Polygenic Risk, Personality Dimensions, and Adolescent Alcohol Use Problems: A Longitudinal Study

James J. Li¹, Jeanne E. Savage², Kenneth S. Kendler², Matthew Hickman³, Liam Mahedy³, John Macleod³, Jaakko Kaprio⁴, Richard J. Rose⁵, and Danielle M. Dick⁶

¹Waisman Center, University of Wisconsin-Madison
²Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University
³School of Social and Community Medicine, University of Bristol
⁴University of Helsinki, Institute for Molecular Medicine FIMM & Department of Public Health National Institute for Health and Welfare, Helsinki
⁵Indiana University
⁶College Behavioral and Emotional Health Institute, Virginia Commonwealth University

Abstract word count: 231
Word count (not including Abstract, Acknowledgements, References, Tables or Figures): 3,997
Tables: 4; Figures: 1
Correspondence concerning his article should be addressed to James J. Li, Department of Psychology, University of Wisconsin – Madison, 1202 West Johnson Street, Madison, WI 53706. E-mail: james.li@wisc.edu
Abstract

Objective: Alcohol use problems (AUP) are common during adolescence and can predict serious negative outcomes in adulthood, including substance dependence and psychopathology. The current study examines the notion that AUP are driven by polygenic influences and that genetic influences may indirectly affect AUP through multiple pathways of risk, including variations in personality. Method: We used a genome-wide approach to examine associations between genetic risk for AUP, personality dimensions, and adolescent AUP in two separate longitudinal population-based samples, the Finnish Twin Cohort (FinnTwin12) and the Avon Longitudinal Study of Parents and Children (ALSPAC). Participants were 933 young adults from FinnTwin12 and 3,160 adolescents from ALSPAC. Polygenic risk scores (PRS) were calculated for ALSPAC using genome-wide association results (on DSM-IV alcohol dependence symptoms) from FinnTwin12. A parallel multiple mediator model was tested to examine whether the association between PRS and AUP assessed at age 16 could be explained by variations in personality dimensions assessed at age 13, including sensation-seeking (SS) and negative emotionality (NE). Results: PRS was marginally predictive of age 16 AUP; this association was partially mediated by SS. Polygenic variation underlying risk for AUP may directly influence the effects of SS, which in turn influence the development of AUP in later adolescence. Conclusions: These findings contribute to the increasing evidence regarding the salience of SS during early adolescence as a potential constituent in the risk pathway underlying the development of AUP. Keywords: alcohol use, polygenic risk scores, personality, adolescence, ALSPAC, FinnTwin12
Alcohol use problems (AUP) refer to a pattern of consumption that leads to negative consequences (Stice et al., 1998), such as failing to uphold responsibilities, regretting things the next day after having engaged in heavy drinking the night before, or injuring or hurting someone as a result of drinking (Windle, 2000). Adolescence is a critical period for alcohol and other substance use experimentation (Rogosch et al., 2010), as the majority of adolescents have engaged in some form of alcohol use (Grant et al., 2001; Swendsen et al., 2012). By early adulthood, approximately 20% reported binge drinking (i.e., 5 or more drinks on a single occasion) and nearly 11% reported extreme binge drinking (10 or more drinks on a single occasion) in the past two weeks (Patrick et al., 2013). While drinking is quite prevalent among youth, the emergence of AUP are associated with a multitude of risky behaviors that set the stage for serious long-term consequences including poor physical health, psychopathology and higher rates of mortality (Guttmannova et al., 2011; Sipila et al., 2015). Considering the individual, familial, and societal consequences of risky alcohol use in adolescents, considerable effort has been focused on identifying the mechanisms and risk factors underlying its etiology.

The importance of genetic factors for alcohol-related phenotypes has been well-established through behavioral genetic studies (Dick et al., 2011; Knopik et al., 2004; Prescott & Kendler, 1999). The past decade of gene identification studies has led to the conclusion that complex traits are likely influenced by many common genetic variants of very small effects (Purcell et al., 2009; Yang et al., 2011). The aggregate effects of common genetic variants for complex traits [i.e., polygenic risk scores (PRS)] have been used to predict risk for schizophrenia and bipolar disorder (Purcell et al., 2009) and alcohol-use outcomes (Edwards et al., 2014; Kos et al., 2013; Salvatore et al., 2014). However, complex traits are quite distal from the level of
gene action, and genetic influences may be more strongly associated with other processes that *underlie* disease risk instead (i.e., endophenotypes; Gottesman & Gould, 2003; Lenzenweger, 2013). Studying the role of endophenotypes may help to delineate the precise genetic architecture underlying AUP, as well as to understand how genetic risks for AUP unfold throughout the course of development.

