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Associations between polygenic risk for tobacco and alcohol use and liability to tobacco and alcohol use, and psychiatric disorders in an independent sample of 13,999 Australian adults

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ABSTRACT

Background: Substance use, substance use disorders (SUDs), and psychiatric disorders commonly co-occur. Genetic risk common to these complex traits is an important explanation; however, little is known about how polygenic risk for tobacco or alcohol use overlaps the genetic risk for the comorbid SUDs and psychiatric disorders.

Methods: We constructed polygenic risk scores (PRSs) using GWAS meta-analysis summary statistics from a large discovery sample, GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN), for smoking initiation (SI; N = 631,564), age of initiating regular smoking (AI; N = 258,251), cigarettes per day (CPD; N = 258,999), smoking cessation (SC; N = 312,273), and drinks per week (DPW; N = 527,402). We then estimated the fixed effect of these PRSs on the liability to 15 phenotypes related to tobacco and alcohol use, substance use disorders, and psychiatric disorders in an independent target sample of Australian adults.

Results: After adjusting for multiple testing, 10 of 75 combinations of discovery and target phenotypes remained significant. PRS-SI (R^2 range: 1.98%–5.09 %) was positively associated with SI, DPW, and with DSM-IV and FTND nicotine dependence, and conduct disorder. PRS-AI (R^2: 3.91 %) negatively associated with DPW. PRS-CPD (R^2: 1.56 %–1.77 %) positively associated with DSM-IV nicotine dependence and conduct disorder. PRS-DPW (R^2: 3.39 %–6.26 %) positively associated with only DPW. The variation of DPW was significantly influenced by sex*PRS-SI, sex*PRS-AI and sex*PRS-DPW. Such interaction effect was not detected in the other 14 phenotypes.

Conclusions: Polygenic risks associated with tobacco use are also associated with liability to alcohol consumption, nicotine dependence, and conduct disorder.

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1. Introduction

1.1. Common genetic risk underlying substance use and psychiatric disorders

Tobacco smoking and alcohol use are among the most important risk factors contributing to the global burden of diseases. These two addictive substances together were responsible for 255.9 million disability-adjusted life-years (DALYs) in 2015 (Peacock et al., 2018). Use or misuse of these two substances commonly occurs in people with substance use disorders (SUDs) or psychiatric disorders (Kessler et al., 1997; Pal and Balhara, 2016; Talati et al., 2016). One of the possible explanations for the co-occurring conditions is that genetic predisposition to substance use (SU) overlaps genetic predisposition to a co-occurring or comorbid disorder (Morisano et al., 2014). This theory is commonly tested by computing genetic correlations between two traits using twin designs (Kendler et al., 2003) or genome-wide association study (GWAS) summary statistics (e.g. Linkage disequilibrium (LD) score regression).

1.2. GWAS findings on the liability to licit substance use

Recent meta-analyses of genome-wide association studies (GWAS) provide additional evidence that SU and SUDs are highly polygenic (Minica et al., 2018; Pasman et al., 2018; Prom-Wormley et al., 2017; Walters et al., 2018) with multiple genetic variants of small effect contributing to the variation of the risk. Despite their complex genetic architecture (Pan et al., 2013; Robinson et al., 2014) the direct effects of individual SU and SUD loci and genes are becoming clearer. Multiple loci have been associated with the liability of consuming nicotine (Liu et al., 2019; Stephens et al., 2013; Thorgeirsson et al., 2010; Tobacco and Genetics Consortium, 2010), alcohol (Agrawal et al., 2011; Bierut et al., 2012, 2010; Edenberg et al., 2010; Frank et al., 2012; Heath et al., 2011; Kendler et al., 2011; Lind et al., 2010; Liu et al., 2019; Schumann et al., 2011; Treutlein and Rietschel, 2011; Walters et al., 2018; Wang et al., 2012; Zuo et al., 2012, 2011), and a combination of SU and SUDs (Sherva et al., 2010). Among the largest GWAS meta-analytic results to date, Pasman et al. identified 35 significant genes in 16 regions associated with lifetime cannabis use (Pasman et al., 2018). Liu et al. identified 566 genetic variants in 406 loci associated nicotine initiation, cessation, cigarettes per day and drinks per week (Liu et al., 2019). Both Walters and Liu et al. replicated the association with the alcohol metabolism gene ADH1B reported by others (Liu et al., 2019; Walters et al., 2018). Based on the increasing number of identified loci each with very small effects plus the observation that most of the variance in SNP heritabilities is accounted for by variants below standard GWAS thresholds, these GWAS and meta-analytic results are consistent with SU and SUDs traits being highly polygenic. Findings from these GWAS pave the way for subsequent analysis on identifying common genetic risk underlying substance use and associated phenotypes.

