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Polygenic risk for alcohol consumption and its association with alcohol-related phenotypes: Do stress and life satisfaction moderate these relationships?

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ABSTRACT

Background: Genetic and environmental factors contribute about equally to alcohol-related phenotypes in adulthood. In the present study, we examined whether more stress at home or low satisfaction with life might be associated with heavier drinking or more alcohol-related problems in individuals with a high genetic susceptibility to alcohol use.

Methods: Information on polygenic scores and drinking behavior was available in 6705 adults (65% female; 18–83 years) registered with the Netherlands Twin Register. Polygenic risk scores (PRSs) were constructed for all subjects based on the summary statistics of a large genome-wide association meta-analysis on alcohol consumption (grams per day). Outcome measures were quantity of alcohol consumption and alcohol-related problems assessed with the Alcohol Use Disorders Identification Test (AUDIT). Stress at home and life satisfaction were moderating variables whose significance was tested by Generalized Estimating Equation analyses taking familial relatedness, age and sex into account.

Results: PRSs for alcohol were significantly associated with quantity of alcohol consumption and alcohol-related problems in the past year (R^2 = 0.11% and 0.10% respectively). Participants who reported to have experienced more stress in the past year and lower life satisfaction, scored higher on alcohol-related problems (R^2 = 0.27% and 0.29 respectively), but not on alcohol consumption. Stress and life satisfaction did not moderate the association between PRSs and the alcohol outcome measures.

Conclusions: There were significant main effects of polygenic scores and of stress and life satisfaction on drinking behavior, but there was no support for PRS-by-stress or PRS-by-life satisfaction interactions on alcohol consumption and alcohol-related problems.

1. Introduction

Heavy drinking, hazardous and harmful drinking, and alcohol dependence are moderately to highly heritable in the Dutch population (Derks et al., 2014; Distel et al., 2012; Mbarek et al., 2015; van Beek et al., 2012). In addition to genetic factors, unique environmental factors contribute to drinking behavior in adults.

The identification of genetic risk variants involved in alcohol-related phenotypes is complex. Until recently, gene finding efforts have mainly focused on candidate genes. Strongest associations with *alcohol use disorder* have been found for the alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) genes (Macgregor et al., 2009; van Beek et al., 2010), because of their role in alcohol metabolism. Recent genome-wide association (GWA) studies for alcohol use disorder have largely confirmed these associations (see for a review Tawa et al., 2016). GWA studies for quantity of alcohol consumption, however, have only identified a handful of genes so far (Chen et al., 2012; Schumann et al., 2011; Takeuchi et al., 2011). The largest GWA meta-analyses to date (Jorgenson et al., 2017, N = 86,627, Schumann et al., 2016; N = 105,00, Clarke et al., 2017; N = 112,117), have described

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associations between quantity of alcohol use and previously reported alcohol metabolizing genes, as well as novel genes including KLB, GCKR and CADM2.

Besides genetic factors, other factors play a role in alcohol-related phenotypes. For example, disadvantageous life circumstances, including early life stress and stressful life events (e.g., death of a loved one, divorce) (Ayer et al., 2011; Boden et al., 2014; Bolton et al., 2009; Holgate and Bartlett, 2015). The relation between stress and alcohol use or heavy drinking is complex and not yet fully understood. Alcohol is often consumed for relief from stressful situations, i.e., drinking to cope (Anthenelli, 2012; Spanagel et al., 2014). Stress is known to influence the amount of alcohol one consumes, how much one craves alcohol, and to trigger relapse in abstinent individuals (Holgate and Bartlett, 2015; Sinha, 2012; Spanagel et al., 2014). In turn, alcohol consumption causes a stress response in the brain (Anthenelli, 2012), which is thought to affect the transcriptional regulation of genes involved in the promotion of addiction (Lu and Richardson, 2014). This implies that stress, whether alcohol-induced or not, might increase the risk for alcohol-related problems.

Similar to stress, poor life satisfaction has been associated with alcohol use and heavy drinking (Fischer et al., 2015; Murphy et al., 2005; Paul et al., 2011; Peltzer and Pengpid, 2016). Fischer et al. (2015), for example, found that poor quality of life – reflecting low life satisfaction and happiness – was associated with earlier onset of drinking in adolescence and alcohol use disorder in young adulthood.