Endophenotypes that map onto the stringent criteria established by Gottesman and Gould (2003) have rarely been investigated in genetically-informed studies (Waldman, 2005; Li & Lee, 2014). Dimensions of personality are compelling endophenotypes in molecular genetic studies because they are moderately to strongly heritable (Vikasovic & Bratko, 2015), reliably associated with substance use outcomes (Kotov et al., 2010), state-independent (Rothbart, Ahadi, & Evans, 2000) and co-segregate with alcohol-related phenotypes within families (Martin & Sher, 1994; Chassin et al., 2004). Among the personality dimensions, sensation-seeking (SS) may be an especially strong endophenotype for adolescent AUP. SS is characterized by a tendency to seek out novel sensations and experiences (see reviews by Hittner and Swickert, 2006 and Dick et al., 2010) and has been well-studied in the development of AUP during adolescence (Ibanez et al., 2008). High SS is associated with an earlier onset of alcohol use (Jurk et al., 2015; Viken et al., 2007; Zuckerman, 1994) and has been shown to mediate the association between early risk factors, such as family histories of substance use, and later AUP (Bidwell et al., 2015; Dick et al., 2013). High SS may also be transmitted along with risk for alcohol-related outcomes, as one large family-based study found that novelty-seeking was more strongly associated with alcohol dependence among individuals with at least one parent diagnosed with alcohol dependence than in individuals without an alcohol-dependent parent (Grucza et al., 2006). Genetically, SS has been found to be moderately heritable (40% to 60%; Eysenck, 1983; Fulker et al., 1980; Koopmans, Boomsma, Heath, & van Doornen, 1998) and genes associated
with SS have been found to overlap with those for alcohol-related outcomes (Aliev et al., 2015; Derringer et al., 2010; Laucht et al., 2007; Ray et al., 2009; Schuckit, 2009). SS meets the criteria of an endophenotype according Gottesman and Gould (2003) but has yet to be explicitly tested as one using a genetically-informed mediation model.

Another personality dimension that may mediate genetic associations for adolescent AUP is negative emotionality (NE), which is characterized by the tendency to experience unpleasant emotional states such as nervousness, fear, and anger. High NE co-develops with AUP in adolescents and young adults (Blonigen et al., 2015; Belcher et al., 2014). In a large sample of control and high-risk adolescents (at least one biological parent diagnosed with alcohol dependence), youth who exhibited heavy drinking/drug use behaviors were highest on NE and impulsivity compared to other groups that had more modest drinking and drug use behaviors (Chassin et al., 2004). High NE may also co-segregate in families with a high liability for AUP. Martin and Sher (1994) found that familial risk for alcoholism was associated with high NE. Furthermore, NE is moderately heritable (Scott et al., 2016) and there is evidence of genetic overlap between NE and AUP (Few et al., 2014). One study of young adults found that associations between single nucleotide polymorphisms (SNPs) in nicotinic acetylcholine receptor genes and DSM-IV alcohol and nicotine dependence were partially mediated by high NE (Criado et al., 2014). Like SS, high NE is strongly associated with AUP, is likely to co-segregate within families with high risk for AUP, and demonstrates moderate heritability that may overlap with AUP, suggesting that NE is plausible endophenotype for AUP.

An important consideration in studying personality dimensions for AUP is that they tend to “hang together.” A recent meta-analysis that included eight population-based cohort studies found that a personality profile of high NE, high extraversion, and low conscientiousness was prospectively associated with an increased risk of heavier alcohol consumption over time,
whereas high agreeableness and low openness to experience was related to abstinence and a decrease in consumption over time (Hakulinen et al., 2015). Similar personality profiles have also been reported in clinical populations (i.e., high NE and low conscientiousness; Kotov et al., 2010). Yet, relatively few studies of SS and NE have accounted their covariation with other dimensions of personality. By accounting for dimensions of personality simultaneously, the current study is positioned to test the hypothesis that high SS and NE constitute unique risk pathways for AUP.

The primary goal of this study was to test the hypothesis that high SS and NE may constitute plausible risk pathways from genetic risk to adolescent AUP. We examined the association between PRS estimated from GWAS results from a population-based longitudinal Finnish Twin Cohort (FinnTwin12) and adolescent AUP in a separate population-based longitudinal sample in the Avon Longitudinal Study of Parents and Children (ALSPAC). To account for the covariation among the personality dimensions, we used a parallel multiple mediator model to test whether the association between PRS and adolescent AUP could be explained by variation across different dimensions of personality, including SS, NE, extraversion, conscientiousness, agreeableness, and openness/imagination.

