Title: Predicting alcohol use from genome-wide polygenic scores, environmental factors, and their interactions in young adulthood

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Keywords: alcohol use, gene-environment interaction, polygenic scores, young adulthood, TEDS

Running title: GxE IN ALCOHOL USE

Word count (Introduction and Discussion):1899

Declaration of competing interest: None

Study preregistration: osf.io/ugk3n

Abstract

Alcohol use during emerging adulthood is associated with adverse life outcomes but its risk factors are not well known. Here, we predicted alcohol use in 3,153 adults aged 22 years from (a) genome-wide polygenic scores (GPS) based on genome-wide association studies for the target phenotypes number of drinks per week and Alcohol Use Disorders Identification Test (AUDIT) scores, (b) 30 environmental factors, and (c) their interactions (i.e. GxE effects). The GPS accounted for up to 1.9% of the variance in alcohol use (i.e. AUDIT-C score), while the 30 measures of environmental factors together accounted for 21.1%. The 30 GPS-environment interactions did not explain any additional variance and none of the interaction terms exceeded the significance threshold corrected for multiple testing. Our findings suggest that GPS and environmental factors have primarily direct, additive effects rather than interacting systematically.

Statement of Relevance

We consider our research to be of interest and significance to the wider public in addition to the academic community. A wide range of social, economic and health outcomes are attributed to alcohol use in emerging adulthood; however, its risk factors are not well known. Twin studies suggest that genetics account for about 40% of the difference in alcohol use between people. Identifying the environments that moderate the influence of individuals' genetic predispositions on their alcohol use is key for developing and implementing effective interventions. In the current study, we show that individual-level genetic data and a wide range of environmental factors predict alcohol use in emerging adulthood. However, we did not find any evidence for the moderation of the individual's genetic propensity for alcohol use by any of the environmental factors, suggesting that genes and the environment have additive effects rather than interacting systematically.

INTRODUCTION

Alcohol use in emerging adulthood, including early initiation, frequent consumption, and drunkenness, is associated with adverse psychological and physical health outcomes (Richardson & Budd, 2003; Sipila, Rose, & Kaprio, 2016). However, few environmental risk factors that reliably predict alcohol use in emerging adulthood have been identified (Stephenson et al., 2020). Alcohol consumption is a complex behavioural trait influenced by many genetic variants called single-nucleotide polymorphisms (SNPs) that each have a very small effect size (Liu et al., 2019; Schumann et al., 2016) and can be identified in large genome-wide association (GWA) studies. The identified SNPs can then be aggregated into genome-wide polygenic scores (GPS) that capture a person's genetic propensity for alcohol consumption.

Over the past few years, a number of GWA studies for alcohol consumption have been published with sample sizes ranging from ~67,000 to nearly one million individuals with a vast range of target phenotypes, including the number of alcoholic drinks/units consumed per week (Clarke et al., 2017; Liu et al., 2019), alcohol intake in grams per day (Schumann et al., 2016), maximum habitual alcohol intake (Gelernter et al., 2019), and alcohol use and dependence (i.e. Alcohol Use Disorder Identification Test (AUDIT) scores (Kranzler et al., 2019; Sanchez-Roige et al., 2019)). GPS based on these GWA studies predict alcohol use, with the variance accounted for ranging from 0.1% to 2.5% (Barr, Kuo et al. 2019; Liu, Jiang et al. 2019; Mies, Verweij et al. 2018; Schumann, Liu et al. 2016). In general, the predictive power of a GPS depends on the GWA sample size, SNP heritability of the trait, selection thresholds for selecting markers for creating the score, etc., among many other factors (Dudbridge, 2013).

GPS provide the current best platform to directly and robustly test if a genetic predisposition for alcohol use develops differently across environmental contexts, a phenomenon known as

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gene-environment interactions (GxE) (Pasman, Verweij, & Vink, 2019). Four previous

studies tested GxE effects using GPS in the prediction of alcohol use, with mixed results.