High levels of stress or low life satisfaction are not always associated with heavy drinking. Possibly, only in individuals who have a high genetic susceptibility to heavy drinking or alcohol dependence, high stress levels or low life satisfaction might result in this genetic susceptibility being expressed (i.e., gene-stress interaction). To date, most gene-environment interaction studies on alcohol use – including twin and adoption studies, and molecular studies with candidate genes – have focused on *adolescent* alcohol use. These studies have rather consistently found that higher peer deviance and lower parental monitoring, i.e., less restrictive environments with easier access to alcohol, increased genetic influences on alcohol use (Cooke et al., 2015; Dick and Kendler, 2012; Young-Wolff et al., 2011). Although candidate gene (and to a lesser extent adoption) studies have also shown gene-by-stress interactions on alcohol use in youth and young adults (for reviews see Dick and Kendler, 2012; Young-Wolff et al., 2011), the picture appears to be less clear for stress than for peer deviance and parental monitoring (see also Cooke et al., 2015). One of the reasons these candidate gene studies do not show consistent results, is that they focused on variants in single genes. Lack of power to detect interactions, low probability that the environmental variable of interest interacts with the specific candidate gene, false positives, and publication bias are the most important pitfalls of gene-environment interaction studies focusing on single genes (Duncan and Keller, 2011; Keller, 2014).

Many genetic variants – each with a very small effect size – are thought to contribute to complex behavioral traits, including alcohol (ab)use (e.g., Salvatore et al., 2014). So in contrast to a candidate gene approach, a more powerful approach to assess genetic risk for complex behavioral traits might be to aggregate the effects of many (or all) individual risk alleles into a single polygenic risk score (PRS). Such a polygenic approach has been successfully used to predict alcohol use (Taylor et al., 2016). In this study the PRS was based on 89 SNPs that were associated with alcohol use in the literature, and explained 0.3–0.7% of the variance in alcohol consumption in the target sample.

Interaction studies using PRSs are likely to lead to more accurate results than those based on single genes due to the better predictive power of polygenic scores (e.g., Dick and Kendler, 2012). To date, only two studies have examined gene-environment interactions in alcohol use using a polygenic approach. Salvatore et al. (2014) found that polygenic risk for alcohol problems, derived from genome-wide results, was more pronounced under conditions of high peer deviance or low parental knowledge in adolescents, and Li et al. (2017) found that substance use of close friends was not associated with increased expression of polygenic risk for heavy episodic drinking – also derived from genome-wide results – in adolescents. No studies yet have examined the interaction between stress or life satisfaction and polygenic risk for alcohol use measures.

In the present study we therefore examined in adults whether stress at home and satisfaction with life in the past year moderated the association between polygenic risk for quantity of alcohol consumption and 1) quantity of alcohol consumption (average weekly alcohol use) in the past year, and 2) alcohol-related problems (i.e., hazardous drinking, harmful drinking or alcohol dependence) in the past year. We expected to find positive associations between a PRS for quantity of alcohol consumption and both quantity of alcohol consumption and alcohol-related problems in the past year, and that these associations would be stronger with higher levels of stress experienced in the past year, and with lower life satisfaction.

2. Methods

2.1. Participants

The sample comprised participants registered at the Netherlands Twin Register (NTR; Willemsen et al., 2013), an ongoing longitudinal study of twins and their family members. Approval for this study was obtained from the local medical ethics committee. NTR participants were included for whom genotype data were available and who completed questions on alcohol use, stress and satisfaction with life between 2009 and 2014. We used data from the 10th survey of the NTR (sent out in 2013–2014), complemented with data from a previous survey (8th survey, 2009–2012) when data were missing on the 10th survey.

Genotype and alcohol use data for at least one of the two outcome measures – glasses of alcohol per week, Alcohol Use Disorders Identification Test (AUDIT) score – and at least one of the two moderating variables (stress at home, life satisfaction score) were available from 6705 participants (65% female) aged between 18 and 83 years (M = 43 years, SD = 16) from 3180 families. For quantity of alcohol consumption, data were available from 6475 participants, and for alcohol-related problems measured with the AUDIT, data were available from 6086 participants. From 5856 participants information was available for both outcome measures.

