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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