Two studies found no evidence for GxE: Using a GPS based on a GWA study of 67,000

individuals and their daily alcohol intake Schumann et al. (2016), found no interactions

between the GPS and stress and life satisfaction in the prediction of alcohol use and alcohol-

related problems in a sample of 6,705 Dutch adults (Mies et al., 2018). Similarly, a study

detected no interaction between peer drinking and a GPS based on a GWA study of alcohol

consumption in 112k UK Biobank participants (Clarke et al., 2017) on alcohol use in a

sample of 755 university students (Smith et al., 2019). However, two later studies reported

significant GxE effects: Using a GPS* based on the publicly available summary statistics

from a GWAstudy of 535,000 individuals for the number of alcoholic drinks consumed per

week (Liu et al., 2019), being in a romantic partnership was found to reduce the association

between the genetic propensity for alcohol use and drinking frequency, intoxication

frequency and alcohol dependence in 1201 young Finns (Barr et al., 2019). Also, the

influence of a GPS based on the GWA study mentioned above (Clarke et al., 2017) on

alcohol use per week was shown to be moderated by socioeconomic status (SES) in 6,567

Dutch adults (Pasman et al., 2020). Alas, this finding could not be replicated with a GPS

based on the GWA study by (Liu et al., 2019). Other studies that used 'simpler' GPS, which

included fewer SNPs identified in smaller GWA study samples, suggested that genetic

influences on alcohol use varied as a function of peer relations and parental knowledge (Li et

al., 2017; Salvatore et al., 2014). Overall, the current evidence for GxE in the prediction of

alcohol use is inconclusive because studies employed different GWA studies to build GPS,

including some with small sample sizes that afford low statistical power, and tested different

environmental moderators, rendering direct comparisons of findings across studies

impossible.

Here, we overcome previous studies' limitations. For one, we used two large-scale, well-powered GWA studies to build GPS for alcohol use, including (1) a GWA study with an overall sample of 941,280 individuals that used the number of drinks consumed per week as target phenotype (Liu et al., 2019), and (2) the largest GWA study for AUDIT scores in 141,932 individuals from the UK Biobank and 23&Me (Sanchez-Roige et al., 2019). For the other, we considered a broad spectrum of environments that are likely to influence the association between the genetic propensity for and actual alcohol consumption, rather than exploring only one or two environmental moderators. To this end, we analysed data from a large British cohort study, whose participants reported alcohol related behaviours at age 22 and were assessed on 30 environmental measures, broadly categorised under four domains - home environment, adversity, lifestyles, and social and emotional learning competencies (SELC). SELC summarize traits of recognizing and managing emotions, setting and achieving positive goals, appreciating the perspectives of others, establishing and maintaining positive relationships, making responsible decisions, and handling interpersonal situations constructively (Elias et al., 1997). Our preregistered hypotheses included finding positive associations between the GPS and alcohol use, but we made no predictions about main effects of specific environments or the effect sizes associated with their GxE interactions due to the exploratory nature of our study.

METHODS

Sample

Participants were drawn from the Twins Early Development Study (TEDS) (Rimfeld et al., 2019). TEDS recruited over 15,000 twin pairs born between 1994-1996 in England and Wales, who have been assessed in multiple waves across their development up until the present date. TEDS participants and their families are representative of families in the UK (Haworth, Davis, & Plomin, 2013). Written informed consent was obtained from parents prior to data collection. Project approval was granted by King's College London's ethics committee for the Institute of Psychiatry, Psychology and Neuroscience (05.Q0706/228). Genotypes were processed using stringent quality control procedures followed by SNP imputation using the Haplotype Reference Consortium (release 1.1) reference panels. Following imputation, we excluded variants with minor allele frequency <0.5%, Hardy-Weinberg equilibrium p-values of $<1 \times 10^{-5}$. Full description of quality control and imputation procedures are provided in the **Supplementary Methods**. For this study we included unrelated participants, for who genotype data were available at age 22 and who reported AUDIT-C scores (N = 3,390). We excluded 104 participants (3%), who reported never having had a drink containing alcohol, and 133 individuals (4%), who responded inconsistently to the AUDIT-C items. Our analysis sample consisted of a maximum of 3,153 individuals.

Measures

Alcohol use. TEDS participants completed the 10 item AUDIT scale developed by the World Health Organization (WHO) to identify hazardous and harmful alcohol use (Saunders 1993) using paper, app- or web-based questionnaires at age 22. The first three items provide information pertaining to alcohol consumption and are often combined to create an alcohol

subdomain score termed AUDIT-C. These items measure the frequency and quantity of typical alcohol drinking and the frequency of binge drinking. For the current analysis, the AUDIT-C score was created by aggregating the scores across all three items (see **Supplementary Methods** for details).