2.2. Alcohol use variables

Because the PRSs were based on alcohol consumption (grams of alcohol per day), the primary outcome measure was self-reported average number of glasses of alcohol consumed per week in the past year. The sum of reported number of glasses of beer, wine and liquor per week was used for this measure. Individuals with an estimated number of alcoholic drinks > 140 per week were excluded from analysis (n = 3). In addition, those with a high number of drinks (i.e., number of alcoholic drinks > 70), but an AUDIT score < 8 (suggesting no alcohol-related problems) (n = 55), and those who reported other strong inconsistencies between different alcohol variables (n = 12) were also excluded. Missing consumption scores were imputed (set to zero) if someone reported life-time exposure to alcohol, but no alcohol consumption in the past year or only once a month or less. Never-drinkers (n = 194) were not included in the analyses due to lack of exposure. There was a significant correlation (test-retest reliability) between consumption scores in the two surveys ($r = 0.73$, $p < 0.001$, n = 2794).

Alcohol-related problems in the past year were identified by the AUDIT (Saunders et al., 1993). The AUDIT targets three domains: hazardous alcohol use (quantity and frequency of drinking), dependence symptoms (impaired control over drinking, increased salience of drinking, morning drinking), and harmful alcohol use (guilt after drinking, blackouts, alcohol-related injuries, others concerned about

their drinking). Eight items were rated on a 5-point scale ranging from 'never' to 'daily or almost daily', and two items on a 3-point scale ('no, "yes, but not in the last year", 'yes, during the last year'). We used the total score of the 10 items as a measure of alcohol-related problems. Internal consistency was 0.79 and test-retest reliability was 0.68 ($p < 0.001$, $n = 1809$).

2.3. Stress and life satisfaction variables

In both the 8th and 10th survey of the NTR, participants were asked to rate on a 4-point scale how often they experienced stress at home in the past year ('never', 'once in a while', 'regularly', 'constantly'). There was a significant correlation (test-retest reliability) between the two surveys ($r = 0.42$, $p < 0.001$, $n = 3393$).

Life satisfaction was defined as the sum score of the five items of the Satisfaction with Life Scale (SWLS) (Diener et al., 1985). Items such as 'the conditions of my life are excellent', and 'so far I have gotten the important things I want in life' were answered on a 7-point scale ranging from strongly disagree to strongly agree. The SWLS covered the complete range of scores from 5 to 35 in our sample (slightly negatively skewed). Internal consistency was high ($\alpha = 0.88$, $n = 6379$), and test-retest reliability between the two surveys was relatively high too ($r = 0.61$, $p < 0.001$, $n = 3402$).

2.4. Genotyping

Genotyping was performed on several SNP arrays (see Fedko et al., 2015). The genotype data were then cross-platform imputed against a Dutch reference dataset (GONL) to infer missing SNPs per platform (Boomsma et al., 2014; Francioli et al., 2014). Before imputation, standard quality control checks were performed (see Treur et al., 2017 for description). After imputation, SNPs that were significantly associated with genotyping platform ($p < 10^{-5}$), that had an allele frequency difference of > 10% with the Dutch reference dataset, HWE $p < 10^{-4}$, MAF < 0.01, Mendelian error rate > 5 SD from mean over all markers, or an imputation quality $R^2 < 0.90$ were omitted. We then performed a Principal Components Analysis (PCA) following procedures described in Abdellaoui et al. (2013). Information from the PCA was used to exclude individuals with non-Dutch ancestry and control for Dutch population stratification.

2.5. Data analyses

The summary statistics for alcohol consumption, excluding NTR participants, of a large meta-analysis of GWA studies on alcohol use (Schumann et al., 2016) were used to generate PRSs for alcohol consumption (grams per day) in our independent target sample of the NTR by LDpred (Vilhjálmsson et al., 2015). PRSs were based on approximately 67,000 participants in the discovery sample (N = 1,093,667 SNPs). LDpred computes SNP weights based on their effect size estimates, their LD with other SNPs, and the degree of polygenicity of the trait, quantified as the expected fraction of causal SNPs. PRSs were calculated for nine fractions of the genome (0.01%, 0.03%, 0.1%, 0.3%, 1%, 3%, 10%, 30% and 100%), please see Vilhjálmsson et al. (2015). These PRSs were transformed into z-scores before analysis. The PRSs significantly correlated with each other (*r*s between 0.063 and 1.00, all *p*s < 0.001). The PRS fraction that was the best predictor of alcohol use in our sample, was used for all subsequent analyses.

