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

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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

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

Longitudinal Study

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.

<div align="center">Method</div>

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 α=.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; Goldbert, 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 α=.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 ($p<$

$5x10^{-7}$). 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

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→personality dimensions→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 ($b=-4\times10^{-4}$, $SE=2\times10^{-4}$, $p=.09$).

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 (ab_1=.02, SE=.01 [95% CI .003 to .05]). PRS did not affect

AUP indirectly through extraversion (ab_2=.02, SE=.02 [95% CI -.01 to .06], agreeableness

(ab_3=.01, SE=.01 [95% CI -.001 to .02]), NE (ab_4=.003, SE=.01 [95% CI -.01 to .02]),

conscientiousness (ab_5=.01, SE=.01 [95% CI -.01 to .03]) or openness/imagination (ab_6=.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 *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.

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References

Ali, B., Seitz-Brown, C. J., & Daughters, S. B. (2015). The interacting effect of depressive symptoms, gender, and distress tolerance on substance use problems among residential treatment-seeking substance users. *Drug and Alcohol Dependence*, *148*, 21-26. doi:http://dx.doi.org/10.1016/j.drugalcdep.2014.11.024

Aliev, F., Wetherill, L., Bierut, L., Bucholz, K. K., Edenberg, H., Foroud, T., & Dick, D. M.

    (2015). Genes associated with alcohol outcomes show enrichment of effects with broad

    externalizing and impulsivity phenotypes in an independent sample. *Journal of Studies on*

    Alcohol and Drugs, *76*, 38-46. doi:http://dx.doi.org/10.15288/jsad.76.1.38

Allen, H. L., Estrada, K., Lettre, G., Berndt, S. I., Weedon, M. N., Rivadeneira, F., ... & Ferreira,

    T. (2010). Hundreds of variants clustered in genomic loci and biological pathways affect

    human height. *Nature*, *467*, 832-838. doi:http://dx.doi.org/10.1038/nature09410

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental*

    Disorders (revised 4th ed.). Washington, DC: American Psychiatric Association.

Anttila, V., Bulik-Sullivan, B., Finucane, H. K., Bras, J., … & Neale, B. (2016). Analysis of

    shared heritability in common disorders of the brain. Manuscript submitted for

    publication. doi:http://dx.doi.org/10.1101/048991

Arnett, J. (1994). Sensation seeking: A new conceptualization and a new scale. *Personality and*

    Individual Differences, *16*, 289-296. doi:http://dx.doi.org/10.1016/0191-8869(94)90165-1

Babor, T. F., Higgins-Biddle, J. C., Saunders, J. B., & Monteiro, M. G. (2001). *AUDIT, the*

    alcohol use disorders identification test: Guidelines for use in primary care (2nd ed.).

    Geneva, Switzerland: World Health Organization, Dept. of Mental Health and Substance

    Dependence.

Belcher, A. M., Volkow, N. D., Moeller, F. G., & Ferré, S. (2014). Personality traits and

    vulnerability or resilience to substance use disorders. *Trends in Cognitive Sciences*, *18*,

    211-217. doi:http://dx.doi.org/10.1016/j.tics.2014.01.010

Bidwell, L. C., Knopik, V. S., Audrain-McGovern, J., Glynn, T. R., Spillane, N. S., Ray, L. A.,

    ... & Leventhal, A. M. (2015). Novelty seeking as a phenotypic marker of adolescent

substance use. *Substance Abuse: Research and Treatment*, *9*, 1-10.

doi:http://dx.doi.org/10.4137/SART.S22440

Blonigen, D. M., Timko, C., Jacob, T., & Moos, R. H. (2015). Patient-centered feedback on the

results of personality testing increases early engagement in residential substance use

disorder treatment: a pilot randomized controlled trial. *Addiction Science & Clinical*

Practice, *10*, 1. doi:http://dx.doi.org/10.1186/s13722-015-0030-9

Blum, K., Oscar-Berman, M., Demetrovics, Z., Barh, D., & Gold, M. S. (2014). Genetic

addiction risk score (GARS): molecular neurogenetic evidence for predisposition to

reward deficiency syndrome (RDS). *Molecular Neurobiology*, *50*, 765-796.

