Drug and Alcohol Dependence 209 (2020) 107948

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Substance use: Interplay between polygenic risk and neighborhood environment

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ARTICLE INFO

Keywords:
Gene-environment correlation
Gene-environment interaction
Neighborhood
Polygenic scores
Socioeconomic status
Substance use

ABSTRACT

Background: Tobacco, alcohol, and cannabis use are prevalent behaviors that pose considerable health risks. Genetic vulnerability and characteristics of the neighborhood of residence form important risk factors for substance use. Possibly, these factors do not act in isolation. This study tested the interaction between neighborhood characteristics and genetic risk (gene-environment interaction, GxE) and the association between these classes of risk factors (gene-environment correlation, rGE) in substance use.

Methods: Two polygenic scores (PGS) each (based on different discovery datasets) were created for smoking initiation, cigarettes per day, and glasses of alcohol per week based on summary statistics of different genome-wide association studies (GWAS). For cannabis initiation one PGS was created. These PGS were used to predict their respective phenotype in a large population-based sample from the Netherlands Twin Register (N = 6,567). Neighborhood characteristics as retrieved from governmental registration systems were factor analyzed and resulting measures of socioeconomic status (SES) and metropolitanism were used as predictors.

Results: There were (small) main effects of neighborhood characteristics and PGS on substance use. One of the 14 tested GxE effects was significant, such that the PGS was more strongly associated with alcohol use in individuals with high SES. This was effect was only significant for one out of two PGS. There were weak indications of rGE, mainly with age and cohort covariates.

Conclusion: We conclude that both genetic and neighborhood-level factors are predictors for substance use. More research is needed to establish the robustness of the findings on the interplay between these factors.

1. Introduction

Use of tobacco, alcohol, and cannabis is prevalent in the Western world. Twenty percent of European and US individuals older than 14 smoke on a regular basis (WHO, 2016a). The worldwide average daily intake of alcohol is 13.9 g in this age group (about one glass; WHO, 2018a). In Europe, around 23 % has ever used cannabis (in the age group ≥15 years) versus 52 % in the US (age ≥16; European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2011). Smoking, alcohol use, and cannabis use can have deleterious health effects (World Health Organization (WHO, 2016b, 2017; 2018a), making the etiology of these behaviors an important topic of study.

Heritability estimates for tobacco, alcohol, and cannabis use are substantial (Kendler et al., 2008), with even higher estimates for abuse and dependence (Ducci and Goldman, 2012; Mbarek et al., 2015; Verweij et al., 2010; Vink et al., 2005). Molecular genetic studies aim to identify specific genetic variants that increase risk for substance use. Hypothesis-free, large genome-wide association studies (GWASs) of smoking (Liu et al., 2019; The Tobacco and Genetics Consortium, 2010), alcohol use (Clarke et al., 2017; Liu et al., 2019), and lifetime cannabis use (Pasman et al., 2018) have had success in achieving this, but heritability estimates based on the accumulative effect of measured SNPs are still lower than estimates from twin and family studies. One of the causes of this 'missing heritability' might be the neglect of the interplay between the environment and genes (Manolio et al., 2009).

Neighborhood characteristics might increase risk for substance use,

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https://doi.org/10.1016/j.drugalcdep.2020.107948
Received 23 September 2019; Received in revised form 14 February 2020; Accepted 26 February 2020
Available online 28 February 2020

although results are often mixed. For instance, urbanicity has been associated with higher rates of smoking (Idris et al., 2007), cannabis use (Martino et al., 2008), and alcohol use (Atav and Spencer, 2002), but there is also evidence for associations in the opposite direction (Donath et al., 2011; Leatherdale et al., 2007; Lutfiyya et al., 2008). Some studies find that substance use is associated with a low average socioeconomic status (SES), but results seem to depend on study characteristics and the type of substance under investigation (for reviews, see Galea et al., 2004; Karriker-Jaffe, 2011). General measures of low neighborhood SES or deprivation have been shown to be positively associated to smoking (Stimpson et al., 2007). Alcohol and cannabis use might be more prevalent in high SES neighborhoods, but results have been mixed (Karriker-Jaffe, 2011).