First, the associations of the PRSs for alcohol consumption with alcohol consumption (glasses of alcohol per week) in our target sample were examined. Generalized Estimating Equation (GEE; normal distribution with identity link function and an exchangeable covariance matrix) analyses were conducted taking familial relatedness, age (at time of survey), and sex (0 = male, 1 = female) into account. In order to control for population stratification, 10 genetic principal components were also taken into account. The PRS for the fraction that showed the strongest association with glasses of alcohol consumed per week was used in all subsequent analyses.

Second, to examine stress as a potential moderator of the relationship between PRS and alcohol consumption, we repeated the analysis including stress as a continuous measure (zero-centered) and its interaction with PRS into the model. In addition, the two-way interactions between the covariates age and sex with stress and with PRS were included in the model to control for effects of these covariates on our interaction of interest (Keller, 2014). Life satisfaction was examined in the same way.

Third, the PRS was examined in relation to alcohol-related problems (AUDIT).

Fourth, stress and life satisfaction were examined as potential moderators of the relationship between PRS for alcohol consumption and AUDIT (in the same way as the analyses for alcohol per week).

All analyses were conducted in SPSS, and $\alpha = 0.05$ was used as the threshold for statistical significance.

3. Results

On average, participants included in the analyses reported to drink 6.45 (SD = 7.94, range 0–133) glasses of alcohol per week, scored 4.47 (SD = 3.61, range 0–34) on the AUDIT, scored 1.96 (SD = 0.69, range 1–4) on stress experienced at home, and 27.2 (SD = 5.2, range 5–35) on life satisfaction. The main outcome measures – quantity of alcohol consumption and AUDIT scores – were positively correlated with each other ($r = 0.62$, $p < 0.001$, $n = 5856$). Stress at home and life satisfaction were also correlated with each other ($r = -0.32$, $p < 0.001$, $n = 6420$). Stress did not differ between drinkers (M = 1.96, SD = 0.69, n = 6439) and never-drinkers who were excluded from analyses (M = 1.87, SD = 0.78, n = 173) ($t(6612) = 1.63$, $p = 0.11$, *Cohen's d* = 0.13), neither did satisfaction with life differ significantly between drinkers (M = 27.2, SD = 5.2, n = 6454) and never-drinkers (M = 26.3, SD = 5.9, n = 173) ($t(6627) = 1.98$, $p = 0.05$, *Cohen's d* = 0.16).

There was a significant association between PRS for quantity of alcohol consumption and quantity of alcohol consumption in the target sample, with the strongest association for the 100% and 10% fractions ($R^2 = 0.11\%$, $B = 0.243$, $p = 0.015$; Table 1). There was also an effect of sex and age on quantity of alcohol consumption: male sex ($B = 4.592$, $p < 0.001$) and older age ($B = 0.066$, $p < 0.001$) were associated with higher consumption (Table 2).

No main effects of stress and life satisfaction on quantity of alcohol consumption were found, neither did these variables moderate the relationship between PRS and alcohol consumption (all *p*s > 0.21; Table 2).

A positive association was observed between the PRS (100% fraction) for alcohol consumption and AUDIT scores ($R^2 = 0.10\%$, $B = 0.10$, $p = 0.032$; Table 3). Similar to what was found for quantity of alcohol consumption, male sex was associated with higher AUDIT

Table 1
Associations between all PRS fractions for alcohol consumption and quantity of alcohol consumption.

PRS fraction	B	95% CI	p-value	R^2 (%)
0.0001 (0.01%)	0.016	−0.171–0.202	0.870	0.00
0.0003 (0.03%)	0.000	−0.198–0.199	0.997	0.00
0.001 (0.1%)	**0.173**	**0.001–0.345**	**0.048**	**0.04**
0.003 (0.3%)	0.179	−0.028–0.386	0.091	0.05
0.01 (1%)	**0.225**	**0.024–0.427**	**0.028**	**0.09**
0.03 (3%)	**0.241**	**0.043–0.438**	**0.017**	**0.10**
0.1 (10%)	**0.243**	**0.047–0.440**	**0.015**	**0.11**
0.3 (30%)	**0.242**	**0.046–0.438**	**0.016**	**0.11**
1 (100%)	**0.243**	**0.047–0.439**	**0.015**	**0.11**

Note: statistically significant results ($\alpha = 0.05$) are presented in bold.