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

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., ... & Smith, G. D.

(2012). Cohort profile: the 'children of the 90s'—the index offspring of the Avon

Longitudinal Study of Parents and Children. *International Journal of Epidemiology*, 1-

17. doi:http://dx.doi.org 10.1093/ije/dys064.

Chassin, L., Flora, D. B., & King, K. M. (2004). Trajectories of alcohol and drug use and

dependence from adolescence to adulthood: the effects of familial alcoholism and

personality. *Journal of Abnormal Psychology*, *113*, 483-498.

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

Criado, J. R., Gizer, I. R., Edenberg, H. J., & Ehlers, C. L. (2014). CHRNA5 and CHRNA3

variants and level of neuroticism in young adult Mexican American men and

women. *Twin Research and Human Genetics*, *17*, 80-88.

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

Derringer, J., Krueger, R. F., Dick, D. M., Saccone, S., Grucza, R. A., Agrawal, A., ... &

Nurnberger, J. I. (2010). Predicting sensation seeking from dopamine genes a candidate-

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

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

Dick, D. M., Smith, G., Olausson, P., Mitchell, S. H., Leeman, R. F., O'Malley, S. S., & Sher, K.

(2010). Understanding the construct of impulsivity and its relationship to alcohol use

disorders. *Addiction Biology*, *15*, 217-226. doi:http://dx.doi.org/10.1111/j.1369-

1600.2009.00190.x

Dick, D. M., Meyers, J. L., Rose, R. J., Kaprio, J., & Kendler, K. S. (2011). Measures of current

alcohol consumption and problems: two independent twin studies suggest a complex

genetic architecture. *Alcoholism: Clinical and Experimental Research*, *35*, 2152-2161.

doi:10.1111/j.1530-0277.2011.01564.x

Dick, D. M., Aliev, F., Viken, R., Kaprio, J., & Rose, R. J. (2011). Rutgers alcohol problem

index scores at age 18 predict alcohol dependence diagnoses 7 years later. *Alcoholism:

Clinical and Experimental Research*, *35*, 1011-1014.

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

Dick, D. M., Aliev, F., Latendresse, S. J., Hickman, M., Heron, J., Macleod, J., ... & Kendler, K.

S. (2013). Adolescent alcohol use is predicted by childhood temperament factors before

age 5, with mediation through personality and peers. *Alcoholism: Clinical and

Experimental Research*, *37*, 2108-2117. doi:http://dx.doi.org/10.1111/acer.12206

Dudbridge, F. (2013) Power and predictive accuracy of polygenic risk scores. *PLoS Genetics*, 9,

e1003348. doi:10.1371/journal.pgen.1003348

Edwards, A. C., Gardner, C. O., Hickman, M., & Kendler, K. S. (2015). A prospective

longitudinal model predicting early adult alcohol problems: evidence for a robust

externalizing pathway. *Psychological Medicine*, 1-12.

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

Ehrhart, K. H., Roesch, S. C., Ehrhart, M. G., & Kilian, B. (2008). A test of the factor structure

    equivalence of the 50-item IPIP five-factor model measure across gender and ethnic

    groups. *Journal of Personality Assessment*, *90*, 507-516.

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

Fatemifar, G., Hoggart, C. J., Paternoster, L., Kemp, J. P., Prokopenko, I., Horikoshi, M., ... &

    Toma, A. M. (2013). Genome-wide association study of primary tooth eruption identifies

    pleiotropic loci associated with height and craniofacial distances. *Human Molecular*

    Genetics, doi:http://dx.doi.org/10.1093/hmg/ddt231.

Few, L. R., Grant, J. D., Trull, T. J., Statham, D. J., Martin, N. G., Lynskey, M. T., & Agrawal,

    A. (2014). Genetic variation in personality traits explains genetic overlap between

    borderline personality features and substance use disorders. *Addiction*, *109*, 2118-2127.