Method

Participants

The primary analyses used data from ALSPAC, an on-going population-based study that was designed to investigate factors that influence health and development across the lifespan. Data were originally collected on all pregnant women residing in the Avon district of South West England in the early 1990’s. In total, 14,541 pregnant women were initially enrolled in the ALSPAC study. The child participants were 49.4% male and 74.8% Caucasian. The current study used the subsample of ALSPAC participants (n=3,160) who had full genotypic and
phenotypic data available. Descriptive statistics of the main variables of interest are presented in Table 1. Detailed information about ALSPAC is available online (www.bris.ac.uk/alspac) and in the cohort profiles (Boyd et al., 2013; Fraser et al., 2013). A fully searchable data dictionary is available on the study’s website (www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

FinnTwin12, a prospective population-based twin study of five sequential cohorts of Finnish twins beginning at age 11-12 (Wave 1), served as the discovery sample to conduct GWAS on DSM-IV alcohol dependence symptom counts and to calculate PRS (full details of this study can be found in Kaprio, 2006 and Kaprio, 2013). The original sample was comprised of 2,800 families of twins ascertained from the Finnish population register. Parents, teachers and twins completed assessments related to alcohol, smoking, lifestyle, and health status (Kaprio, 2006) across several waves of data collection. The current study used data from Wave 4, when the participants were approximately 22 years of age, as most had initiated alcohol use by this age. Data for GWAS was available from 1,035 participants after passing quality control thresholds and non-missing alcohol dependence (AD) symptom count (one twin from MZ pairs removed for genetic analysis).

Measures

Adolescent AUP in ALSPAC. The Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001) is a 10-item questionnaire that was administered to adolescents at their age 16 assessment in ALSPAC. Items on the AUDIT pertained to alcohol consumption (e.g., “how often do you have a drink containing alcohol?”), drinking behavior and dependence (e.g., “how often during the last year have you found that you were not able to stop drinking once you had started?”), and consequences or problems related to drinking (e.g., “how often during the last
year have you had a feeling of guilt or remorse after drinking?”). Eight items were rated on a 5-point scale and two items were rated on a 3-point scale. The total score was the sum of the responses to all 10-items, where the maximum total score was 40. This scale demonstrated adequate internal consistency (Cronbach’s $\alpha=.79$).

*Personality dimensions in ALSPAC.* The Big Five personality dimensions were measured at the participants’ age 13 self-reported assessment in ALSPAC using an abbreviated, 50 item version of the International Personality Item Pool (Ehrhart et al., 2008; Goldberg, 1999). All items were rated on a 5-point scale (1=”not like me at all” to 5=”very like me”). The Big Five dimensions are extraversion (e.g., “feels comfortable around people”), agreeableness (e.g., “feels they are interested in people”), conscientiousness (e.g., “feels they are always prepared”), openness to experience/imagination (e.g., “feels they have excellent ideas”), and NE (e.g., “feels they get stressed out easily”). SS was measured from the Arnett Inventory of Sensation Seeking (AISS) (Arnett, 1994). This AISS consists of 20 items that are measured on a 4-point scale (1=”not like me at all” to 4=”very like me”). Representative items from the AISS include: “feels it would be interesting to see a car accident happen” and “enjoys playing sports or activities which could be dangerous.” To account for covariation among other personality variables as well as their possible unique contributions to the prediction of AUP, analyses were conducted using all six dimensions of personality in the model. Variables were created using sum scores of the items representing their dimensions. Internal consistencies for the Personality Item Pool and AISS were adequate (Cronbach’s $\alpha=.73$ and .74, respectively).

**ALSPAC genotyping**

ALSPAC samples were genotyped using the Illumina HumanHap 550 quad genome-wide SNP genotyping platform, as described previously (Fatemifar et al., 2013; Edwards et al., 2014). Individuals were excluded from analyses on the basis of excessive or minimal heterozygosity,
gender mismatch, individual missingness, cryptic relatedness as measured by identity-by-decent (IBD; genome-wide IBD 10%) and sample duplication. Population stratification was assessed using multi-dimensional scaling modeling seeded with HapMap Phase II release 22 reference populations, and those of non-European ancestry were excluded from further analysis (Fatemifar et al., 2013). Additional quality-control measures included SNPs with a final call rate <95%, minor allele frequency <1%, and evidence of departure from Hardy-Weinberg equilibrium ($p < 5 \times 10^{-7}$). The remaining genotyped markers were used to impute sample genotypes to the 1000 Genomes reference panel (phase 1, v3).