Environmental factors. Information on the environment measures was collected using paper, app- or web-based questionnaires administered to TEDS participants and their parents from birth through to age 22. In total, we included 30 quantitative, ordinal and categorical measurements of environmental factors that represented four main domains: home environment, adversity, lifestyles, and social and emotional learning competencies (SELC) **(Figure 1, Supplementary Table S1, Supplementary Methods**). Home environment included (i) relationship with twin, (ii) CHAOS (confusion, hubbub and order scale), (iii) relationship status, (iv) whether on benefits, (v) education status, and (vi) parenthood. Adversity included (i) peer victimisation, (ii) life events, (iii) negative childhood experiences, and (iv) online bullying. Lifestyles included (i) conflict with the law, (ii) life satisfaction, (iii) healthy diet, (iv) BMI, (v) physical activity, (vi) involvement in sports, (vii) sleep quality, and (viii) online media use. SELC included social-emotional traits and behaviours, ranging from (i) self-control, (ii) risk-taking behaviour, (iii) aggressive behaviour, (iv) purpose in life, (v) volunteering, (vi) mood, (vii) peer pressure, (viii) ambition, (ix) general anxiety, (x) hassles to (xi) antisocial behaviour. For a detailed description of these measures see **Supplementary Methods.** We used continuous measures of environments wherever possible to optimise the statistical power of our models.
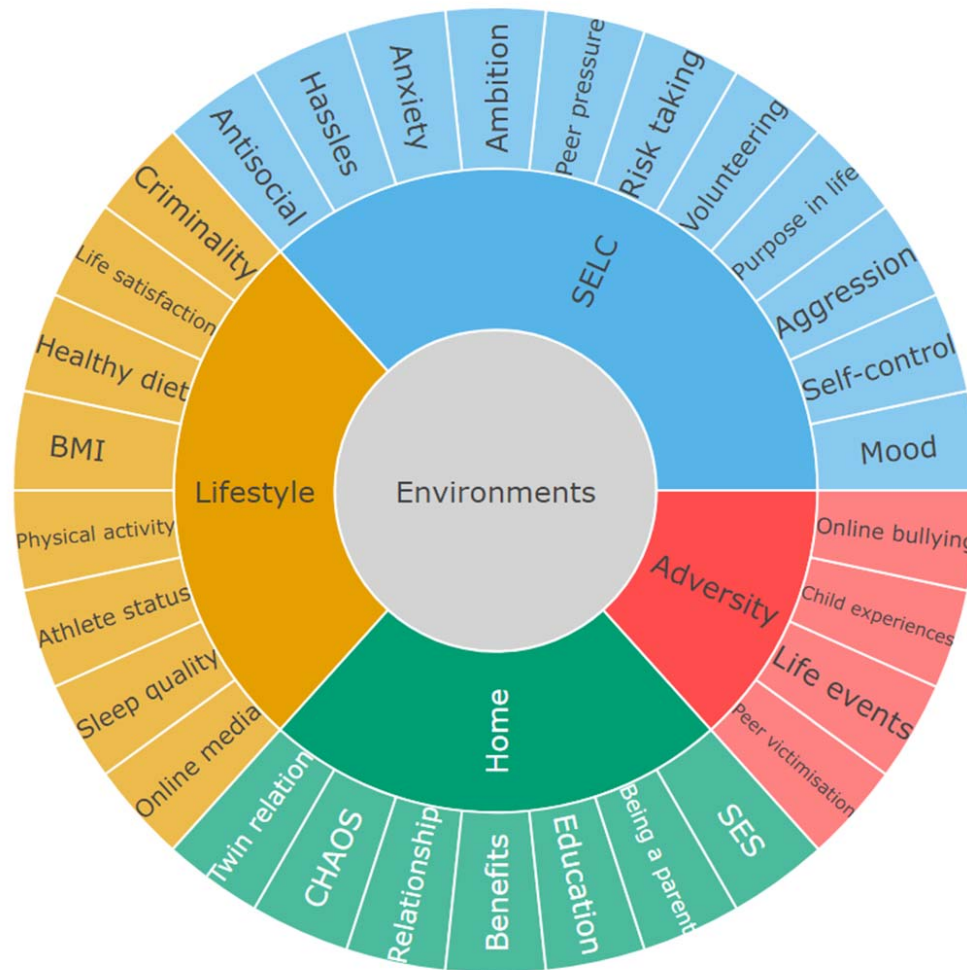
Figure 1: Summary of environment measures used in the study. *SELC, social and emotional learning competencies; SES, socioeconomic status; CHAOS, Confusion, Hubbub and Order Scale; BMI, body mass index.*

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Genome-wide polygenic scores (GPS).