1.3. What is polygenic risk scoring?

Polygenic risk score (PRS) analysis is usually conducted as one of the post-GWAS analyses. The PRS analysis aggregates the effects of thousands of genetic variants that are associated with a trait using a spectrum of significance levels. A PRS is calculated as a weighted sum of the number of risk alleles at the selected single-nucleotide polymorphism (SNPs) that are carried by an individual. The weight is obtained from the effect size (e.g. beta for a continuous trait; log-transformed odds ratio for a binary trait) associated with each SNP in the discovery GWAS. PRSs are typically calculated using independent SNPs that meet association p-value thresholds ranging from formal genome-wide significance (association p values $< 5 \times 10^{-8}$) to less stringent thresholds (association p values $< 10^{-5}$ to < 1 including all SNPs). These scores allow us to compare and correlate PRSs between different individuals or PRSs constructed for different phenotypes.

1.4. Polygenic risk of substance use

The criterion validity of PRS to predict a variety of important behavioural outcomes has clearly been demonstrated. For example, PRSs based on much smaller discovery samples are already capable of predicting complex traits (Agerbo et al., 2015; Clarke et al., 2015; Jervis et al., 2015; Moor et al., 2015) including cannabis use and cannabis use frequency (Power et al., 2014). Liu et al. reported that PRS based on the GSCAN summary statistics significantly predicted nicotine and alcohol use in the independent Add Health and Health and Retirement Study datasets (Liu et al., 2019). Likewise, Walters et al.'s alcohol dependence GWAS results significantly predicted out of sample alcohol misuse (Walters et al., 2018). These findings combined with the repeatedly observed genetic correlations based on linkage disequilibrium score regression (LDSC) between licit and illicit substance use and misuse traits (Liu et al., 2019; Munn-Chernoff et al., 2019; Pasman et al., 2018; Polimanti et al., 2019; Walters et al., 2018) are consistent with twin-based genetic epidemiological results (Kendler et al., 2012) arguing that familial aggregation in comorbid substance use is best explained by common genetic risk factors. Given the availability of summary statistics based on the world's largest GWAS to identify loci associated with nicotine and alcohol phenotypes (GWAS & Sequencing Consortium of Alcohol and Nicotine use, GSCAN; Liu et al., 2019), there exists the opportunity to examine the degree to which individual differences in SU and SUD risk can be explained by loci identified by GSCAN.

1.5. Aims

We hypothesised that shared genetic risk is underlying use of alcohol, nicotine, alcohol or nicotine use disorders, and even psychiatric disorders. We tested this hypothesis by testing the associations between GSCAN PRSs and individual differences in the liability to SUDs and psychiatric disorders in an independent sample of Australian adults while adjusting for multiple testing. In sample sizes up to 1.2 million individuals, the GSCAN consortium has identified 566 loci that are associated with nicotine and alcohol use (Liu et al., 2019). With PRSs derived from this very large discovery sample, the current study is likely to maximise the power to detect an association between PRSs, and related traits. We focused our risk prediction on not only SUDs but also psychiatric traits because they are commonly comorbid with SU or SUDs (Batel et al., 1995; Falk et al., 2006; Ferreira et al., 2019; Lasser et al., 2000).

2. Material and methods

2.1. Design

We constructed PRSs for individuals in an independent sample using recently published GWAS meta-analytic summary statistics for tobacco and alcohol use (see discovery sample for details). We then tested associations between these PRSs and the liability of SUDs, and psychiatric disorders.

2.2. Discovery sample

We obtained GWAS meta-analysis summary statistics from GSCAN (Liu et al., 2019), an international meta-analysis that aggregated genetic association findings from over 30 contributing studies and over one million participants to find genetic variants associated with smoking and drinking. This meta-analysis was performed for four tobacco and one alcohol-related phenotypes in a sample that excluded the contribution of QIMR samples and 23andMe before we constructed PRSs for: smoking initiation (SI; N = 631,564; 52 % smokers; 53.6 % females); age of initiation of regular smoking (AI; N = 258,251; 50.0 %

females); cigarettes per day (CPD; N = 258,999; 55.1 % females); smoking cessation (SC; N = 312,273; 40 % current smokers; 50.6 % females); and drinks per week (DPW; N = 527,402; 53.2 % females). We ensured that the discovery sample did not overlap the target sample (see next section). Non-independence of these two samples can inflate the prediction R-squared for the target sample (Wray et al., 2013).