Possibly, genetic vulnerability to substance use influences the relationship between these neighborhood characteristics and substance use. In the case of gene-environment interaction (GxE) adverse environmental circumstances may lead to deleterious outcomes only (or more strongly) in genetically vulnerable individuals ('contextual triggering'), or reversely, a beneficial environment can protect against the effect of genetic vulnerability ('compensation,' Shanahan and Hofer, 2005). In other words, some individuals have a higher innate reactivity to environmental circumstances, meaning that there is 'differential susceptibility' (Belsky and Pluess, 2009). Previous studies into GxE have mainly used twin or candidate-gene methodology. For example, heritability of alcohol use was found to be higher when neighborhood alcohol outlet density (selling points) was high than when the density was low (Slutske et al., 2018). Some twin studies have suggested that the genetic contribution to alcohol use and abuse is larger for people living in urban areas than for people living in rural areas (Davis et al., 2017; Legrand et al., 2008; Rose, 1998; Rose et al., 2001). Few studies have investigated GxE in the neighborhood using polygenic scores. A polygenic score (PGS) is a weighted count of risk alleles for a trait, where the weights are based on the SNP effect sizes in a GWAS. PGS might be the best available measure of genetic risk to date for use in GxE studies (Pasman et al., 2019). The only study to our knowledge that has used a PGS to test gene-neighborhood interaction focused on smoking and showed that more social cohesion in the neighborhood buffered against the effect of genetic risk (Meyers et al., 2013). No interaction effect was found for a measure of neighborhood poverty and disrepair.

Even less studied in this context is gene-environment correlation (rGE). In rGE, there is an association between genetic predisposition and the environment, such that genetic factors are associated both with the outcome of interest and with the environmental context. For example, if lower intelligence is associated with both substance use and with living in low-SES environments (Fergusson et al., 2005) this can lead to rGE when a genetic measure for substance use includes variants that are also predictive of lower intelligence (i.e., variants that are pleiotropic). Also, 'evocative' rGE arises when genes contribute to some behavior (e.g., aggression) that elicits a response in the environment (e.g., rejection; Plomin et al., 1977). Few studies to our knowledge investigated rGE with neighborhood characteristics specifically. One study showed that a PGS for alcohol dependence was positively related to neighborhood social deprivation (Clarke et al., 2016). Another showed significant correlations between substance use PGS and Townsend neighborhood deprivation indices (Abdellaoui et al., 2019). Some GxE studies report the (uncorrected) correlation between their G and E factors (e.g., Meyers et al., 2013). Not accounting for rGE effects can lead to an overestimation of genetic or (shared) environmental variance (Blokland et al., 2013; Purcell, 2002), and to misinterpreted or even spurious GxE findings (Jaffee and Price, 2007).

The current study looked at the main effects of neighborhood characteristics and polygenic risk on substance use, and the interplay (interaction and correlation) between these factors.

2. Methods

2.1. Participants

We used cross-sectional data (survey 5, 6, 7, 8, and 10) collected between 2000 and 2014 from an ongoing longitudinal study in twin pairs and their family members registered at the Netherlands Twin Register (NTR; Willemsen et al., 2013). For the current study, a subsample of 6567 Dutch ancestry participants was selected. We linked the most recent substance use data to neighborhood information as obtained from governmental registration systems that was closest in time (either from 2010 or 2004; Centraal Bureau voor de Statistiek (CBS, 2012), using postal code at time of survey completion. Table 1 summarizes this data selection procedure and the resulting sample composition. There were small differences in distributions or mean values for the variables depending on what survey was used (Supplementary Table S1). These differences in predictor and outcome variables may stem from cohort effects (for example due to the economic crisis), age effects, or they may represent random fluctuations. However, results did not change when we controlled for the effects of measurement wave (results not shown).

About half (55 %) of the sample consisted of twins. The sample included 65 % females and 38 % highly educated individuals (higher vocational education or university). Mean age at the time of completing

Table 1
Participant data from each measurement year (survey number) per phenotype.