The predictive power of a GPS depends on GWA study sample sizes, SNP heritability, and selection thresholds for selecting the markers for creating the score (Dudbridge 2013). For this reason we computed two GPS using PRSice-2 (Choi & O'Reilly, 2019) and publicly available summary statistics* from (i) the largest GWA study (GWAS and Sequencing Consortium of Alcohol and Nicotine use, GSCAN) on "average number of alcoholic drinks consumed per week" that sampled ~1 million individuals (after excluding 23andMe N=537,349) (Liu et al., 2019), and (ii) the GWA study of AUDIT-C score (the same phenotype used in the current study) including UK Biobank research participants of European ancestry (after excluding 23andMe $N = 121,604$) (Sanchez-Roige et al., 2019). The GPS were generated as the sum of alleles associated with the phenotypic trait and weighted by their effect sizes reported in the discovery GWA studies. We performed clumping with $r^2 = 0.25$ cut-off within a 250-kb window to remove SNPs in linkage disequilibrium and created eight scores for each discovery GWA study based on differing thresholds of discovery GWA study p-values (5e-08, 0.0001, 0.001, 0.01, 0.05, 0.1, 0.5, 1).

Statistical analyses

First, we compared the predictive validity of each of the GPS created using the two GWA studies and differing p-value thresholds described in the section above for phenotypic alcohol use (AUDIT-C score) in our sample using individual linear regression models, controlling for gender, age, the first ten principal components (PCs) (i.e., population stratification), and genotyping array. We then determined the GPS that explained the largest amount of variance in the target phenotype (based on Model R^2, $p<0.05/16$ tests $= 0.003$) and used that in all further analyses. Second, we tested the direct effects of each of the 30 environments on alcohol use in individual linear regressions models. The p-value was Bonferroni-corrected for identifying significant predictors (conventional p=0.05/30 models $= 0.002$). We then

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performed a multiple linear regression including all 30 environments to predict alcohol use.

Third, we individually tested moderation effects of each of the environments on the

association between GPS and alcohol use (i.e. 30 models) by adding interaction terms to the

regression models including the GPS and each environment, controlling again for gender,

age, the first ten PCs, and genotyping array as covariates, as well as for all GPS x covariate

and E x covariate interaction terms (Keller, 2014). Finally, we fitted a multiple regression

model that included all interaction terms for the 30 environments and the GPS to assess their

combined predictive power for alcohol use, controlling again for gender, age, the first ten

PCs, and genotyping array as covariates, as well as for all GPS x covariate and E x covariate

interaction terms. Predictor variables were scaled to mean 0 and unit variance prior to the

analyses. All statistical analyses were conducted using R statistical software (R Core Team,

2019). All our analyses were preregistered at osf.io/ugk3n.

RESULTS

Predicting alcohol use from GPS

Among the GPS generated using the GWA study for the number of drinks consumed per week (Liu et al., 2019) and for AUDIT-C scores (Sanchez-Roige et al., 2019) using eight selection p-value thresholds, 14 out of 16 exceeded the multiple testing significance threshold of $p<0.003$ in the prediction of phenotypic alcohol use in our sample (**Supplementary Figure S1, Supplementary Table S2**). In general, the GPS based on both the GWA studies explained more variance in the phenotypic alcohol use as the selection p-value became less stringent. Specifically, GPS based on GSCAN study for the number of drinks consumed per week accounted for a maximum of 1.9% at the selection threshold of $p<0.1$, while GPS based on the GWA study for AUDIT-C scores accounted for only 0.9% of the variance at best (**Supplementary Figure S1, Supplementary Table S2**). We therefore carried forward the best predictive $GPS_{p<0.1}$ based on GSCAN study for the number of drinks consumed per week (Liu et al., 2019) for all further analyses.