2.3. Target sample and outcome measures

Participants in our target sample were drawn from a pool of Australian twins who were initially recruited through the Australian Twin Registry (ATR; Hopper, 2002), and other members of their families. The ATR is a volunteer registry that recruited participants through the media, schools and a variety of other sources (Hansell et al., 2008). Response rates (Heath et al., 1997), sampling bias (Slutske et al., 1997), and sample representativeness (Slutske et al., 1998) have been previously examined for the ATR sample. Target phenotypes related to substance use and psychiatric disorders were selected from 15,440 individuals who were part of three coordinated studies: (1) the Nicotine Addiction Genetics (Loukola et al., 2014, 2008) study, which targeted families based on heavy smoking index cases identified in earlier interviews and questionnaires (Pergadia et al., 2009), (2) the Australian Alcohol Extreme Discordant and Concordant Sibship (OZALC-EDAC; Hansell et al., 2008) study, which ascertained index cases with a history of heavy drinking or alcohol dependence, and (3) the Australian Alcohol Large Sibship (OZALC-BIGSIB) study, designed to study families with five or more offspring sharing both biological parents and unselected for phenotype (Hansell et al., 2008; Heath et al., 2011; Saccone et al., 2007). Our final target sample consisted of 13,999 individuals (59.0% females, median age: 42 years, age range: 20–89 years) who were genotyped and not ancestry outliers, including 6,578 twins, their 23 spouses, and their 7398 family members (2047 parents, 5200 siblings, and 151 offspring). Diagnostic phone interviews modified from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994; Hesselbrock et al., 1999) were used to collect data through a computer-assisted telephone interview (CATI) program. These CATI interviews assessed a wide range of variables across tobacco use, specific phobia and social phobia, alcohol and drug dependence, mental, conduct, and anti-social personality disorders. This project was approved by the QIMR Human Research Ethics Committee. Data were stored in compliance with national regulations regarding personal data protection. Informed consent was obtained from all the participants.

Fifteen target phenotypes (i.e. outcome measures) used in this study included six self-reported phenotypes that were identical to those used in GSCAN discovery analyses: (1) smoking initiation (SI); (2) age at starting regular smoking (AI); (3) cigarettes per day (CPD); (4) smoking cessation (SC); (5) drinking initiation (DI); (6) drinks per week (DPW), and nine binary phenotypes: (7) alcohol dependence defined by the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994); (8) DSM-IV nicotine dependence; (9) nicotine dependence defined by the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991); (10) DSM-IV conduct disorder (CD); (11) DSM-IV antisocial personality disorder (ASPD); (12) DSM-IV major depressive disorder (MDD); (13) DSM-IV panic disorder; (14) DSM-IV social anxiety disorder (SAD); and (15) a screen for mania. The nine binary phenotypes were calculated according to the DSM-IV criteria. Definitions of the 15 phenotypes were provided in the supporting information (see Definitions of six self-reported phenotypes and Definitions of nine binary phenotypes in supporting information). The prevalence of the three self-reported binary phenotypes ranged from 44 % for smoking cessation to 80 % for drinking initiation. Lower prevalence of the nine binary phenotypes ranged from 1% for mania screen to 39 % for DSM-IV nicotine dependence (Table 1). Significantly different prevalence was seen between males and females in these 12 phenotypes, except for mania screen.

2.4. Construction of polygenic risk scores

Our quality control (QC) procedure for the discovery and target sample SNPs is discussed in detail elsewhere (Chang et al., 2019). We performed LD-based clumping on the QCed SNPs that were common to both samples. PRSs were calculated using the clumped SNPs that met eight association p-value thresholds of 5×10^{-8}, 10^{-5}, 10^{-3}, 10^{-2}, 5×10^{-2}, 0.1, 0.5 and 1 (i.e. all SNPs), and were standardised to a mean of zero and a standard deviation of one, resulting in one standardised PRS per p-value threshold and individual in the target sample.

2.5. Univariate mixed modelling

Linear mixed models were constructed using genetic restricted maximum likelihood (GREML) in the GCTA (Yang et al., 2011) software package to obtain the effect estimates of PRSs on the individual differences in SU, SUD, and psychiatric disorders:

$$Y = X\,\beta + g + \varepsilon$$

where Y is a n x1 vector of either a binary phenotype or continuous phenotype with n being the number of individuals in the input data, X is a vector of fixed-effect covariates, and β is the effect estimate of the X. In addition to PRSs, covariates were included to control for the effects of categorical variables to capture sex (males coded as 1; females coded as 2), GWAS array, quantitative variables to capture the interaction between PRS and sex (PRS*sex), age, age^2, age*sex, age^2*sex, and the first ten principal components derived from the SNP data (to control for population stratification). The g and ε denote the random genetic effect and error term respectively. Given that our target sample consisted of twins and their relatives, it is important to accounted for cryptic relatedness in the estimation. The genetic effect has a known variance-covariance structure that is defined by a genetic relationship matrix (GRM), which estimates the genetic relatedness between individuals using the SNP data. In addition to the modelling with sex*PRS interaction, we conducted additional modelling by stratifying the target sample by sex. This design was used in our earlier study (Chang et al., 2019) and may allow us to compare the PRS predictive performance between the two designs.