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

Glaser, Y. G., Zubieta, J., Hsu, D. T., Villafuerte, S., Mickey, B. J., Trucco, E. M., . . . Heitzeg,

    M. M. (2014). Indirect effect of corticotropin-releasing hormone receptor 1 gene

    variation on negative emotionality and alcohol use via right ventrolateral prefrontal

    cortex. *The Journal of Neuroscience, 34*, 4099-4107.

    doi:http://dx.doi.org/10.1523/JNEUROSCI.3672-13.2014

Goldberg, L. R. (1999). A broad-bandwidth, public domain, personality inventory measuring the

    lower-level facets of several five-factor models. *Personality Psychology in Europe*, *7*, 7-

    28.

Gottesman, I. I., & Gould, T. D. (2003). The endophenotype concept in psychiatry: etymology

    and strategic intentions. *American Journal of Psychiatry*, *160*, 636-645.

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

Grant, B. F., Stinson, F. S., & Harford, T. C. (2001). Age at onset of alcohol use and DSM-IV alcohol abuse and dependence: a 12-year follow-up. *Journal of Substance Abuse*, *13*, 493-504. doi:http://dx.doi.org/10.1016/S0899-3289(01)00096-7

Guttmannova, K., Bailey, J. A., Hill, K. G., Lee, J. O., Hawkins, J. D., Woods, M. L., & Catalano, R. F. (2011). Sensitive Periods for Adolescent Alcohol Use Initiation: Predicting the Lifetime Occurrence and Chronicity of Alcohol Problems in Adulthood. *Journal of Studies on Alcohol and Drugs*, *72*, 221-231. doi:http://dx.doi.org/10.15288/jsad.2011.72.221

Hakulinen, C., Elovainio, M., Batty, G. D., Virtanen, M., Kivimäki, M., & Jokela, M. (2015). Personality and alcohol consumption: Pooled analysis of 72,949 adults from eight cohort studies. *Drug and Alcohol Dependence*, *151*, 110-114.

Hansell, N. K., Agrawal, A., Whitfield, J. B., Morley, K. I., Gordon, S. D., Lind, P. A., ... & Heath, A. C. (2009). Can we identify genes for alcohol consumption in samples ascertained for heterogeneous purposes? *Alcoholism: Clinical and Experimental Research*, *33*, 729-739. doi:http://dx.doi.org/10.1111/j.1530-0277.2008.00890.x

Hayes, A. F. (2013). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. Guilford Press, New York, NY. Retrieved from http://search.proquest.com/docview/1449311595?accountid=14509

Heath, A. C., Whitfield, J. B., Martin, N. G., Pergadia, M. L., Goate, A. M., Lind, P. A., ... & Zhu, R. (2011). A quantitative-trait genome-wide association study of alcoholism risk in the community: findings and implications. *Biological Psychiatry*, *70*, 513-518. doi:http://dx.doi.org/10.1016/j.biopsych.2011.02.028

Hesselbrock, V., Begleiter, H., Porjesz, B., O'Connor, S., & Bauer, L. (2001). P300 event-related potential amplitude as an endophenotype of alcoholism—evidence from the collaborative

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

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

Hesselbrock, M., Easton, C., Bucholz, K. K., Schuckit, M., & Hesselbrock, V. (1999). A validity

study of the SSAGA-a comparison with the SCAN. *Addiction*, *94*, 1361-1370.

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

Hink, L. K., Rhee, S. H., Corley, R. P., Cosgrove, V. E., Hewitt, J. K., Schulz-Heik, R. J., ... &

Waldman, I. D. (2013). Personality dimensions as common and broadband-specific

features for internalizing and externalizing disorders. *Journal of Abnormal Child

Psychology*, *41*, 939-957. doi:http://dx.doi.org/10.1007/s10802-013-9730-3

Hittner, J. B., & Swickert, R. (2006). Sensation seeking and alcohol use: A meta-analytic

review. *Addictive Behaviors*, *31*, 1383-1401.

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

Jurk, S., Kuitunen-Paul, S., Kroemer, N. B., Artiges, E., Banaschewski, T., Bokde, A. L., ... &

Frouin, V. (2015). Personality and substance use: psychometric evaluation and validation

of the Substance Use Risk Profile Scale (SURPS) in English, Irish, French, and German

adolescents. *Alcoholism: Clinical and Experimental Research*, *39*, 2234-2248.