Table 2
Association between PRS for alcohol consumption (100% fraction), covariates of interest, and quantity of alcohol consumption with/without stress and satisfaction with life included.

predictor	B	95% CI	p-value	R^2 (%)
Model 1 (n = 6472)				
PRS	**0.243**	**0.047–0.439**	**0.015**	**0.11**
sex (male)	**4.592**	**4.142–5.043**	**< 0.001**	**7.70**
Age	**0.066**	**0.053–0.080**	**< 0.001**	**1.66**
Model 2A (stress at home included, n = 6437)				
PRS	**0.214**	**0.018–0.409**	**0.032**	**0.02**
sex (male)	**4.546**	**4.080–5.013**	**< 0.001**	**7.13**
age	**0.066**	**0.053–0.080**	**< 0.001**	**1.62**
stress	0.025	−0.242–0.293	0.852	0.03
stress × PRS	0.007	−0.275–0.289	0.963	0.00
stress × sex	−0.386	−1.058–0.286	0.260	0.02
stress × age	0.012	−0.007–0.032	0.213	0.06
PRS × sex	0.076	−0.373–0.525	0.741	0.01
PRS × age	0.000	−0.013–0.014	0.950	0.00
Model 2B (life satisfaction included, n = 6452)				
PRS	**0.212**	**0.018–0.406**	**0.032**	**0.03**
sex (male)	**4.575**	**4.124–5.027**	**< 0.001**	**7.63**
age	**0.066**	**0.053–0.080**	**< 0.001**	**1.67**
SWLS	0.023	−0.014–0.061	0.226	0.01
SWLS × PRS	−0.016	−0.054–0.022	0.406	0.00
SWLS × sex	−0.034	−0.124–0.057	0.465	0.01
SWLS × age	0.000	−0.003–0.003	0.996	0.00
PRS × sex	0.079	−0.377–0.536	0.734	0.01
PRS × age	0.000	−0.013–0.013	0.996	0.00

Note: statistically significant results (α = 0.05) are presented in bold; SWLS = Satisfaction With Life Scale.

Table 3
Association between PRS for alcohol consumption (100% fraction), covariates of interest, and AUDIT scores with/without stress and satisfaction with life included.

predictor	B	95% CI	p-value	R^2 (%)
Model 1 (n = 6085)				
PRS	**0.100**	**0.008–0.191**	**0.032**	**0.10**
sex (male)	**2.070**	**1.867–2.274**	**< 0.001**	**7.59**
age	**−0.011**	**−0.018 to −0.005**	**< 0.001**	**0.29**
Model 2A (stress at home included, n = 6050)				
PRS	0.050	−0.049 to 0.149	0.320	0.05
sex (male)	**2.210**	**1.991–2.428**	**< 0.001**	**8.26**
age	**−0.009**	**−0.015 to −0.002**	**0.009**	**0.15**
stress	**0.236**	**0.098–0.374**	**0.001**	**0.27**
stress × PRS	−0.036	−0.161 to 0.088	0.568	0.01
stress × sex	**0.353**	**0.047–0.659**	**0.024**	**0.10**
stress × age	0.006	−0.003 to 0.014	0.182	0.05
PRS × sex	0.119	−0.076 to 0.315	0.232	0.02
PRS × age	0.003	−0.003 to 0.008	0.374	0.01
Model 2B (life satisfaction included, n = 6066)				
PRS	0.054	−0.045 to 0.154	0.282	0.05
sex (male)	**2.075**	**1.872–2.278**	**< 0.001**	**7.63**
age	**−0.012**	**−0.018 to −0.006**	**< 0.001**	**0.32**
SWLS	**−0.032**	**−0.054 to −0.009**	**0.006**	**0.29**
SWLS × PRS	0.007	−0.010 to 0.024	0.392	0.02
SWLS × sex	**−0.057**	**−0.104 to −0.010**	**0.017**	**0.13**
SWLS × age	0.001	−0.001 to 0.002	0.462	0.01
PRS × sex	0.120	−0.070 to 0.310	0.216	0.02
PRS × age	0.003	−0.002 to 0.009	0.254	0.02

Note: statistically significant results (α = 0.05) are presented in bold; SWLS = Satisfaction With Life Scale.

scores ($B = 2.07, p < 0.001$). Older age, however, was associated with *lower* AUDIT scores ($B = -0.011, p < 0.001$).