The fixed effect estimates from the GCTA-GREML analysis were used to calculate the proportion of variance of target phenotypes explained by PRS, R^2, as

$$R^2 = \left(\frac{\beta_{PRS}}{SD_Y} \times SD(\beta_{PRS})\right)^2$$

where β_{PRS} is the regression coefficient of a PRS, SD_Y is the standard deviation of a binary or continuous target phenotype Y, and $SD(\beta_{PRS})$ is the standard deviation of the β_{PRS}. The R^2 is defined as the square of the correlation between Y and PRS. We calculated two-sided p-values from a t-distribution in R.

2.6. Types of associations between PRS and target phenotypes

To make it easy to interpret results from a large number of associations, we divided the 75 combinations based on the five GWAS discovery phenotypes and 15 target phenotypes into four groups: (1) **same-trait associations** where discovery and target phenotypes are identical (e.g. smoking initiation and smoking initiation; five associations), (2) **cross-trait associations between the use of same substances** where discovery and target phenotypes are different traits but based on the same substances (e.g. smoking initiation and cigarettes per day; 22 associations), (3) **cross-trait associations between the use of different substances** where discovery and target phenotypes are based on different substances (e.g. smoking initiation and drinks per week in active drinkers; 18 associations), and (4) other **cross-trait associations** where target phenotypes are non-substance traits (e.g. DSM-IV conduct disorder and smoking initiation; 30 associations).

Table 1
Summary of outcome variables related to use of licit substances, substance use disorders, and psychiatric disorders in Australian adults aged between 20 and 89 years. For binary outcomes (Type = binary), the number of individuals with non-missing data and prevalence was presented separately in females (F), males (M) and both sexes together (F + M). The sex difference was tested using Chi-squared test of association. For continuous outcomes (Type = continuous), the number of individuals with non-missing data, median and interquartile range (IQR) were presented. The sex difference was tested using the Wilcoxon rank-sum test with continuity correction.

		Females (F)		Males (M)		F + M		Sex differences	
Type	Target phenotypes	Num	Summary	Num	Summary	Num	Summary	Test stat	p value
binary	Smoking initiation	7,640	Prevalence: 52 %	5,193	Prevalence: 64 %	12,833	Prevalence: 57 %	167.1	< .0001
	Smoking cessation	2,894	Prevalence: 45 %	2,635	Prevalence: 41 %	5,529	Prevalence: 43 %	11.51	0.0007
	Drinking initiation	7,594	Prevalence: 76 %	5,276	Prevalence: 86 %	12,870	Prevalence: 80 %	173.1	< .0001
	DSM-IV alcohol dependence	3,946	Prevalence: 17 %	3,290	Prevalence: 33 %	7,499	Prevalence: 24 %	254.3	< .0001
	DSM-IV nicotine dependence	3,893	Prevalence: 38 %	3,435	Prevalence: 40 %	7,603	Prevalence: 39 %	4.68	0.0304
	Fagerstrom Test Nicotine Dependence	3,893	Prevalence: 25 %	3,435	Prevalence: 32 %	7,603	Prevalence: 28 %	43.65	< .0001
	DSM-IV conduct disorder	3,874	Prevalence: 1.8 %	3,247	Prevalence: 4.9 %	7,383	Prevalence: 3.2 %	55.18	< .0001
	DSM-IV antisocial personality disorder	3,947	Prevalence: 0.8 %	3,291	Prevalence: 3.8 %	7,501	Prevalence: 2.1 %	75.83	< .0001
	DSM-IV Major depressive disorder	3,889	Prevalence: 36 %	3,252	Prevalence: 25 %	7,402	Prevalence: 31 %	90.60	< .0001
	DSM-IV panic disorder	3,941	Prevalence: 5.5 %	3,283	Prevalence: 3.5 %	7,487	Prevalence: 4.5 %	16.11	< .0001
	DSM-IV social anxiety disorder	3,944	Prevalence: 20 %	3,286	Prevalence: 17 %	7,493	Prevalence: 19 %	11.25	0.0008
	Mania screen	3,091	Prevalence: 1.2 %	2,629	Prevalence: 1.0 %	5,977	Prevalence: 1.1 %	0.26	0.6090
continuous	Drinks per week	5,446	Median: 5, IQR: 8	4,450	Median:12, IQR:16	9,896	Median: 7, IQR:12	174E5	< .0001
	Age at starting regular smoking	2,344	Median:16, IQR: 3	1,593	Median:16, IQR: 4	3,937	Median:16, IQR: 3	166E4	< .0001
	Cigarettes per day	2,461	Median: 4, IQR: 1	1,687	Median: 4, IQR: 2	4,148	Median: 4, IQR: 1	239E4	< .0001

2.7. Multiple testing

We tested the association between each of the 15 target phenotypes and each of the 40 PRS, giving a total of 600 association tests (i.e. 15 target phenotypes * 5 discovery phenotypes * 8 p value thresholds). To account for multiple testing, we presented p-values adjusted for the effective number of independent target and discovery phenotypes ($p < 7.14 \times 10^{-4}$, see threshold T4 in **Table S1**). Details of the multiple testing were provided in the supporting information.