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

Kapoor, M., Chou, Y. L., Edenberg, H. J., Foroud, T., Martin, N. G., Madden, P. A. F., ... &

Chan, G. (2016). Genome-wide polygenic scores for age at onset of alcohol dependence

and association with alcohol-related measures. *Translational Psychiatry*, *6*, e761.

doi:10.1038/tp.2016.27

Kaprio, J. (2006). Twin studies in Finland 2006. *Twin Research and Human Genetics*, *9*, 772-

777. doi:http://dx.doi.org/10.1375/twin.9.6.772

Kaprio, J. (2013). The Finnish twin cohort study: an update. *Twin Research and Human Genetics*, *16*, 157-162. doi:http://dx.doi.org/10.1017/thg.2012.142

Kendler, K. S., Kalsi, G., Holmans, P. A., Sanders, A. R., Aggen, S. H., Dick, D. M., ... & Gejman, P. V. (2011). Genomewide association analysis of symptoms of alcohol dependence in the molecular genetics of schizophrenia (MGS2) control sample. *Alcoholism: Clinical and Experimental Research*, *35*, 963-975. doi:http://dx.doi.org/10.1111/j.1530-0277.2010.01427.x

Kendler, K. S., Liu, X. Q., Gardner, C. O., McCullough, M. E., Larson, D., & Prescott, C. A. (2003). Dimensions of religiosity and their relationship to lifetime psychiatric and substance use disorders. *American Journal of Psychiatry*, *160*, 496-503. doi:http://dx.doi.org/10.1176/appi.ajp.160.3.496

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*, 929-937. doi:http://dx.doi.org/10.1001/archpsyc.60.9.929

Kendler, K. S., Schmitt, E., Aggen, S. H., & Prescott, C. A. (2008). Genetic and environmental influences on alcohol, caffeine, cannabis, and nicotine use from early adolescence to middle adulthood. *Archives of General Psychiatry*, *65*, 674-682. doi:http://dx.doi.org/10.1001/archpsyc.65.6.674

Kos, M. Z., Yan, J., Dick, D. M., Agrawal, A., Bucholz, K. K., Rice, J. P., ... & Goate, A. M. (2013). Common biological networks underlie genetic risk for alcoholism in African-and European-American populations. *Genes, Brain and Behavior*, *12*, 532-542. doi:http://dx.doi.org/10.1111/gbb.12043

Kotov, R., Gamez, W., Schmidt, F., & Watson, D. (2010). Linking "big" personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. *Psychological Bulletin*, *136*, 768. doi:http://dx.doi.org/10.1037/a0020327

Knopik, V. S., Heath, A. C., Madden, P. A., Bucholz, K. K., Slutske, W. S., Nelson, E. C., ... & Martin, N. G. (2004). Genetic effects on alcohol dependence risk: re-evaluating the importance of psychiatric and other heritable risk factors. *Psychological Medicine*, *34*, 1519-1530. doi:http://dx.doi.org/10.1017/S0033291704002922

Lahey, B. B., & Waldman, I. D. (2003). A developmental propensity model of the origins of conduct problems during childhood and adolescence. *Causes of Conduct Disorder and Juvenile Delinquency*, 76-117. Retrieved from http://search.proquest.com/docview/620221291?accountid=14509

Laucht, M., Becker, K., Blomeyer, D., & Schmidt, M. H. (2007). Novelty seeking involved in mediating the association between the dopamine D4 receptor gene exon III polymorphism and heavy drinking in male adolescents: results from a high-risk community sample. *Biological Psychiatry*, *61*, 87-92. doi:http://dx.doi.org/10.1016/j.biopsych.2006.05.025

Lee, S. T., Ryu, S., Kim, S. R., Kim, M. J., Kim, S., Kim, J. W., ... & Hong, K. S. (2012). Association study of 27 annotated genes for clozapine pharmacogenetics: validation of preexisting studies and identification of a new candidate gene, ABCB1, for treatment response. *Journal of Clinical Psychopharmacology*, *32*, 441-448. doi:http://dx.doi.org/10.1097/JCP.0b013e31825ac35c

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.

doi:http://dx.doi.org/10.1146/annurev.clinpsy.4.022007.141157

Li, J. J., & Lee, S. S. (2014). Negative emotionality mediates the association of 5-HTTLPR

genotype and depression in children with and without ADHD. *Psychiatry Research*, *215*,