**Polygenic risk scores (PRS)**

First, a GWAS was conducted using the permutation-based QFAM procedure in PLINK 1.07 (Purcell et al., 2007) in FinnTwin12 discovery sample, which was imputed to the same 1000 Genomes reference panel (see Salvatore et al., 2014 for details). Lifetime DSM-IV criteria for alcohol dependence (AD) symptoms was assessed during a clinic visit or telephone screen with the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Hesselbrock et al., 1999). GWAS was conducted on the unstandardized residuals from a linear regression of AD symptom count on the covariates of sex and age at interview.

Second, the sets of SNPs to be included in the PRS were determined based on their GWAS association $p$-values. A range of $p$-value thresholds (i.e., $p < .05$, $p < .10$, etc.) were used to identify the top SNPs associated with AD symptom counts at decreasingly stringent levels with each threshold. Genome-wide SNPs were first pruned for linkage disequilibrium based on the 1000 Genomes reference panel (phase 1, v3) to obtain a set of 183,124 autosomal SNPs in approximate linkage equilibrium ($R^2 < .25$) for use in the PRS. To calculate PRS for individuals in ALSPAC, genotype information was used to determine the number of minor alleles each individual carried (0, 1 or 2) for each SNP in the SNP set. This allele count was then multiplied...
by the prediction estimate for the SNP that was independently-derived from the FinnTwin12 discovery sample (i.e., negative log of the SNP’s GWAS p-value and the sign of its association statistic) and summed. To harmonize variants across FinnTwin12 and ALSPAC, a set of SNPs were selected that had a minor allele frequency >5% and imputation quality $R^2 > .90$ across both samples. Power analyses were conducted in pwr package in R (Champley, 2015), which resulted in 68% power to detect an $R^2$ of .002 and 98% power to detect an $R^2$ of .005 in AUP.

**Analyses**

Parallel multiple mediator models (Hayes, 2013) were tested to examine the simultaneous effects of personality dimensions as mediators in the association between PRS and adolescent AUP. A parallel multiple mediator model was tested for each of the personality dimensions (i.e., SS, NE, conscientiousness, extraversion, agreeableness, and openness/imagination). In this model, the *direct effect* ($c'$) reflects the pathway of PRS to AUP independent of the mediational effects, $a_i$ estimates of the effect of PRS on each mediator and $b_i$ estimates the effect of each mediator on adolescent AUP controlling for PRS and the other mediator variables. As there are multiple mediators in the model, *specific indirect effects* reflect each of these individual pathways (PRS $\rightarrow$ personality dimensions $\rightarrow$ adolescent AUP) while also accounting for the shared association between them (Hayes, 2013). The *total indirect effect* is the sum of the specific indirect effects and the *total effect* is the regression of adolescent AUP on PRS alone (i.e., the completely unmediated model).

The following covariates were included into both parallel multiple mediator models: biological sex of the participant, highest level of education attained for the biological mother and her partner, and the mean frequency of maternal and partner alcohol consumption measured at first 3 months of the mother’s pregnancy, last two months of her pregnancy, and postnatally at 8 weeks, 8 months, 21 months, 33 months, 61 months, and 9 years. These covariates were selected
on the basis of previous evidence showing associations between parental education (Humensky, 2010) and parental substance use (Chassin et al., 1993) on offspring AUP and other substance use behaviors during adolescence and young adulthood.

Results

Pathways from PRS to AUP

Linear regressions of PRS (using nominally-associated sets of SNPs from each of the $p$-value thresholds) were conducted to predict age 16 AUP in ALSPAC (Table 2). PRS were not associated with age 16 AUP at the most conservative $p$-value thresholds ($p<.005$ and $p<.01$), but were positively predictive of AUP at more liberal thresholds ($p<.05$ and above). PRS at $p<.05$ and above explained about .2% of the phenotypic variance, not accounting the effects of covariates (i.e., biological sex of the participant, highest level of education attained for the biological mother and her partner, and the mean frequency of maternal and paternal partner alcohol consumption). We tested our models using the threshold at $p<.05$, as this was the most parsimonious model (i.e., statistically significant predictor of AUP with the fewest SNPs).

Pathways from PRS to personality dimensions and personality dimensions to AUP

After accounting for covariates in the model (i.e., biological sex of the participant, highest level of education attained for the biological mother and her partner, and the mean frequency of maternal and partner alcohol consumption), PRS was positively associated with SS ($b=26.98$, $SE=12.60$, $p=.03$) but not for the other personality dimensions (Table 3). Dimensions of personality were individually associated with AUP, but agreeableness was only marginally associated with AUP ($b=-4x10^{-4}$, $SE=2x10^{-4}$, $p=.09$).