2.8. Statistical software

The data processing and computing for PRS calculation was coded in Bash (Free Software Foundation, 2007) and R (R Core Team, 2017). LD-based SNP clumping and PRS calculation were performed using Plink 1.90b3.38 (Chang et al., 2015). Univariate GREML was performed using GCTA (Yang et al., 2011). We used R and Base SAS 9.4 (SAS Institute Inc., 2015) for cleaning data, conducting statistical analyses, and generating graphs and tables.

3. Results

3.1. Predictive performance of PRSs

In our models that contained sex*PRS interaction, 10 of the 75 target-PRS associations remained significant after correcting for multiple testing at the T4 threshold. Our five PRSs significantly predicted five target phenotypes, including smoking initiation, drinks per week, DSM-IV and FTND-based nicotine dependence, and DSM-IV conduct disorder, explaining 1.56%–6.26% of their variance. The five PRSs were not associated with the other ten outcomes, such as age at starting regular smoking, cigarettes per day, smoking cessation, drinking initiation, DSM-IV alcohol dependence, antisocial personality disorder, major depressive disorder, panic disorder, social anxiety disorder, and mania screen. In terms of the number of target phenotypes predicted, PRS-SI was the most predictive, explaining five target phenotypes. The other four PRSs predicted one or two phenotypes. Significant sex*PRS were identified in the associations between (1) PRS-SI and DPW, (2) PRS-AI and DPW, and (3) PRS-DPW and DPW (Table S2). The main effect of the PRSs was larger in same-trait analyses (panel 1 and 2, Fig. 1) than the cross-trait analyses (panel 3–10, Fig. 1). The R^2 generally increased with less stringent p value thresholds at which the PRSs were calculated against (Fig. 1).

Our models that stratified the target sample by sex identified 26 of the 75 target-PRS associations after correcting the results with the same significance threshold. We provided the number of significant associations in Table S3 and the fixed effect estimates of the PRSs in Table S4.

3.2. Same-trait associations

In the same-trait analyses, significant effects of PRSs were only identified from PRS-SI (panel 1, Fig. 1) and PRS-DPW (panel 2, Fig. 1). Sex*PRS-DPW negatively influenced the variance of DPW ($\beta = -1.396$, SE = 0.354, p value = 0.00008, $R^2 = 2.94\%$), suggesting the greater influence of increased PRS-DPW on the variation of DPW in males than females.

3.3. Cross-trait associations between the use of same substances

In cross-trait analyses based on the same substances, we found that higher PRS-SI, PRS-CPD, and PRS-SC were associated with higher liability to DSM-IV and FTND-based nicotine dependence. PRS-SI showed a similar prediction pattern in the two nicotine dependence phenotypes (panel 3 & 5, Fig. 1), with a significant effect only seen in the PRSs calculated using SNPs at or higher than 10^{-2}. A significant effect of PRS-CPD was only found in the PRS calculated using all SNPs ($\beta = 0.06$, SE = 0.018, p value = 0.00068, $R^2 = 1.56\%$; panel 4, Fig. 1). Significant effect of PRS-SC on FTND-based nicotine dependence was only seen from SNPs at p value $< 10^{-5}$ ($\beta = 0.059$, SE = 0.017, p value = 0.00044, $R^2 = 1.7$ %; panel 6, Fig. 1). Finally, we found no significant sex*PRS effect in these four associations.

3.4. Cross-trait associations between the use of different substances

In cross-trait analyses based on different substances, we found that higher risk of DPW was significantly associated with higher PRS-SI but with lower PRS-AI. PRS-SI calculated at all the eight p value thresholds significantly predicted DPW, explaining 3.01%–4.39% of the trait variation (panel 7, Fig. 1). Significant sex*PRS-SI effect on DPW was found in PRS-SI calculated at p value $< 5 \times 10^{-8}$ ($\beta = -1.26$, SE = 0.353, p value = 0.00036, $R^2 = 2.4$ %; Table S2) and $< 10^{-5}$ ($\beta = -1.361$, SE = 0.355, p value = 0.00013, $R^2 = 2.77\%$; Table S2), indicating greater influence of PRS-SI on DPW in males compared to females. Both PRS-AI ($\beta = -2.714$, SE = 0.583, p value < 0.00001, $R^2 = 3.91\%$; Table S2) and sex*PRS-AI ($\beta = 1.307$, SE = 0.36, p value = 0.00029, $R^2 = 2.48\%$; Table S2) significantly predicted DPW based on PRS-AI