163-169. doi:10.1016/j.psychres.2013.10.026

Malmberg, M., Kleinjan, M., Vermulst, A. A., Overbeek, G., Monshouwer, K., Lammers, J., &

Engels, R. C. (2012). Do substance use risk personality dimensions predict the onset of

substance use in early adolescence? A variable-and person-centered approach. *Journal of*

Youth and Adolescence, *41*, 1512-1525. doi:http://dx.doi.org/10.1007/s10964-012-9775-6

Patrick, M. E., Schulenberg, J. E., Martz, M. E., Maggs, J. L., O'Malley, P. M., & Johnston, L.

D. (2013). Extreme binge drinking among 12th-grade students in the United States:

prevalence and predictors. *JAMA Pediatrics*, *167*, 1019-1025.

doi:http://dx.doi.org/10.1001/jamapediatrics.2013.2392.

Porjesz, B., & Rangaswamy, M. (2007). Neurophysiological endophenotypes, CNS disinhibition,

and risk for alcohol dependence and related disorders. *The Scientific World Journal*, *7*,

131-141. doi: http://dx.doi.org/10.1100/tsw.2007.203

Prescott, C. A., & Kendler, K. S. (1999). Genetic and environmental contributions to alcohol

abuse and dependence in a population-based sample of male twins. *American Journal of*

Psychiatry. *156*, 34-40. Retrieved from

http://search.proquest.com/docview/619380125?accountid=14509

Psychiatric GWAS Consortium Coordinating Committee. (2009). Genomewide association

studies: history, rationale, and prospects for psychiatric disorders. *American Journal of*

Psychiatry. doi:http://dx.doi.org/10.1176/appi.ajp.2008.08091354

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

Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., ... &

  O'Dushlaine, C. T. (2009). Common polygenic variation contributes to risk of

  schizophrenia and bipolar disorder. *Nature*, *460*, 748-752.

  doi:http://dx.doi.org/10.1038/nature08185

Ray, L. A., Bryan, A., MacKillop, J., McGeary, J., Hesterberg, K., & Hutchison, K. E. (2009).

  Genetic Study: The dopamine D4 Receptor (DRD4) gene exon III polymorphism,

  problematic alcohol use and novelty seeking: direct and mediated genetic

  effects. *Addiction Biology*, *14*, 238-244. doi:http://dx.doi.org/10.1111/j.1369-

  1600.2008.00120.x

Ray, L. A., Mackillop, J., & Monti, P. M. (2010). Subjective responses to alcohol consumption

  as endophenotypes: advancing behavioral genetics in etiological and treatment models of

  alcoholism. *Substance Use and Misuse*, *45*, 1742-1765.

  doi:http://dx.doi.org/10.3109/10826084.2010.482427

Rhee, S. H., Lahey, B. B., & Waldman, I. D. (2015). Comorbidity among dimensions of

  childhood psychopathology: Converging evidence from behavior genetics. *Child

  Development Perspectives*, *9*, 26-31. doi:http://dx.doi.org/10.1111/cdep.12102

Rogosch, F. A., Oshri, A., & Cicchetti, D. (2010). From child maltreatment to adolescent

  cannabis abuse and dependence: A developmental cascade model. *Development and

  Psychopathology*, *22*, 883-897. doi:http://dx.doi.org/10.1017/S0954579410000520

Rose, R. J., Dick, D. M., Viken, R. J., & Kaprio, J. (2001). Gene-environment interaction in

    patterns of adolescent drinking: Regional residency moderates longitudinal influences on

    alcohol use. *Alcoholism: Clinical and Experimental Research*, *25*, 637-643.

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

Salvatore, J. E., Aliev, F., Edwards, A. C., Evans, D. M., Macleod, J., Hickman, M., ... &

    Latvala, A. (2014). Polygenic scores predict alcohol problems in an independent sample

    and show moderation by the environment. *Genes*, *5*, 330-346.

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

Salvatore, J. E., Gottesman, I. I., & Dick, D. M. (2015). Endophenotypes for Alcohol Use

    Disorder: An Update on the Field. *Current Addiction Reports*, *2*, 76-90.