Multiple Mediation Model

A multiple mediator model was tested with all six personality dimensions included as mediators simultaneously (i.e., SS, NE, extraversion, conscientiousness, agreeableness, and
openness/imagination), controlling for biological sex of the participant, highest level of
education attained for the biological mother and her partner, and the mean frequency of maternal
and partner alcohol consumption (Table 4). The bootstrapped CI for the total indirect effect of
PRS on age 16 AUP through the simultaneous effect from the personality dimensions was above
zero [95% CI .003 to .05], but the only specific indirect effect of PRS on AUP with a bootstrap
95% CI above zero was through SS (ab1=.02, SE=.01 [95% CI .003 to .05]). PRS did not affect
AUP indirectly through extraversion (ab2=.02, SE=.02 [95% CI -.01 to .06], agreeableness
(ab3=.01, SE=.01 [95% CI -.001 to .02]), NE (ab4=.003, SE=.01 [95% CI -.01 to .02]),
conscientiousness (ab5=.01, SE=.01 [95% CI -.01 to .03]) or openness/imagination (ab6=.001,
SE=.01 [95% CI -.01 to .01]). There was no evidence that PRS was associated with AUP
independent of its effect on SS (c’=.10, SE=.07, p=.14).

Discussion

The current study investigated the association between PRS, personality dimensions, and
adolescent AUP from a population-based longitudinal sample in ALSPAC. Parallel multiple
mediator models were tested to examine whether the effect of PRS on age 16 AUP was mediated
by the dimensions of personality assessed at age 13. Without accounting for the personality
dimensions, there was evidence of a modest association between PRS and AUP. The test of
mediation revealed that this association was explained by SS, but not any of the other personality
dimensions. The current results add to the growing body of literature that SS may play a role in
increasing vulnerability to AUP during adolescence.

The cross-sample predictions of PRS on AUP revealed a modest magnitude of
association, which is not surprising based on results from previous investigations (Kos et al.,
2013; Salvatore et al., 2014). Importantly, the percentage of variance explained by common
 genetic variants is linked to the size of the sample. For instance, GWAS meta-analysis of height
showed that increasing the sample size from ~130,000 to ~250,000 increased the phenotypic variance explained by all common SNPs from 45% to 50% (Wood et al., 2014). Similar conclusions have been made about psychiatric traits (e.g., Purcell et al., 2009), suggesting that having a larger GWAS sample may potentially strengthen the prediction signal from PRS. Traits with only moderate heritability (such as AD) may potentially require even larger samples relative to model traits (e.g., height) to achieve comparable gains in terms of variance explained. From a developmental perspective, the small magnitude of effect of PRS and AUP may also reflect a lesser role of genetic factors for alcohol-related phenotypes during the earlier stages of development compared to the later stages (Dick et al., 2011; Kendler et al., 2008; Rose et al., 2001), highlighting the salience of environmental factors such as easier access to alcohol and enhanced social pressures which allow genetic liabilities to develop (Edwards et al., 2015). An important note is that we created our PRS using GWAS estimates from FinnTwin12 due to the similarity of the sample to ALSPAC, with it also being a population-based study of alcohol use outcomes in young adulthood; however, it is plausible that with an older adult sample, PRS may have also had a larger magnitude of effect on AUP.

Results from the parallel multiple mediator model supported the hypothesis regarding the indirect effect of PRS on AUP through SS (although not through NE, as originally hypothesized). Furthermore, although each personality dimension was associated with AUP, SS explained the largest amount of variance in AUP (11%) whereas conscientiousness explained the least amount of the variance (1%). This suggest that high SS may contribute to a strong liability to developing AUP, over and above the effects of NE, extraversion, conscientiousness, agreeableness, and openness/imagination. The indirect effect of PRS on AUP through SS converges with recent evidence regarding the possibility of shared genetic variation between SS and AUP (Aliev et al., 2015) and is consistent with the broader molecular literature regarding the
role of SS as possible endophenotype for adolescent substance use (Bidwell et al., 2015). For instance, molecular genetic studies have found that SS mediated the association between a variable number of tandem repeat polymorphism in the \textit{DRD4} gene and alcohol-related outcomes in adolescents and college-aged adults (Laucht et al., 2007; Ray et al., 2009). SS assessed during adolescence was also a significant contributor to a developmental model (along with early conduct problems and adolescent AUP) that explained over 30% of the variance in liability for AUP by early adulthood (Edwards et al., 2016). Taken together with the current findings, high SS during childhood or early adolescence may be an important constituent in the risk pathway underlying later AUP.