Predicting alcohol use from environmental factors

Correlations between AUDIT-C and GSCAN GPS and the environmental factors ($p<0.01$) are displayed in **Supplementary Figure S2**. When testing the individual, direct effects of the 30 environments on alcohol use, 14 exceeded the Bonferroni-corrected significance threshold (*Bonf $p<0.002$*, **Supplementary Table S3A-D, Figure 2A**). From the domain of home environments (7 measures), being a parent, being on benefits and SES were associated with alcohol use, such that higher SES individuals consumed more alcohol and individuals with children or on benefits consumed less alcohol (**Supplementary Table S3A**). In the adversity domain (4 measures), only peer victimization was significantly associated with alcohol use, with individuals who experienced more victimization by peers consuming more alcohol

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(**Supplementary Table S3B**). From the lifestyles (8 measures), life satisfaction, physical

activity, involvement in sports at a competitive level (i.e. athlete status) and online media use

were associated with higher alcohol use (**Supplementary Table S3C**). Among the 11 factors

in the SELC domain, lower self-control and higher risk taking, aggression, peer pressure,

ambition and antisocial behaviour were significantly associated with greater alcohol use

(**Supplementary Table S3D**). The amount of variance explained by each of these

environments ranged from 0.4% for ambition to 11.5% for risk-taking behavior

(**Supplementary Table S3A-D**).

Jointly, the 30 environments accounted for 21.1% of the variance in alcohol use. The

environments that remained significant predictors in the multiple regression model included

being a parent (home environment domain), online media use (lifestyles domain), and peer

pressure, risk-taking and antisocial behaviour (SELC domain) (**Supplementary Table S4**).

Akin to the univariate regression results, risk-taking emerged as the strongest predictor of

alcohol use, independently accounting for 6% of the variance after adjusting for all other

environmental effects. The GPS and all the 30 environments together accounted for 22.2% of

the variance in alcohol use (**Supplementary Table S5**).

Testing GxE in alcohol use

When testing the individual interaction effects of the GPS and the 30 environment factors on

alcohol use, none exceeded the Bonferroni-corrected significance threshold (*Bonf p*<0.002;

(**Supplementary Table S3A-D, Figure 2B**). A multiple regression model with all the

interaction terms between the GPS and each of the 30 environments together with the main

effects of the GPS and the environments accounted for a total of 22.5% of the variance in

alcohol use (**Supplementary Table S6**). However, the GxE interaction terms did not explain

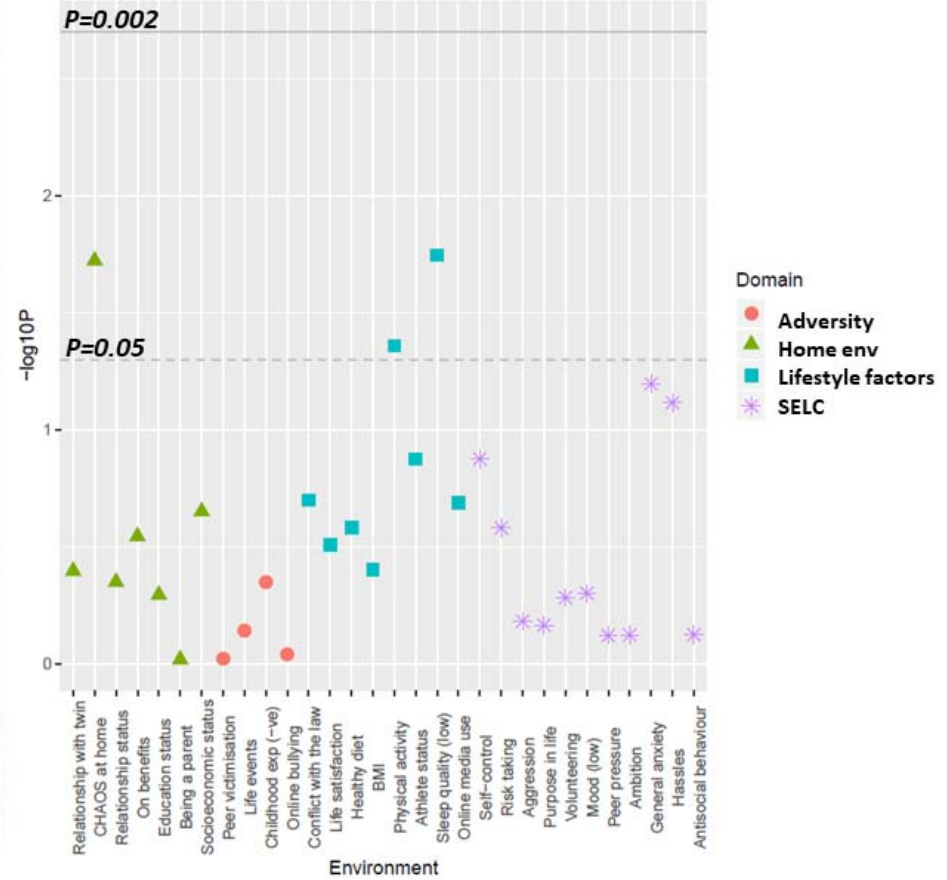any additional variance in alcohol use beyond the confounding effects of G x covariates and

E x covariates. None of the G x E interaction terms reached statistical significance after

multiple testing correction (**Supplementary Table S6**).

