-risk for externalizing and alcohol use, especially during sensitive developmental periods such as adolescence.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S0954579422000980>

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Conflicts of interest. None.

References

- Achenbach, T. M., Dumenci, L., & Rescorla, L. A. (2001). *Ratings of relations between DSM-IV diagnostic categories and items of the CBCL/6-18, TRF, and YSR* (pp. 1–9). University of Vermont.
- Agrawal, A., & Bierut, L. J. (2012). Identifying genetic variation for alcohol dependence. *Alcohol Research: Current Reviews*, 34(3), 274–281.
- Barr, P. B., Salvatore, J. E., Wetherill, L., Anokhin, A., Chan, G., Edenberg, H. J., Kuperman, S., Meyers, J., Nurnberger, J., Porjesz, B., Schuckit, M., Dick, D. M. (2020). A family-based genome wide association study of Externalizing Behaviors. *Behavior Genetics*, 50(3), 175–183. <https://doi.org/10.1007/s10519-020-09999-3>
- Brick, L. A., Keller, M. C., Knopik, V. S., McGeary, J. E., & Palmer, R. H. (2019). Shared additive genetic variation for alcohol dependence among subjects of African and European ancestry. *Addiction Biology*, 24(1), 132–144. <https://doi.org/10.1111/adb.12578>
- Brook, J. S., Whiteman, M., Finch, S. J., & Cohen, P. (1996). Young adult drug use and delinquency: Childhood antecedents and adolescent mediators. *Journal of the American Academy of Child & Adolescent Psychiatry*, 35(12), 1584–1592. <https://doi.org/10.1097/00004583-199612000-00009>
- Burns, L., & Teesson, M. (2002). Alcohol use disorders comorbid with anxiety, depression and drug use disorders: Findings from the Australian National Survey of Mental Health and Well Being. *Drug and Alcohol Dependence*, 68(3), 299–307. [https://doi.org/10.1016/S0376-8716\(02\)00220-X](https://doi.org/10.1016/S0376-8716(02)00220-X)
- Centers for Disease Control and Prevention (CDC). (2019). *Alcohol and Public Health: Alcohol-Related Disease Impact (ARDI)*. https://nccd.cdc.gov/DPH_ARDI/Default/Report.aspx?T=AAM&P=1A04A664-0244-42C1-91DE-316F3AF6B447&R=B885BD06-13DF-45CD-8DD8-AA6B178C4ECE&M=32B5FFE7-81D2-43C5-A892-9B9B3C4246C7&F=AAMCauseGenderNew&D=H
- Chang, C. C., Chow, C. C., Tellier, L. C., Vattikuti, S., Purcell, S. M., & Lee, J. J. (2015). Second-generation PLINK: Rising to the challenge of larger and richer datasets. *Gigascience*, 4(1), 7.
- Chen, P., & Jacobson, K. C. (2012). Developmental trajectories of substance use from early adolescence to young adulthood: Gender and racial/ethnic differences. *Journal of Adolescent Health*, 50(2), 154–163. <https://doi.org/10.1016/j.jadohealth.2011.05.013>
- Derringer, J., Corley, R. P., Haberstick, B. C., Young, S. E., Demmitt, B. A., Howrigan, D. P., Kirkpatrick, R. M., Iacono, W. G., McGue, M., Keller, M. C. (2015). Genome-wide association study of behavioral disinhibition in a selected adolescent sample. *Behavior Genetics*, 45(4), 375–381. <https://doi.org/10.1007/s10519-015-9705-y>
- Dick, D. M., Pagan, J. L., Viken, R., Purcell, S., Kaprio, J., Pulkkinen, L., & Rose, R. J. (2007). Changing environmental influences on substance use across development. *Twin Research and Human Genetics*, 10(2), 315–326.
- Dise-Lewis, J. E. (1988). The life events and coping inventory: An assessment of stress in children. *Psychosomatic Medicine*, 50(5), 484–499. <https://doi.org/10.1097/00006842-198809000-00005>
- Dishion, T. J., & Kavanagh, K. (2003). *Intervening in adolescent problem behavior: A family-centered approach*. Guilford.