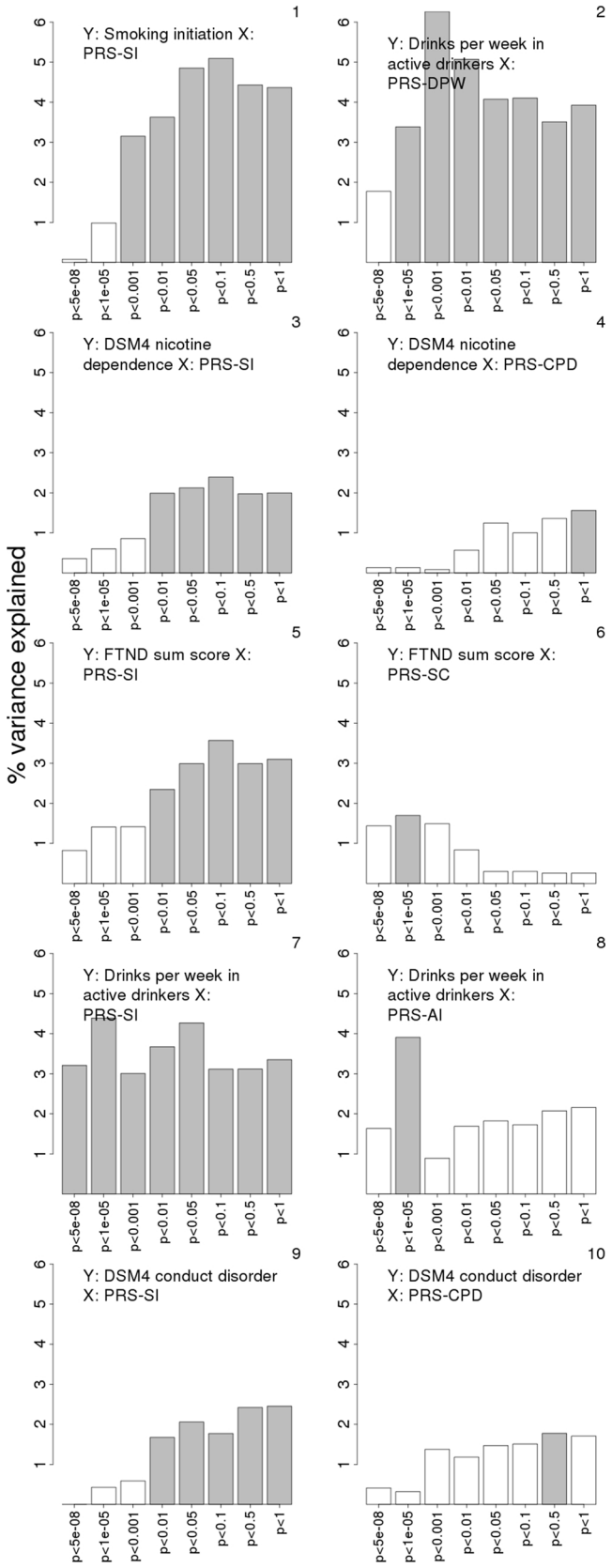

Fig. 1. Proportion of variance of target phenotypes (Y) explained by polygenic risk scores (PRS, X) in Australian adults aged between 20 and 89 years. Bar height represents the percentage of the phenotypic variation explained by a PRS. Associations that remained significant after accounting for multiple testing (adjusted p-value threshold: 7.14×10^{-4}) are shown in grey bars whereas associations that did not survive multiple testing are shown in white bars. Bar groups on the x-axis indicate the eight p-value thresholds at which the PRSs were calculated: 5×10^{-8}, 10^{-5}, 10^{-3}, 10^{-2}, 0.05, 0.1, 0.5, and 1 (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

calculated at p value < 10^{-5}suggesting that polygenic risk for starting regular smoking at an earlier age was associated with higher DPW but this association was stronger in females than males.

3.5. Cross-trait associations between SU and psychiatric disorders

In the other cross-trait analyses, higher liability to DSM-IV conduct disorder was associated with higher PRS-SI (panel 9, Fig. 1) and PRS-CPD (panel 10, Fig. 1). The effect sizes were generally smaller than 0.03. We had no evidence for significant sex*PRS effect in these associations.

4. Discussion

This study examined the association between SNP-based polygenic risk for tobacco or alcohol consumption and the risk of SUs, SUDs, and psychiatric disorders. Our results lend support to genetic risk factors that were common between cigarette smoking, and nicotine dependence, or conduct disorder. PRS for smoking initiation (PRS-SI) was the most predictive among our five PRSs, explaining not only the liability of smoking phenotypes expectedly, but also alcohol consumption and conduct disorder. Our PRSs showed higher prediction R^2 in the same-trait associations (2.46%–6.26 %) than cross-trait associations (1.56%–4.39 %). Finally, we reported the first evidence for PRS*sex interactions influencing the variation in alcohol consumption measured by the number of drinks per week.