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

Scott, B. G., Lemery-Chalfant, K., Clifford, S., Tein, J. Y., Stoll, R., & Goldsmith, H. H. (2016).

    A twin factor mixture modeling approach to childhood temperament: differential

    heritability. *Child Development*. Doi:10.1111/cdev.12561

Schuckit, M. A. (2009). An overview of genetic influences in alcoholism. *Journal of Substance

    Abuse Treatment*, *36*, S5-14. doi:http://dx.doi.org/10.1016/j.jsat.2008.10.010

Sipilä, P., Rose, R. J., & Kaprio, J. (2015). Drinking and mortality: Long-term follow-up of

    drinking-discordant twin pairs. *Addiction*, *111*, 245-254. doi:10.1111/add.13152

Slutske, W. S., Heath, A. C., Madden, P. A., Bucholz, K. K., Statham, D. J., & Martin, N. G.

    (2002). Personality and the genetic risk for alcohol dependence. *Journal of Abnormal

    Psychology*, *111*, 124-133. doi:http://dx.doi.org/10.1037/0021-843X.111.1.124

Smith, C. J. W., Wilkins, K. B., Mogavero, J. N., & Veenema, A. H. (2015). Social Novelty

    Investigation in the Juvenile Rat: Modulation by the µ-Opioid System. *Journal of

    Neuroendocrinology*, *27*, 752-764. doi:http://dx.doi.org/10.1111/jne.12301

Speliotes, E. K., Willer, C. J., Berndt, S. I., Monda, K. L., Thorleifsson, G., Jackson, A. U., ... &
Randall, J. C. (2010). Association analyses of 249,796 individuals reveal 18 new loci
associated with body mass index. *Nature Genetics*, *42*, 937-948.
doi:http://dx.doi.org/10.1038/ng.686

Stautz, K., & Cooper, A. (2013). Impulsivity-related personality traits and adolescent alcohol
use: a meta-analytic review. *Clinical Psychology Review*, *33*, 574-592.
doi:http://dx.doi.org/10.1016/j.cpr.2013.03.003

Steinberg, L. (2008). A social neuroscience perspective on adolescent risk-
taking. *Developmental Review*, *28*, 78-106. doi:http://dx.doi.org/10.1016/j.dr.2007.08.002

Stice, E., Barrera Jr, M., & Chassin, L. (1998). Prospective differential prediction of adolescent
alcohol use and problem use: examining the mechanisms of effect. *Journal of Abnormal
Psychology*, *107*, 616. doi:http://dx.doi.org/10.1037/0021-843X.107.4.616

Swendsen, J., Burstein, M., Case, B., Conway, K. P., Dierker, L., He, J., & Merikangas, K. R.
(2012). Use and abuse of alcohol and illicit drugs in US adolescents: Results of the
National Comorbidity Survey–Adolescent Supplement. *Archives of General
Psychiatry*, *69*, 390-398. doi:http://dx.doi.org/10.1001/archgenpsychiatry.2011.1503

Tackett, J. L., Lahey, B. B., Van Hulle, C., Waldman, I., Krueger, R. F., & Rathouz, P. J. (2013).
Common genetic influences on negative emotionality and a general psychopathology
factor in childhood and adolescence. *Journal of Abnormal Psychology*, *122*, 1142-1153.
doi:http://dx.doi.org/10.1037/a0034151

Waldman, I. D. (2005). Statistical approaches to complex phenotypes: evaluating
neuropsychological endophenotypes for attention-deficit/hyperactivity
disorder. *Biological Psychiatry*, *57*, 1347-1356.
doi:http://dx.doi.org/10.1016/j.biopsych.2005.03.002

Viken, R. J., Kaprio, J., & Rose, R. J. (2007). Personality at Ages 16 and 17 and Drinking Problems at Ages 18 and 25: Genetic Analyses of Data from FinnTwin 16–25. *Twin Research and Human Genetics, 10*, 25-32. doi:http://dx.doi.org/10.1375/twin.10.1.25

Wills, T. A., Sandy, J. M., Shinar, O., & Yaeger, A. (1999). Contributions of positive and negative affect to adolescent substance use: Test of a bidimensional model in a longitudinal study. *Psychology of Addictive Behaviors*, *13*, 327-338. doi:http://dx.doi.org/10.1037/0893-164X.13.4.327