		Phenotype			
	Year (survey)	Smoking initiation	Cigarettes/ day	Alcohol/ week	Cannabis initiation
N retrieved from survey	2014 (10)	3,958	666	2,509	3,059
	2010 (8)	814	1,408	1,457	1,645
	2004 (7)	146	328	671	not available
	2002 (6)	1,326	586	1,308	not available
	2000 (5)	227	108	229	972
	Total*	6,471	3,096	6,174	5,676

*For $N = 6567$ data were complete for at least one analysis.
Shaded rows: for these participants, postal code data were linked to information on neighborhood characteristics available from 2010; for the others, these data were linked to information available from 2004.

the survey was $M = 45.3$ years (SD = 15.7; range 18–91 years). Average birth year was 1964 (for more details on the NTR sample, see e.g., Geels et al., 2013; Willemsen et al., 2013).

2.2. Substance use outcomes

Substance use outcomes were based on self-report measures (Supplementary Table S2). For smoking initiation, participants were coded as ever smokers if they classified as current smokers at any survey (smoking at least weekly) or ex-smokers. When answers to these questions were incomplete or inconsistent, information was complemented with answers to different questions (Treur et al., 2016).

For tobacco use, we used an open-ended question asking how many cigarettes per day someone smoked at their heaviest period of smoking for survey 7, 8, and 10. For survey 5 and 6, cigarettes per day was available only for current smokers and was measured on an ordinal scale. For these surveys, the mid-point of each answering category was analyzed on a continuous scale.

For alcohol use, glasses of alcohol consumed per week was used as an outcome. If individuals drank less than 1 glass per week (N = 1,297) their value was put to 0. Individuals who never drank alcohol (N = 87) were excluded from analysis. We deemed it likely that a response of more than 70 glasses per week (N = 7) represented an invalid answer rather than a true estimate; these responses were excluded. In survey 8 and 10 alcohol use was measured continuously; we used the midpoint of the answering categories in survey 7, 6, and 5.

For lifetime cannabis use, participants were asked if they had ever used cannabis (yes/no). This measure was only available for survey 5, 8, and 10.

2.3. Neighborhood characteristics

In the Netherlands postal codes exist of four digits, identifying areas at the level of neighborhoods, and two letters, identifying areas at the level of streets. We linked the four digits of the postal codes to registered neighborhood characteristics from governmental registration systems (Centraal Bureau voor de Statistiek (CBS, 2012). Information was available on urbanicity in addresses/km^2, housing values, percentage of non-western immigrants (% immigrants), monthly income, percentage of inhabitants receiving low income (% low income), percentage receiving high income (% high income), and percentage receiving governmental benefit payments (% benefits; Table 2). For some variables, there were large proportions of missing data on the neighborhood characteristics. We selected variables that had less than 30 % missing data: urbanicity, % immigrants, housing values, and monthly income. We used the automatic multiple imputation procedure in SPSS to complete missing data in these variables. Five imputed datasets were created and merged back to one dataset by averaging the estimations of the missing data points. Because of the conceptual and statistical overlap between the variables we performed principal component analysis (PCA) in SPSS with an oblimin rotation. The PCA yielded two factors (see Table 2) with Eigenvalues of 1.62 and 1.34. The first factor was defined by high urbanicity and a high percentage of non-western immigrants; we dubbed this factor **metropolitanism**. The second factor was defined by housing values and monthly income; this variable was called **socioeconomic status** (SES). The factor solution explained 74 % of the variance in these variables.