- Dishion, T. J., Shaw, D., Connell, A., Gardner, F., Weaver, C., & Wilson, M. (2008). The family check-up with high-risk indigent families: Preventing problem behavior by increasing parents' positive behavior support in early childhood. *Child Development*, 79(5), 1395–1414.
- Elam, K. K., Clifford, S., Shaw, D., Wilson, M., & Lemery-Chalfant, K. (2019). Gene set enrichment analysis to create polygenic risk scores for childhood aggression: A developmental examination of aggression. *Translational Psychiatry*, 9, 212. <https://doi.org/10.1038/s41398-019-0513-7>
- Elam, K. K., Ha, T., Neale, Z., Aliev, F., Dick, D., & Lemery-Chalfant, K. (2021). Polygenic effects on alcohol use in African Americans and European Americans: Age varying associations from adolescence to adulthood. *Scientific Reports*, 11, 22425. <https://doi.org/10.1038/s41598-021-01923-x>
- Ge, T., Chen, C. Y., Ni, Y., Feng, Y. C. A., & Smoller, J. W. (2019). Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nature Communications*, 10(1), 1–10. <https://doi.org/10.1038/s41467-019-09718-5>
- Gizer, I. R., Otto, J. M., & Ellingson, J. M. (2016). Molecular genetics of the externalizing spectrum. In T. P. Beauchaine, & S. P. Hinshaw (Eds.), *The Oxford handbook of externalizing spectrum disorders* (pp. 149–169). Oxford University Press.
- Hicks, B. M., Clark, D. A., Deak, J. D., Liu, M., Durbin, C. E., Schaefer, J. D., Wilson, S., Iacono, W. G., & Vrieze, S. I. (2021). Polygenic score for smoking is associated with externalizing psychopathology and disinhibited personality traits but not internalizing psychopathology in adolescence. *Clinical Psychological Science*, 9(6), 1205–1213. <https://doi.org/10.1177/21677026211002117>
- Hicks, B. M., Krueger, R. F., Iacono, W. G., McGue, M., & Patrick, C. J. (2004). Family transmission and heritability of externalizing disorders: A

- twin-family study. *Archives of General Psychiatry*, 61(9), 922–928. <https://doi.org/10.1001/archpsyc.61.9.922>
- Hicks, B. M., Schalet, B. D., Malone, S. M., Iacono, W. G., & McGue, M. (2011). Psychometric and genetic architecture of substance use disorder and behavioral disinhibition measures for gene association studies. *Behavior Genetics*, 41(4), 459–475. <https://doi.org/10.1007/s10519-010-9417-2>
- Iacono, W. G., Malone, S. M., & McGue, M. (2008). Behavioral disinhibition and the development of early-onset addiction: Common and specific influences. *Annual Review of Clinical Psychology*, 4, 325–348. <https://doi.org/10.1146/annurev.clinpsy.4.022007.141157>
- Johnson, E. C., Sanchez-Roige, S., Acion, L., Adams, M. J., Bucholz, K. K., Chan, G., Chao, M. J., Chorlian, D. B., Dick, D. M., Edenberg, H. J., Foroud, T., Hayward, C., Heron, J., Hesselbrock, V., Hickman, M., Kendler, J. S., Kinreich, S., Kramer, J., Kuo, S. I., ... Edwards, A. C. (2021). Polygenic contributions to alcohol use and alcohol use disorders across population-based and clinically ascertained samples. *Psychological Medicine*, 51(7), 1147–1156. <https://doi.org/10.1017/S0033291719004045>
- Kandaswamy, R., Allegrini, A., Plomin, R., & von Stumm, S. (2021). Predictive validity of genome-wide polygenic scores for alcohol use from adolescence to young adulthood. *Drug and Alcohol Dependence*, 219, 108480. <https://doi.org/10.1016/j.drugalcdep.2020.108480>
- Kendler, K. S., Gardner, C., & Dick, D. M. (2011). Predicting alcohol consumption in adolescence from alcohol-specific and general externalizing genetic risk factors, key environmental exposures and their interaction. *Psychological Medicine*, 41(7), 1507–1516. <https://doi.org/10.1017/S003329171000190X>