Vink, J. M., Hottenga, J. J., Geus, E. J., Willemsen, G., Neale, M. C., Furberg, H., & Boomsma, D. I. (2014). Polygenic risk scores for smoking: predictors for alcohol and cannabis use? *Addiction*, *109*, 1141-1151. doi:http://dx.doi.org/10.1111/add.12491

Vukasović, T., & Bratko, D. (2015). Heritability of personality: A meta-analysis of behavior genetic studies. *Psychological Bulletin*, *141*, 769-785. doi:http://dx.doi.org/10.1037/bul0000017

Windle, M. (2000). Parental, sibling, and peer influences on adolescent substance use and alcohol problems. *Applied Developmental Science*, *4*, 98-110. doi:http://dx.doi.org/10.1207/S1532480XADS0402_5

Yan, J., Aliev, F., Webb, B. T., Kendler, K. S., Williamson, V. S., Edenberg, H. J., ... & Schuckit, M. A. (2014). Using genetic information from candidate gene and genome-wide association studies in risk prediction for alcohol dependence. *Addiction Biology*, *19*, 708-721. doi: 10.1111/adb.12035

Yang, J., Benyamin, B., McEvoy, B. P., Gordon, S., Henders, A. K., Nyholt, D. R., ... & Goddard, M. E. (2010). Common SNPs explain a large proportion of the heritability for human height. *Nature Genetics*, *42*, 565-569. doi:10.1038/ng.608

Zuckerman, M. (1994). *Behavioral expressions and biosocial bases of sensation seeking*.

Cambridge University Press, New York, NY. Retrieved from

http://search.proquest.com/docview/618567929?accountid=14509

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

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

Partner education

CSE/none	435	13.8
Vocational	201	6.4
O Level	614	19.4
A Level	854	27
Degree	837	26.5
Missing	219	6.9

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

PRS p-value thresholds	# of SNPs	Coeff.	SE	p	ΔR^2
p < .005	1,994	.02	.02	.34	.001
p < .01	3,391	.02	.02	.38	.001
p < .05	17,008	.14	.06	.03	.002
p < .10	31,569	.21	.09	.02	.002
p < .20	57,428	.34	.14	.02	.002
p < .50	121,868	.72	.26	< .01	.003

Note. PRS = polygenic risk score, SNPs = single nucleotide polymorphism, coeff. = unstandardized beta, SE = standard error, ΔR^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

Predictor	Paths from PRS to personality dimensions				Paths from personality dimensions to AUP				
	Path	Coeff.	*SE*	*P*	Path	Coeff.	*SE*	*p*	R^2
Sensation-seeking	a_1	26.98	12.60	.03	b_1	8×10^{-4}	1×10^{-4}	< .001	.11
Extraversion	a_2	14.63	11.15	.19	b_2	.002	2×10^{-4}	< .001	.02
Agreeableness	a_3	-10.85	7.79	.16	b_3	-4×10^{-4}	2×10^{-4}	.09	.11
Negative emotionality	a_4	3.09	8.74	.72	b_4	9×10^{-4}	2×10^{-4}	< .001	.07
Conscientiousness	a_5	-12.87	10.66	.23	b_5	-9×10^{-4}	2×10^{-4}	< .001	.01
Openness/imagination	a_6	-2.07	8.42	.81	b_6	-6×10^{-4}	2×10^{-4}	.02	.06

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

	Effect	*SE*	*p*	95% Bootstrap corrected CI	
				Lower bound	Upper bound
Total effect	.17	.08	.03	---	---
Direct effect	.11	.07	.14	---	---
Total indirect effect	.06	.03	---	.01	.12
Specific indirect effects					
Sensation-seeking	.02	.01	---	.003	.05
Extraversion	.02	.02	---	-.01	.06
Agreeableness	.01	.01	---	-.001	.02
Negative emotionality	.003	.01	---	-.01	.02
Conscientiousness	.01	.01	---	-.01	.03
Openness/imagination	.001	.01	---	-.01	.01

Figure 1. Parallel multiple mediator model of adolescent AUP