When stress was included in the model, a positive association was found between stress and AUDIT scores ($B = 0.236$, $p = 0.001$; Table 3), suggesting that higher stress levels were associated with more alcohol-related problems. This was especially the case for males, reflected by an interaction between stress and sex ($B = 0.353$, $p = 0.024$). Against expectations, though, no interaction between stress and PRS on AUDIT scores was found ($B = -0.036$, $p = 0.568$). Similarly, there was a main effect of life satisfaction on AUDIT scores ($B = -0.032$, $p = 0.006$), but life satisfaction did not moderate the relationship between PRS and AUDIT ($B = 0.007$, $p = 0.392$). It did interact with sex: lower life satisfaction was more strongly associated with higher AUDIT scores in males than females ($B = -0.057$, $p = 0.017$). Note that the association between PRS and AUDIT scores no longer reached statistical significance when stress or life satisfaction, and all two-way interactions with sex and age, were included in the model (Table 3).

4. Discussion

In this study we examined whether stress and life satisfaction moderated the relationships of polygenic risk for alcohol consumption with quantity of alcohol consumption and alcohol-related problems. We found, as expected, a positive association between PRS for alcohol consumption and both quantity of alcohol consumption and alcohol-related problems in the last year, but stress and life satisfaction did not moderate these relationships. Participants – especially males – who reported to have experienced more stress in the past year or who reported lower life satisfaction, scored higher on alcohol-related problems, but not on alcohol consumption.

The variance explained by the PRSs was rather low (max 0.11%), but this is in line with previous studies. In a recent study of Clarke et al. (2017), the PRS for alcohol consumption (based on a much larger GWAS of 105,000 participants) explained 0.6% of the variance in an independent sample. PRSs for other alcohol-related phenotypes, such as age at onset of alcohol dependence and alcohol problems in adolescence, have shown effect sizes varying between 0.06 and 2.3%, but mostly between 0.3 and 0.7% (Kapoor et al., 2016; Li et al., 2017; Salvatore et al., 2014; Taylor et al., 2016). The heritability of alcohol consumption is not generally as high as the heritability of alcohol abuse/dependence (for example SNP heritability 13% for alcohol consumption (Clarke et al., 2017) versus 33% for alcohol dependence (Mbarek et al., 2015)), so PRS of alcohol consumption might be less predictive as those for alcohol dependence.

Other substance use phenotypes including smoking and cannabis use have shown slightly larger effect sizes, even across traits (e.g., PRS for age at smoking onset explained 1.5% of the variance in age at regular drinking) (Allegrini et al., under revision; Carey et al., 2016; Verweij et al., 2017; Vink et al., 2014). A possible reason for the relatively small effect size in our study could also be that self-reported quantity of alcohol consumption is less reliable than, for example, lifetime cannabis use or number of cigarettes smoked per day. Most people drink alcohol, but not everyone drinks alcohol on a regular basis, or weekly intake might largely vary and depend on situation, which may cause difficulties when one has to report the average number of glasses consumed per week in the past year. On the other hand, a continuous phenotype as used here is often more powerful than a dichotomous phenotype such as lifetime cannabis use. It should be noted though, that in general PRS studies on psychiatric traits have shown small effect sizes (Wray et al., 2014).

Higher levels of stress and lower life satisfaction were associated with more alcohol-related problems, but not with the number of glasses alcohol per week. Although the two outcome measures were highly correlated, alcohol-related problems obviously includes more than heaviness of drinking per se, such as negative consequences of drinking (injuries due to drinking, feelings of guilt). We also observed that higher alcohol intake was associated with older age, while higher AUDIT scores were associated with younger age. A recent study that comprised a much larger sample of individuals registered at the NTR ($n > 16{,}000$), found that frequency of alcohol use was highest among people aged 65 or older and lowest between 18 and 25 (Geels et al., 2013). At the same time, symptoms of alcohol use disorder were most prevalent in this younger group and least prevalent in the elderly.

Together, this suggests that older individuals may drink more frequently but moderately, while younger individuals may drink less frequently but may drink much more when they drink, which may lead to more alcohol intoxications (Geels et al., 2013), and associated problems that are reflected in higher AUDIT scores.