No indirect effects were detected on AUP through any of the other personality dimensions, including NE. High NE may reflect a general risk for psychopathology that may not be strongly specific to AUP, whereas SS may be more specific to externalizing dimensions of psychopathology (Lahey & Waldman, 2003; Rhee et al., 2015). A study of 6- to 17-year-old twin pairs found that genetic influences on a general factor of internalizing and externalizing psychopathology was correlated with those influencing NE, whereas genetic influences on the general factor and the specific externalizing factor (but not the internalizing factor) was correlated with SS (Tackett et al., 2013), indicating the possibility that there may be a more specific genetic overlap for SS and externalizing disorders. This is also consistent with prior evidence of a Type II subtype of alcohol use disorder in adults, which is characterized as being primarily driven by genetic factors, originating with an earlier onset, and frequently associated with high SS (Cloninger et al., 1996).

The findings should be interpreted in light of a few limitations. First, this report focused on AUP and not on other substances or externalizing problems. Evidence suggests that AUP frequently co-occur with externalizing disorders, which may reflect the role of genetic influences.
that are shared across the different externalizing phenotypes that were not assessed in the current investigation (Iacono et al., 2008). Second, PRS was calculated from DSM-IV symptoms counts of AD in FinnTwin12 while our primary analyses in ALSPAC examined AUDIT scores as the outcome variable. Although the measures were not identical across studies, AUDIT scores have been shown to be modestly correlated with DSM-IV AD symptoms \((r=.43)\) (Conley, 2001). Furthermore, genetic variants underlying AD symptoms are likely to overlap with alcohol-related phenotypes (Quillen et al., 2014) and there are genetic factors in common over a wide spectrum of alcohol related phenotypes (Dick et al., 2011). Finally, both samples were fully (Finntwin12) or predominantly (ALSPAC) Caucasian and thus, the results may not generalize across racial-ethnic samples, indicating the need for the current findings to be replicated.

Identifying mechanisms that lie in the pathway between genotype and phenotype (Lenzenweger, 2013) may aid in unraveling the precise etiology of complex psychiatric outcomes. In light of the current findings, future investigations of AUP focusing on neurochemical systems and networks involved in the neurobiology of SS may be especially compelling. However, enthusiasm over the endophenotype approach should also be tempered given that certain candidate endophenotypes may not be any “genetically simpler” than the psychiatric outcomes they are associated with (Salvatore, Gottesman, & Dick, 2015). We await future genetically-informed investigations that may shed light on other important neurobiological pathways and mechanisms underlying the risk for AUP that have yet to be uncovered.
Acknowledgements

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. The UK Medical Research Council and the Wellcome Trust (Grant ref: 092731) and the University of Bristol provide core support for ALSPAC. This publication is the work of the authors and the corresponding author will serve as guarantor for the contents of this paper. Various Authors on this project were supported by the National Institute on Alcohol Abuse and Alcoholism (R01-AA014516 to D.M.D., R01-AA018333 to D.M.D., and K02-AA018755 to J.E.S.), a core grant to the Waisman Center from the National Institute on Child Health and Human Development (P30-HD03352). The MRC and Alcohol Research UK (MR/L022206/1) supports L.M. GWAS data was generated by Sample Logistics and Genotyping Facilities at the Wellcome Trust Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. Data collection and genotyping in FinnTwin12 was supported by National Institute of Alcohol Abuse and Alcoholism (R01-AA-12502, R01-AA-00145, R01-AA-09203), the Academy of Finland Center of Excellence in Complex Disease Genetics (grant numbers: 213506, 129680), and the Academy of Finland (grants 265240, 263278, 264146, 118555 & 141054).

References


doi:http://dx.doi.org/10.1016/j.drugalcdep.2014.11.024


substance use. *Substance Abuse: Research and Treatment, 9*, 1-10.
doi:http://dx.doi.org/10.4137/SART.S22440


doi:http://dx.doi.org/10.1007/s12035-014-8726-5


doi:http://dx.doi.org/10.1037/0021-843X.113.4.483

doi:http://dx.doi.org/10.1017/thg.2014.11

system approach. Psychological Science, 21, 1282-1290.

doi:http://dx.doi.org/10.1177/0956797610380699


doi:http://dx.doi.org/10.1111/j.1530-0277.2010.01432.x


doi:http://dx.doi.org/10.1017/S0033291715002457
doi:http://dx.doi.org/10.1080/00223890802248869


doi:http://dx.doi.org/10.1111/add.12690


doi:http://dx.doi.org/10.1176/appi.ajp.160.4.636


study on the genetics of alcoholism. *Journal of Biomedical Science, 8*, 77-82.