- Kendler, K. S., Prescott, C. A., Myers, J., & Neale, M. C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry*, 60(9), 929–937. <https://doi.org/10.1001/archpsyc.60.9.929>
- Khera, A. V., Chaffin, M., Aragam, K. G., Haas, M. E., Roselli, C., Choi, S. H., Natarajan, P., Lander, E. S., Lubitz, S. A., Ellinor, P. T., Kathiresan, S. (2018). Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nature Genetics*, 50(9), 1219–1224. <https://doi.org/10.1038/s41588-018-0183-z>
- Kranzler, H. R., Zhou, H., Kember, R. L., Vickers Smith, R., Justice, A. C., Damrauer, S., Tsao, P. S., Klarin, D., Baras, A., Reid, J., Overton, J., Rader, D. J., Cheng, Z., Tate, J. P., Becker, W. C., Concato, J., Xu, K., Polimanti, R., Zhao, H., & Gelernter, J. (2019). Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations. *Nature Communications*, 10(1), 1499. <https://doi.org/10.1038/s41467-019-09480-8>
- Krueger, R. F., Hicks, B. M., Patrick, C. J., Carlson, S. R., Iacono, W. G., & McGue, M. (2002). Etiologic connections among substance dependence, antisocial behavior, and personality: Modeling the externalizing spectrum. *Journal Abnormal Psychology*, 111(3), 411–424. <https://doi.org/10.1037/11855-003>
- Ksinan, A. J., Smith, R. L., Barr, P. B., & Vazsonyi, A. T. (2022). The associations of polygenic scores for risky behaviors and parenting behaviors with adolescent externalizing problems. *Behavior Genetics*, 52(1), 26–37.
- Lewis, C. M., & Vassos, E. (2020). Polygenic risk scores: From research tools to clinical instruments. *Genome Medicine*, 12(1), 44. <https://doi.org/10.1186/s13073-020-00742-5>
- Li, J. J., Savage, J. E., Kendler, K. S., Hickman, M., Mahedy, L., Macleod, J., Kaprio, J., Rose, R. J., & Dick, D. M. (2017). Polygenic risk, personality dimensions, and adolescent alcohol use problems: A longitudinal study. *Journal of Studies on Alcohol and Drugs*, 78(3), 442–451. <https://doi.org/10.15288/jsad.2017.78.442>
- Maher, B. S. (2015). Polygenic scores in epidemiology: Risk prediction, etiology, and clinical utility. *Current Epidemiology Reports*, 2(4), 239–244. <https://doi.org/10.1007/s40471-015-0055-3>
- Martin, A. R., Gignoux, C. R., Walters, R. K., Wojcik, G. L., Neale, B. M., Gravel, S., Daly, M. J., Bustamante, C. D., & Kenny, E. E. (2017). Human demographic history impacts genetic risk prediction across diverse populations. *American Journal of Human Genetics*, 100(4), 635–649. <https://doi.org/10.1016/j.ajhg.2017.03.004>
- Martin, A. R., Kanai, M., Kamatani, Y., Okada, Y., Neale, B. M., & Daly, M. J. (2019). Clinical use of current polygenic risk scores may exacerbate health disparities. *Nature Genetics*, 51, 584–591. <https://doi.org/10.1038/s41588-021-00797-z>
- Mavaddat, N., Michailidou, K., Dennis, J., Lush, M., Fachal, L., Lee, A., Tyrer, J. P., Chen, T. H., Wang, Q., Bolla, M. K., Yang, X., Adank, M. A., Ahearn, T., Aittomäki, K., Allen, J., Andrulis, I. L., Anton-Culver, H., Antonenkova, N. N., Arndt, V., & Aronson, K. J. (2019). Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. *American Journal Human Genetics*, 104(1), 21–34. <https://doi.org/10.1016/j.ajhg.2018.11.002>
- McGue, M., Zhang, Y., Miller, M. B., Basu, S., Vrieze, S., Hicks, B., Malone, S., Oetting, W. S., & Iacono, W. G. (2013). A genome-wide association study of behavioral disinhibition. *Behavior Genetics*, 43(5), 363–373. <https://doi.org/10.1007/s10519-013-9606-x>
- Moffitt, T. E. (2003). Life-course persistent and adolescence-limited antisocial behavior. In B. Lahey, T. Moffitt, & A. Caspi (Eds.), *Causes of conduct disorder and juvenile delinquency* (pp. 49–75). Guilford Press.