Our results suggested that stress and life satisfaction do not moderate the association between genetic susceptibility to heavy drinking and alcohol behavior, i.e., we found no support for an interaction. This was not in line with our expectations. Two influential models, the diathesis-stress model (e.g., Monroe and Simons, 1991) and the susceptibility hypothesis (Belsky and Pluess, 2009), argue that, in the face of adversity, some people develop a disorder (those who are vulnerable), while others are resilient, or even benefit from supportive, or positive, factors. In line with these models, we expected that more stress and lower life satisfaction would lead to a stronger expression of genetic susceptibility to heavy drinking and associated problems with alcohol. Perhaps other wellbeing variables, such as adverse life events or other forms of stress than stress experienced at home (e.g., workplace conflict), would interact with the association. It should be noted though, that our wellbeing measures were associated with AUDIT scores. As expected, participants who had experienced more stress at home and who were less satisfied with life reported more alcohol-related problems in the past year.

It is important to realize that stress and life satisfaction are also under the influence of genetic factors, the heritability varies between 5 and 45% (Bartels, 2015). The association between the wellbeing measures and the alcohol scores could be due to genetic pleiotropy (meaning that the same genetic factors influence both variation in alcohol use as well as in the wellbeing measures). In our study the PRSs for alcohol was not associated with the stress or life satisfaction measures (results not shown). However, our PRS only explained a small amount of the total variance in alcohol consumption so we cannot exclude that there is genetic pleiotropy. A large twin study showed for example genetic overlap between posttraumatic stress disorder and alcohol dependence.

We did not detect an interaction between PRS for alcohol outcome measures and stress or life satisfaction. In general, the power to detect interactions is typically lower than the power to detect main effects. As explained by Duncan and Keller (2011), the primary reason that power to detect interactions tends to be low is that the variance of the product term (in our case PRS × stress) tends to be low. This is particularly relevant to GxE study as it is generally not possible to sample from the genotypic extremes. Duncan and Keller investigated the power as a function of sample size for 3 potential GxE effect sizes in candidate gene studies. If we consider the explained variance by a candidate gene comparable to our PRS, the power of our study should be sufficient to detect an GxE interaction effect with a sample size > 6000 participants even for a moderate GxE effect (R^2 = 0.1%).

This is one of the first genetic interaction studies that appropriately accounted for confounding variables, that is, we not only included the covariates sex and age in our models, but also included the covariate-by-gene (e.g., age × PRS) and covariate-by-moderator (age × stress) interactions to prevent any misinterpretation of our interactions of interest (stress × PRS) (see Keller, 2014). There are also a few limitations. First, we did not correct for multiple testing. The tests we conducted were not completely independent, and since results for different fractions (Table 1) and for both stress and life satisfaction (Tables 2 and 3) were similar, it is unlikely that our findings are due to spurious associations. Second, we only examined stress at home in relation to alcohol use variables; other stressors, such as adverse life events may have had a stronger impact. The fact that we measured stress at home with only one item could be considered as a limitation. However, the SWLS, which is a validated questionnaire, showed similar results and was correlated with our stress measure, supporting the validity of our stress measure (for a discussion on the validity of 1-item measures, see Wanous et al., 1997). Third, our measure of alcohol consumption, i.e., average number of glasses of alcohol per week in the last year, might have been biased by self-report difficulties, as mentioned earlier. However, we took precautions by excluding individuals who reported inconsistently across alcohol use variables, thereby increasing the reliability of our measure. Fourth, although PRSs in general have higher predictive power than single genes, even larger discovery sets may be needed to increase their predictive accuracy especially for alcohol-related phenotypes. Finally, it should be noted that these polygenic risk scores are inherently limited to genetic variance captured by SNPs.

In sum, we found a positive association of PRS for alcohol consumption with quantity of alcohol consumption and alcohol-related problems in the last year, but the variance explained was low, and we found no support for *gene*-by-*stress* or *gene*-by-*life satisfaction* interactions on alcohol consumption and alcohol-related problems.

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Contributors

GWM, KJHV, and JMV were involved in the concept and design of the study. JMV, JLT, LL, GW, MB and DIB contributed to the data collection. JJH was responsible for cleaning and imputation of the genotype data. KJHV computed the polygenic risk scores. IOF conducted the principal component analysis. GWM carried out the analyses reported in the manuscript. GWM, KJHV and JMV wrote the manuscript, and all authors critically reviewed the content and approved the final version for publication.

Conflicts of interest

None.

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