4.1. Same-trait associations

Given the very large sample sizes in the GSCAN discovery GWAS meta-analyses, our *a priori* expectations were that all same-trait associations would be significant. This was not the case for associations based on PRS-AI, PRS-CPD, and PRS-SC. One possible explanation could be the fewer identified loci associated with AI, SC and CPD than the other two discovery phenotypes DPW and SI (see Fig. 2, Liu et al., 2019). Second, pleiotropy across the five discovery phenotypes may partly explain the difference in the prediction result. Every locus associated with AI was found to be pleiotropic for the other four phenotypes. Only two non-pleiotropic loci were found in SC, followed by eight in CPD, 23 in DPW and 138 in SI (Liu et al., 2019). Third, the inclusion of sex*PRS interaction in our models may undermine the predictive performance of PRS-CPD on CPD. However, our additional analyses based on models that were fitted separately in three sex subgroups identified a significant association between PRS-CPD and CPD (Table S4). Liu et al. (2019) reported that GSCAN PRS for AI, CPD, SI, SC, and DPW explained between 1% and 4% of the variance in similar measures. However, their estimates were derived using pseudo-R^2 and did not include sex*PRS interaction as a covariate. Finally, our PRS-DPW explained up to 6.26 % of the variance of DPW, exceeding 2.4 % by GSCAN PRS for DPW in the independent AddHealth sample (Liu et al., 2019). We attributed the performance of our PRS- DPW to predict variance out-of-sample to the fact that the GSCAN meta-analysis was very culturally heterogeneous and included cohorts with varying drinking behaviours and modes of phenotypic assessment. In contrast, our Australian sample was carefully phenotyped.

4.2. Cross-trait associations between the use of same substances

Our PRS-CPD significantly predicted the liability to DSM-IV nicotine

dependence, but not smoking initiation nor age at the initiation. An earlier longitudinal study (Belsky et al., 2013) associated polygenic risk score for cigarettes per day with various stages of smoking behaviour in New Zealanders aged 11–38 years using six top SNPs to construct the PRS. We found that PRS-CPD was not associated with smoking initiation nor with the time of the initiation; however, individuals at higher PRS-CPD were more likely to become nicotine dependent. Our results largely agree with the findings reported by Belsky et al. (2013)

4.3. Cross-trait associations between the use of different substances

We found that PRS-SI and PRS-AI, but not PRS-CPD or PRS-SC, significantly predicted the variation of alcohol consumption, measured by a weekly number of drinks consumed. In contrast, Vink et al. (2014) reported an association between a number of glasses alcohol per week and a PRS for CPD, based on the Tobacco and Genetics Consortium (TAG; Tobacco and Genetics Consortium, 2010), but not with a TAG-based PRS-SI, nor PRS-SC. Aside from the size differences in the two discovery samples, the differences in the prediction for the smoking-related PRSs may be attributable to the heterogeneity in terms of how the discovery GWAS consortia defined their phenotypes. For example, the GSCAN-based SI dichotomised subjects as ever being regular smokers or not, whereas the TAG-based SI classified subjects as ever smoking $\geq$ 100 or $<$ 100 cigarettes, which may be more strictly defined than our SI. The GSCAN-based CPD recorded the average number of cigarettes smoked daily or binned the number of cigarettes in an ordinal scale (1–5, 6–15, 16–25, 26–35, or 36 or more cigarettes smoked per day) while the TAG-based CPD was defined as the average or maximum number of cigarettes smoked daily. While CPD and DPW have been shown to be genetically correlated using LDSC (rG = 0.07, Liu et al., 2019; rG = 0.44, Nivard et al., 2016), we found no evidence for the association using the PRS method.

4.4. Cross-trait associations between substance use and psychiatric disorders

We found evidence that DSM-IV conduct disorder was positively associated with PRS-SI, or PRS-CPD, but not with PRS-AI, PRS-SC, nor PRS-DPW. To the best of our knowledge, this is the first study that associated polygenic risk for smoking with the liability of conduct disorder. Grant et al. (2015) found in their twin study that shared genetic liability explained the comorbidity between nicotine dependence and conduct disorder. Given that our PRS-SI and PRS-CPD predicted both nicotine dependence (ND) and conduct disorder (CD), it may be reasonable to expect an association between polygenic risk for ND and the liability to a CD.

None of our PRSs significantly predicted the risk of antisocial personality disorder. One possible explanation was that the low prevalence of this disorder, 0.8% in females and 3.8% in males, provided insufficient variation for the PRS effect to be detected. Using the LDSC method, Tielbeek et al. (2018) found a significant genetic correlation (rG = 0.59, p = 0.036) between antisocial behaviour (N = 31,968) and cigarettes per day (N = 38,181). However, they inferred that the genetic variance of antisocial behaviour that is overlapping CPD could be very low.