A

B
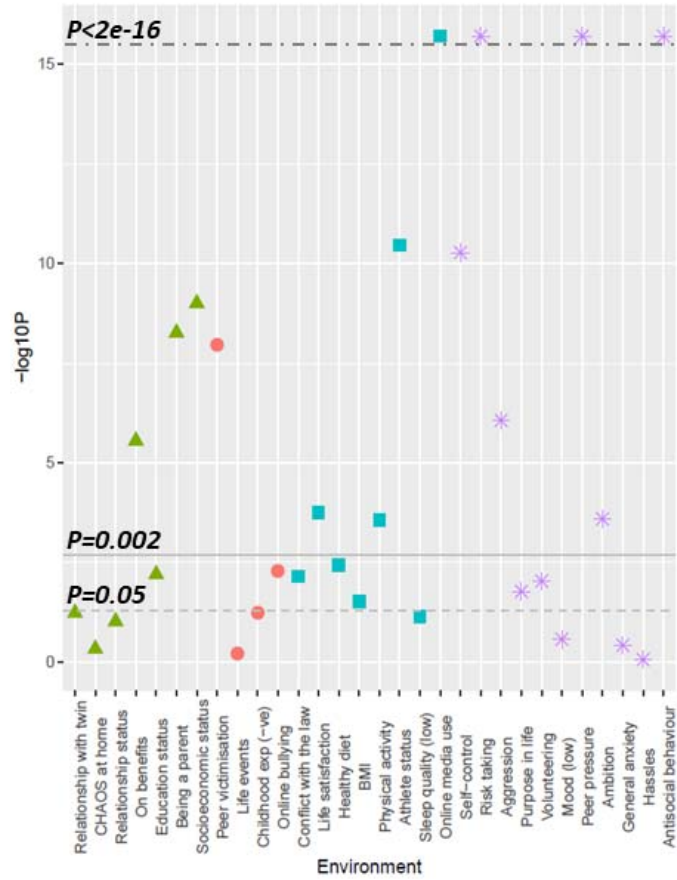
Figure 2. *p*-values for the associations between AUDIT-C scores and environments (Panel A) and GxE interaction terms (Panel B) from the univariate regression models. *Note. Panel A: The p-values are based on the 30 individual regression models for each environment and its association with AUDIT-C scores, controlling for age, gender, PCs, and genotyping array. Panel B: The p-values are based on the 30 individual regression models including the GPS, the environment, and their GxE interaction term, controlling for age, gender, PCs, genotyping array, G x covariates and E x covariates terms. In panels A and B, the grey dotted line refers to p<0.05, while solid grey line refers to the Bonferroni-corrected p<0.002, and dark grey dotted line refers to p<2e-16, which is the lowest p value that R reports. SELC, Social and emotional learning competencies.*

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DISCUSSION

Our study is the first to offer a comprehensive analysis of the influence of 30 factors that broadly map young adults' environments on the genetic contribution to alcohol use in emerging adulthood. We found that a GPS based on the GSCAN study for alcohol consumption (Liu et al., 2019) predicted alcohol use in our sample of young adults, but there was no evidence for moderation of this genetic effect by any of the environmental factors. The discrepancies between our current and previous findings (e.g. Barr, Kuo et al. 2019, Pasman, Verweij et al. 2020) are likely to be due to the vast methodological differences between studies. In particular, previous studies in this area based their GPS on different GWA studies, assessed different phenotypes, and tested populations of different ages (Barr et al., 2019; Mies et al., 2018; Pasman et al., 2020; Smith et al., 2019).