- Mokdad, A. H., Marks, J. S., Stroup, D. F., & Gerberding, J. L. (2005). Correction: Actual causes of death in the United States, 2000. *JAMA*, 293(3), 293–294. <https://doi.org/10.1001/jama.293.3.293>
- Moos, R. H., Schutte, K., Brennan, P., & Moos, B. S. (2004). Ten-year patterns of alcohol consumption and drinking problems among older women and men. *Addiction*, 99(7), 829–838. <https://doi.org/10.1111/j.1360-0443.2004.00760.x>
- Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., Maller, J., Sklar, P., de Bakker, P. I., Daly, M. J., Sham, P. C. (2007). PLINK: A tool set for whole-genome association and population-based linkage analyses. *The American Journal of Human Genetics*, 81(3), 559–575. <https://doi.org/10.1086/519795>
- Rothbart, M. K., Ahadi, S. A., Hershey, K. L., & Fisher, P. (2001). Investigations of temperament at three to seven years: The Children's Behavior Questionnaire. *Child Development*, 72(5), 1394–1408. <https://doi.org/10.1111/1467-8624.00355>
- Ruan, Y., Lin, Y. F., Feng, Y. C. A., Chen, C. Y., Lam, M., Guo, Z., He, L., Sawa, A., Martin, A. R., Qin, S., & Huang, H. (2022). Improving polygenic prediction in ancestrally diverse populations. *Nature Genetics*, 54, 573–580.
- Sacks, J. J., Gonzales, K. R., Bouchery, E. E., Tomedi, L. E., & Brewer, R. D. (2015). 2010 national and state costs of excessive alcohol consumption. *American Journal of Preventive Medicine*, 49(5), e73–e79. <https://doi.org/10.1016/j.amepre.2015.05.031>
- Salvatore, J. E., Aliev, F., Bucholz, K., Agrawal, A., Hesselbrock, V., Hesselbrock, M., Bauer, L., Kuperman, S., Schuckit, M. A., Kramer, J., Edenberg, H. J., Foroud, T. M., & Dick, D. M. (2015). Polygenic risk for externalizing disorders: Gene-by-development and gene-by-environment effects in adolescents and young adults. *Clinical Psychological Science*, 3(2), 189–201. <https://doi.org/10.1177/2167702614534211>
- Samek, D. R., Hicks, B. M., Keyes, M. A., Iacono, W. G., & McGue, M. (2017). Antisocial peer affiliation and externalizing disorders: Evidence for Gene × Environment × Development interaction. *Development and Psychopathology*, 29(1), 155. <https://doi.org/10.1017/S0954579416000109>
- Sartor, C. E., Nelson, E. C., Lynskey, M. T., Madden, P. A., Heath, A. C., & Bucholz, K. K. (2013). Are there differences between young African-American and European-American women in the relative influences of genetics versus environment on age at first drink and problem alcohol use? *Alcoholism: Clinical and Experimental Research*, 37(11), 1939–1946. <https://doi.org/10.1111/acer.12185>
- Schaefer, J. D., Jang, S. K., Clark, D. A., Deak, J. D., Hicks, B. M., Iacono, W. G., Liu, M., McGue, M., Vrieze, S., Wilson, S. (2021). Associations between polygenic risk of substance use and use disorder and alcohol, cannabis, and nicotine use in adolescence and young adulthood in a longitudinal twin study. *Psychological Medicine*, 1–11. <https://doi.org/10.1017/S0033291721004116>
- Scott, M. S. (2017). Commentary: Perspectives on alcohol-related gene and environment interplay in diverse populations. *American Journal on Addictions*, 26(5), 526–531. <https://doi.org/10.1111/ajad.12584>

- Sitnick, S., Shaw, D. S., & Hyde, L. (2014). Precursors of adolescent substance use from early childhood and early adolescence: Testing a developmental cascade model. *Development and Psychopathology*, 26(1), 125. <https://doi.org/10.1017/S0954579413000539>
- Tielbeek, J. J., Vink, J. M., Polderman, T. J., Popma, A., Posthuma, D., & Verweij, K. J. (2018). Genetic correlation of antisocial behaviour with alcohol, nicotine, and cannabis use. *Drug and Alcohol Dependence*, 187, 296–299. <https://doi.org/10.1016/j.drugalcdep.2018.03.020>