None of our associations between PRSs and DSM-IV major depressive disorder, panic disorder, SAD or mania screen survived multiple testing. While genetic correlations of smoking phenotypes with major depressive disorder were reported from twin studies (Edwards et al., 2011) and LDSC-based studies (Liu et al., 2019; The Brainstorm Consortium, 2018), we are unaware of other studies that have tested the associations using PRSs.

4.5. The role of PRS*sex interaction in smoking and alcohol consumption

We included the sex*PRS interaction in our PRS-phenotypic associations to control its effect on the PRS prediction. The main advantage of incorporating this interaction term was that our models can be tested on the full dataset, which can be more statistically powerful than splitting the data by sex and testing the effect of PRSs in each subgroup (Keller, 2014). Moreover, including the interaction allowed us to identify its confounding effect on the PRS risk prediction. For example, the association between PRS-CPD and CPD was significant (Table S4) in our additional analysis but not in our main analysis (Table S2). Note that adding the interaction term may be a problem in a small target sample (e.g. Chang et al., 2019).

However, we noted some impact of the practice of incorporating sex*PRS. Firstly, the number of significant target-PRS associations was reduced from 26 to 10. Second, larger effect sizes, standard errors (SE) and higher prediction R^2 of our PRSs were found in models with the interaction term (β range: -2.71 ~ 3.382; SE range: 0.007–0.594; R^2 range: 1.56%–6.26 %) compared to models without the interaction term (β range: -1.39 ~ 1.85; SE range: 0.002–0.372; R^2 range: 0.17 %–3.69 %).

4.6. Limitations

Our results should be interpreted in the context of the following limitations. First, our discovery sample was based predominantly on Caucasian ancestry. Consequently, the significant PRS-phenotype associations observed here may not be generalised in other ethnic groups. While we found significant associations between PRS-CPD and DSM-IV nicotine dependence in Australians, a similar association was found to be non-significant in native Americans (Otto et al., 2016). Next, our disorder outcomes from the NAG, OZALC-EDAC, and OZALC-BIGSIB study were defined by DSM-IV. Significant changes were made in the diagnostic criteria of substance use disorders (Substance Abuse and Mental Health Services Administration, 2016), as well as psychiatric disorders (Nemeroff et al., 2013) from DSM-IV to the DSM-5 may not allow our results to be directly compared with studies based on the DSM-5 outcomes. Thirdly, we reported the genetic overlap between polygenic risk for alcohol- and nicotine-related phenotypes and self-reported measures of SU, SUDs, and diagnoses. However, these associations do not imply causation. Fourthly, our PRSs explained a relatively small proportion of the genetic variance, especially in the non-SU phenotypic outcomes. This is a common problem in addiction studies (Clarke et al., 2017; Kapoor et al., 2016; Meyers et al., 2013; Mies et al., 2017; Vink et al., 2014) that rely on PRS approaches. Although it remains challenging to discuss the clinical utility of PRSs in genetic risk prediction for substance use, the PRS method does improve risk prediction in other diseases, such as prostate cancer (Helfand et al., 2016), coronary artery disease (Wünnemann et al., 2019). PRS prediction may prove useful for discriminating patients at the top and bottom deciles of risk (Lewis and Vassos, 2017) through larger GWAS discovery samples and use of multi-polygenic scores derived from related traits (Plomin and von Stumm, 2018).

4.7. Implications

While the use of PRS is currently limited to a research context, the possibility of adapting PRS for clinical use is being actively discussed (Khera et al., 2018; Lewis and Vassos, 2017; Zheutlin and Ross, 2018). We demonstrated the genetic overlap between smoking PRSs and alcohol consumption, nicotine dependence, or conduct disorder. To clinicians, a calculated PRS in smokers may be used jointly with existing screening tools to identify individuals at high risk of risky alcohol consumption, nicotine addiction or conduct problems. To geneticists, future studies that aim at maximising risk prediction may consider including genotype-by-sex, or/and genotype-by-age interaction (Santos et al., 2014) in their models.

4.8. Conclusion

In conclusion, using PRSs derived from the very large GSCAN consortium, we identified shared genetic aetiology between smoking or alcohol consumption, and smoking initiation, alcohol consumption, nicotine dependence, or conduct disorder.

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Contributors

LHC performed the analysis and wrote the manuscript; SEM developed the method for estimating PRS; MZL conducted a meta-analysis for the discovery sample GWAS; ACH, PAM, JBW, BV, IBH, NGM, and NAG conceived, designed and assisted drafting this manuscript.

Data statement

Data from our discovery sample was shared through our collaborators at GSCAN. Data for our target sample were obtained from an ongoing project. For these reasons, there is no data that can be shared.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.107704.

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