Our findings contribute to a growing body of literature that struggles to identify GxE effects (Allegrini et al., 2020; Duncan & Keller, 2011; Dunn et al., 2011; Saltz et al., 2018), because of three key challenges. First, studies that examine only one or two environmental moderators are likely to identify false positives, because of residual confounding that is unaccounted for (Keller, 2014). We partly overcome this challenge in the current research by comprehensively assessing the environment and testing 30 environmental moderators simultaneously. Second, testing GxE effects requires extremely large samples that afford sufficient statistical power to detect associations of very small effect size, which are likely to be true for GxE terms (Allegrini et al., 2020; Keller, 2014). In the current study, we analyzed data from more than 3,000 individuals, which compares well with other GxE studies on alcohol use but is small relative to the populations that are typically assessed in GWA studies (Mills & Rahal, 2019). Post-hoc power calculations using G*Power (Faul, Erdfelder et al. 2009) suggested that our study had more than 80% power to detect two-way interactions with an effect size of f^2=0.005 (Pasman et al., 2020) but had less than 37% power to detect GxE when all the

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interaction terms are entered simultaneously with their direct effects. Because interaction models require much more power compared to tests of main effects, the modest predictive validity of the GPS for alcohol use in young adulthood suggests that the sample size required to detect GxE may be far greater than those currently available (Duncan & Keller, 2011). Third, a principal caveat in GxE studies is the discrepancy in the assessment of genes and environment. GPS capture inherited DNA differences that are systematically coded in base pairs of single-nucleotide polymorphisms (SNPs) and remain unchanged from conception throughout life (Plomin & von Stumm, 2018). By comparison, measures of the environment capture broad, stochastic events that continuously change across time and contexts. Identifying interactions between two domains that are so asymmetrically assessed in research is inherently complicated, if not impossible.

Our results suggest that alcohol use in emerging adulthood is best predicted by a plethora of factors, including genetics with our GPS accounting for up to 1.9% of the variance in the AUDIT-C scores. Greater effect sizes were observed when modelling the environmental variables jointly: Together they accounted for ~21% of the variance in alcohol use, with peer pressure, parenthood, online media use, risk-taking and antisocial behaviour emerging as significant predictors. Risk-taking appeared as a particularly strong predictor, accounting independently for 6% of the variance in alcohol use. Risk-taking and alcohol use are genetically correlated (Strawbridge et al., 2018), suggesting a common genetic origin. Future research will have to disentangle if both traits are causally related across development.

Limitations

Our study has several limitations. First, the discovery GWA study for creating the GPS and the target sample were both composed mainly of European ancestry making the GxE findings from this study less generalizable to other ancestry populations. Second, TEDS like all

longitudinal studies has suffered from attrition, although it still remains fairly representative of the population in England and Wales in terms of ethnicity and family SES (Rimfeld et al., 2019). Third, we included 30 factors that map young adults' environments in our analyses; yet, it is possible other environments that we did not assess play an important role in moderating the genetic contributions to alcohol use. Fourth, we Bonferroni-corrected our *p*-values for multiple testing, which might be an overly conservative and stringent approach, which avoids detecting false positives but limits observing effects of small sizes. Finally, we did not explore sex-specific moderation by the environments on the genetic contributions to alcohol use behaviour due to lack of power to detect three-way interactions.

Conclusion

We undertook here for the first time a hypothesis-free approach for identifying GxE interactions by investigating many factors that broadly map young adults' environment, instead of using one or two as moderators of the genetic predisposition to alcohol use. We confirmed findings from previous studies that GPS predict alcohol use in young adults, with small effect sizes, and we found that not having a child, risk-taking, antisocial behaviour, peer pressure, and use of online media increased the risk of alcohol use in emerging adulthood. However, we did not find support for GxE effects on alcohol use. Future studies with larger sample sizes and more powerful polygenic scores, based on bigger GWA studies, that comprehensively assessed the environment are key to unravelling the complex interplay between the genes and environment in predicting alcohol use. At present, the empirical evidence suggests that the effects of genetics and environments on alcohol use are primarily additive rather than due to interactive effects.

Footnote

*The publicly available summary statistics of GWA studies often exclude 23andMe data, and thus the discovery sample size is smaller than the original study.

Author Contributions:

R. Kandaswamy and S. von Stumm developed the study concept. R. Kandaswamy performed the data analysis under the supervision of S. von Stumm and R. Plomin. All authors were involved in the interpretation of the data. R. Kandaswamy drafted the manuscript and all authors provided critical revisions. All authors approved the final version of the manuscript for submission.

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