doi:http://dx.doi.org/10.1007/BF02255974


doi:http://dx.doi.org/10.1046/j.1360-0443.1999.94913618.x


doi:http://dx.doi.org/10.1016/j.addbeh.2005.11.004


doi:http://dx.doi.org/10.1111/acer.12886


doi:10.1038/tp.2016.27


Clinical Psychology, 4, 325-348.
doi: http://dx.doi.org/10.1146/annurev.clinpsy.4.022007.141157


Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., ... & Sham, P. C. (2007). PLINK: a tool set for whole-genome association and population-based linkage analyses. *The American Journal of Human Genetics, 81*, 559-575. doi:http://dx.doi.org/10.1086/519795


doi:http://dx.doi.org/10.1111/j.1530-0277.2001.tb02261.x

doi:http://dx.doi.org/10.3390/genes5020330

doi:http://dx.doi.org/10.1007/s40429-015-0046-y


doi:http://dx.doi.org/10.1038/ng.686


doi:http://dx.doi.org/10.1016/j.cpr.2013.03.003


doi:http://dx.doi.org/10.1037/a0034151


doi:http://dx.doi.org/10.1016/j.biopsych.2005.03.002


doi:http://dx.doi.org/10.1037/0893-164X.13.4.327


doi:http://dx.doi.org/10.1037/bul0000017


doi:http://dx.doi.org/10.1207/S1532480XADS0402_5


Table 1. Frequencies, proportions, means and standard deviations (SD) of study variables in ALSPAC ($n = 3,160$)

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>$n$</th>
<th>%</th>
<th>Variable Name (score ranges)</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>Alcohol Use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,269</td>
<td>40.2</td>
<td>AUDIT total scores (0 - 40)</td>
<td>6.67</td>
<td>5.19</td>
</tr>
<tr>
<td>Female</td>
<td>1,891</td>
<td>59.8</td>
<td>Maternal alcohol consumption (1 - 5)</td>
<td>2.37</td>
<td>.72</td>
</tr>
<tr>
<td>Race-ethnicity</td>
<td></td>
<td></td>
<td>Paternal alcohol consumption (1 - 5)</td>
<td>2.99</td>
<td>.79</td>
</tr>
<tr>
<td>Caucasian</td>
<td>2,940</td>
<td>93</td>
<td>Personality dimensions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>7</td>
<td>.2</td>
<td>Sensation-seeking (20 - 80)</td>
<td>50.38</td>
<td>7.52</td>
</tr>
<tr>
<td>Missing</td>
<td>213</td>
<td>6.7</td>
<td>Negative emotionality (10 - 50)</td>
<td>23.21</td>
<td>5.06</td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
<td>Conscientiousness (10 - 50)</td>
<td>31.95</td>
<td>5.87</td>
</tr>
<tr>
<td>CSE/none</td>
<td>292</td>
<td>9.2</td>
<td>Openness/imagination (10 - 50)</td>
<td>28.49</td>
<td>4.81</td>
</tr>
<tr>
<td>Vocational</td>
<td>194</td>
<td>6.1</td>
<td>Agreeableness (10 - 50)</td>
<td>35.01</td>
<td>4.59</td>
</tr>
<tr>
<td>O Level</td>
<td>970</td>
<td>30.7</td>
<td>Extraversion (10 - 50)</td>
<td>31.85</td>
<td>6.26</td>
</tr>
<tr>
<td>A Level</td>
<td>855</td>
<td>27.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree</td>
<td>668</td>
<td>21.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>181</td>
<td>5.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Partner education

<table>
<thead>
<tr>
<th>Education</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSE/none</td>
<td>435</td>
<td>13.8</td>
</tr>
<tr>
<td>Vocational</td>
<td>201</td>
<td>6.4</td>
</tr>
<tr>
<td>O Level</td>
<td>614</td>
<td>19.4</td>
</tr>
<tr>
<td>A Level</td>
<td>854</td>
<td>27</td>
</tr>
<tr>
<td>Degree</td>
<td>837</td>
<td>26.5</td>
</tr>
<tr>
<td>Missing</td>
<td>219</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Note. AUDIT = Alcohol Use Disorders Identification Test; frequencies of maternal and paternal alcohol consumption were rated on a 6 point scale (1=never drink alcohol to 6 = 10+ glasses per day); sensation-seeking was measured from the AISS; Big Five personality traits were measured from the International Personality Item Pool at age 13.
Table 2. Ordinary least squares regressions of PRS p-value thresholds predicting ALSPAC adolescent AUP