- Tofighi, D., & MacKinnon, D. P. (2011). RMediation: An R package for mediation analysis confidence intervals. *Behavior Research Methods*, 43(3), 692–700. <https://doi.org/10.3758/s13428-011-0076-x>
- Trucco, E. M., Colder, C. R., Wiczorek, W. F., Lengua, L. J., & Hawk, L. W. (2014). Early adolescent alcohol use in context: How neighborhoods, parents, and peers impact youth. *Development and Psychopathology*, 26(2), 425–436. <https://doi.org/10.1017/S0954579414000042>
- Trucco, E. M., Hicks, B. M., Villafuerte, S., Nigg, J. T., Burmeister, M., & Zucker, R. A. (2016). Temperament and externalizing behavior as mediators of genetic risk on adolescent substance use. *Journal of Abnormal Psychology*, 125(4), 565. <https://doi.org/10.1037/abn0000143>
- Trucco, E. M., Villafuerte, S., Heitzeg, M. M., Burmeister, M., & Zucker, R. A. (2014). Rule breaking mediates the developmental association between GABRA 2 and adolescent substance abuse. *Journal of Child Psychology and Psychiatry*, 55(12), 1372–1379. <https://doi.org/10.1111/jcpp.12244>
- van der Laan, C. M., Morosoli-García, J. J., van de Weijer, S. G., Colodro-Conde, L., Lupton, M. K., Mitchell, B. L., McAloney, K., Parker, R., Burns, J. M., Hickie, I. B., Pool, R. (2021). Continuity of genetic risk for aggressive behavior across the life-course. *Behavior Genetics*, 51(5), 592–606. <https://doi.org/10.1007/s10519-021-10076-6>
- Vrieze, S. I., McGue, M., Miller, M. B., Hicks, B. M., & Iacono, W. G. (2013). Three mutually informative ways to understand the genetic relationships among behavioral disinhibition, alcohol use, drug use, nicotine use/dependence, and their co-occurrence: Twin biometry, GCTA, and genome-wide scoring. *Behavior Genetics*, 43(2), 97–107. <https://doi.org/10.1007/s10519-013-9584-z>
- Waldman, I. D., Rhee, S. H., LoParo, D., & Park, Y. (2018). Genetic and environmental influences on psychopathy and antisocial behavior. In C. J. Patrick (Ed.), *Handbook of psychopathy* (pp. 335–353). The Guilford Press.
- Webb, B. T., Edwards, A. C., Wolen, A. R., Salvatore, J. E., Aliev, F., Riley, B. P., Sun, C., Williamson, V. S., Kitchens, J. N., Pedersen, K., Adkins, A. (2017). Molecular genetic influences on normative and problematic alcohol use in a population-based sample of college students. *Frontiers in Genetics*, 8, 30. <https://doi.org/10.3389/fgene.2017.00030>
- Yoon, Y.-H., & Chen, C. M. (2018). *Liver Cirrhosis Mortality in the United States: National, State, and Regional Trends, 2000-2013*. <https://pubs.niaaa.nih.gov/publications/surveillance111/Cirr15.htm>
- Young, S. E., Friedman, N. P., Miyake, A., Willcutt, E. G., Corley, R. P., Haberstick, B. C., & Hewitt, J. K. (2009). Behavioral disinhibition: Liability for externalizing spectrum disorders and its genetic and environmental relation to response inhibition across adolescence. *Journal of Abnormal Psychology*, 118(1), 117. <https://doi.org/10.1037/a0014657>
- Zellers, S. M., Corley, R., Thibodeau, E., Kirkpatrick, R., Elkins, I., Iacono, W. G., Hopfer, C., Hewitt, J. K., McGue, M., Vrieze, S. (2020). Adolescent externalizing psychopathology and its prospective relationship to marijuana use development from age 14 to 30: Replication across independent longitudinal twin samples. *Behavior Genetics*, 50(3), 139–151. <https://doi.org/10.1007/s10519-020-09994-8>
- Zheng, X., Levine, D., Shen, J., Gogarten, S. M., Laurie, C., & Weir, B. S. (2012). A high-performance computing toolset for relatedness and principal component analysis of SNP data. *Bioinformatics*, 28(24), 3326–3328. <https://doi.org/10.1093/bioinformatics/bts606>