<table>
<thead>
<tr>
<th>PRS p-value thresholds</th>
<th># of SNPs</th>
<th>Coeff.</th>
<th>SE</th>
<th>p</th>
<th>$\Delta R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>p &lt; .005</td>
<td>1,994</td>
<td>.02</td>
<td>.02</td>
<td>.34</td>
<td>.001</td>
</tr>
<tr>
<td>p &lt; .01</td>
<td>3,391</td>
<td>.02</td>
<td>.02</td>
<td>.38</td>
<td>.001</td>
</tr>
<tr>
<td>p &lt; .05</td>
<td>17,008</td>
<td>.14</td>
<td>.06</td>
<td>.03</td>
<td>.002</td>
</tr>
<tr>
<td>p &lt; .10</td>
<td>31,569</td>
<td>.21</td>
<td>.09</td>
<td>.02</td>
<td>.002</td>
</tr>
<tr>
<td>p &lt; .20</td>
<td>57,428</td>
<td>.34</td>
<td>.14</td>
<td>.02</td>
<td>.002</td>
</tr>
<tr>
<td>p &lt; .50</td>
<td>121,868</td>
<td>.72</td>
<td>.26</td>
<td>&lt; .01</td>
<td>.003</td>
</tr>
</tbody>
</table>

Note. PRS = polygenic risk score, SNPs = single nucleotide polymorphism, coeff. = unstandardized beta, SE = standard error, $\Delta R^2$ = difference in $R^2$ between model with only covariates and model in which PRS was added to the covariate-only model.
Table 3. Regression coefficients, standard errors, and model summary information ($R^2$) for the adolescent AUP parallel multiple mediator models

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Paths from PRS to personality dimensions</th>
<th>Paths from personality dimensions to AUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Path</td>
<td>Coeff.</td>
</tr>
<tr>
<td>Sensation-seeking</td>
<td>$a_1$</td>
<td>26.98</td>
</tr>
<tr>
<td>Extraversion</td>
<td>$a_2$</td>
<td>14.63</td>
</tr>
<tr>
<td>Agreeableness</td>
<td>$a_3$</td>
<td>-10.85</td>
</tr>
<tr>
<td>Negative emotionality</td>
<td>$a_4$</td>
<td>3.09</td>
</tr>
<tr>
<td>Conscientiousness</td>
<td>$a_5$</td>
<td>-12.87</td>
</tr>
<tr>
<td>Openness/imagination</td>
<td>$a_6$</td>
<td>-2.07</td>
</tr>
</tbody>
</table>

*Note. PRS = polygenic risk score at $p = .05$ threshold (number of genotyped SNPs = 17,008); statistical covariates were included in all models but not presented in the tables. $R^2$ for paths from personality dimensions to AUP are the same as $R^2$ for paths from PRS to personality dimensions, as all pathways were simultaneously tested using the same model (see Figure 1).*
Table 4. Direct and indirect effects of the parallel multiple mediator model for age 16 AUP

<table>
<thead>
<tr>
<th></th>
<th>Effect</th>
<th>SE</th>
<th>p</th>
<th>95% Bootstrap corrected CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower bound</td>
</tr>
<tr>
<td>Total effect</td>
<td>.17</td>
<td>.08</td>
<td>.03</td>
<td>---</td>
</tr>
<tr>
<td>Direct effect</td>
<td>.11</td>
<td>.07</td>
<td>.14</td>
<td>---</td>
</tr>
<tr>
<td>Total indirect effect</td>
<td>.06</td>
<td>.03</td>
<td>---</td>
<td>.01</td>
</tr>
<tr>
<td>Specific indirect effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensation-seeking</td>
<td>.02</td>
<td>.01</td>
<td>---</td>
<td>.003</td>
</tr>
<tr>
<td>Extraversion</td>
<td>.02</td>
<td>.02</td>
<td>---</td>
<td>-.01</td>
</tr>
<tr>
<td>Agreeableness</td>
<td>.01</td>
<td>.01</td>
<td>---</td>
<td>-.001</td>
</tr>
<tr>
<td>Negative emotionality</td>
<td>.003</td>
<td>.01</td>
<td>---</td>
<td>-.01</td>
</tr>
<tr>
<td>Conscientiousness</td>
<td>.01</td>
<td>.01</td>
<td>---</td>
<td>-.01</td>
</tr>
<tr>
<td>Openness/imagination</td>
<td>.001</td>
<td>.01</td>
<td>---</td>
<td>-.01</td>
</tr>
</tbody>
</table>
Figure 1. Parallel multiple mediator model of adolescent AUP