2.4. Polygenic scores

Genome-wide single-nucleotide polymorphism (SNP) data for NTR participants were obtained using several genotyping platforms over time (Lin et al., 2017; Willemsen et al., 2010). The genotyping, imputation, and quality control procedures have been described earlier (Abdellaoui et al., 2018; Nivard et al., 2014). PGS were generated with PLINK (version 1.9; Purcell et al., 2007), summing the one- or two risk allele effects of the weighted beta's for each set of summary statistics. The weighted beta's were calculated with LDpred, taking into account the LD structure in the European population to improve prediction (described in detail in Abdellaoui et al., 2018; Vilhjálmsson et al., 2015). PGS can be calculated for several expected fractions of causal genetic markers to further optimize prediction accuracy; we present results for the 30 % fraction, which has shown good results in previous studies on complex behavioral traits (Hugh-Jones et al., 2016; Vilhjálmsson et al., 2015). We used multiple source GWAS to extrapolate our results because the quality and predictive power of summary statistics can differ. Predictive power does not depend solely on sample size, but for example also on the SNP-based heritability, which is the variance explained in the phenotype by the SNP effects in the GWAS (Dudbridge, 2013). For smoking, PGS were created for smoking initiation and for cigarettes per day. The first set was based on GWAS summary statistics from The Tobacco and Genetics Consortium (2010; excluding the NTR, NESDA and GAIN samples) with N = 69,207 and a SNP-based heritability of $h^2_{SNP} = 12$ % for smoking initiation, and N = 35,173, $h^2_{SNP} = 6\%$ for cigarettes per day. The second set was based on GSCAN summary statistics (excluding NTR; N = 1,224,825, $h^2_{SNP} = 8\%$ for smoking initiation and N = 334,609, $h^2_{SNP} = 8\%$ for cigarettes per day; Liu et al., 2019). For alcohol use, PGS were based on a 2017 GWAS on alcohol consumption in glasses per week (N = 112,117, $h^2_{SNP} = 13$ %; Clarke et al., 2017), and the GSCAN GWAS on the same phenotype (excluding NTR; N = 936,196, $h^2_{SNP} = 4\%$; Liu et al., 2019). For cannabis initiation, the PGS was created based on GWAS data on lifetime cannabis use, (excluding NTR; N = 157,664, $h^2_{SNP} = 11$ %; Pasman et al., 2018).

2.5. Covariates

Sex and age were included as covariate. The participants' birth year had a tri-modal distribution due to recruitment of different age groups. Therefore, we created two cohort dummy variables (for 1960- < 1980

Table 2
The neighborhood variables (with their components and measurement levels) for the main and exploratory analyses. For correlations between the original neighborhood variables, refer to Supplemental Table S3.

Analysis	Variable	Comprises original variables	Variable levels	Loadings
Main	Metropolitan factor	urbanicity: addresses/ km^2	*< 500, 500–1000, 1001–1500, 1501–2500, > 2500*	.83
		% non-western immigrants	< 5%, 5–10 %, 11–20 %, 21–40 %, > 40%	.81
	SES factor	housing value	continuous	.90
		average monthly income	continuous	.89
Exploratory	SES index	housing value	continuous	
		average monthly income	continuous	
		% low income	continuous	
		% high income	continuous	
		% receiving governmental benefits payments	continuous	
	Urbanicity	*NA*	*< 500, 500–1000, 1000–1500, 1500–2500, > 2500*	
	% non-western immigrants	*NA*	< 5%, 5–10 %, 11–20 %, 21–40 %, > 40%	

and ≥1980, with < 1960 as the reference category) to correct for cohort effects. To control for stratification within the Dutch population, ten principal components (PCs) based on systematic ancestry differences were included in each analysis that included genetic predictors (models 2 and 3; Abdellaoui et al., 2013). As over time different genotyping platforms were used, dummy variables were included to control for genotype platform stratification (Boomsma et al., 2013).

2.6. Statistical analyses

We tested the effects of the neighborhood factors, PGS, and their interactions using the generalized estimating equations (GEE) procedure in SPSS, controlling for family relatedness. For the binary outcomes, binary logistic GEE was used. Groups of variables were entered in four blocks. We first regressed the substance use outcomes on sex, age, and cohort (model 0), then added neighborhood characteristics (model 1), and then genetic predictors (model 2). In model 3 we added the interaction terms. In a separate GEE analysis, we used the PGS as outcome and the neighborhood variables as predictors to test rGE while controlling for sex, age, cohort, batch (genotyping platform), and principal components. In all analyses we used standardized predictors. We applied a Bonferroni correction for four independent tests for the four outcomes (the PGS based on different discovery GWAS not being strictly 'independent') resulting in a significance threshold of 0.0125.

3. Results

45.3 % of the participants had ever smoked. Current smokers smoked on average 13.9 cigarettes per day and ex-smokers smoked 14.2 cigarettes per day in their period of most heavy smoking. Individuals drank on average 6.1 standard glasses of alcohol per week and 19.3 % of the participants had ever used cannabis. The correlation between the metropolitan factor and SES factor was small ($r = -0.05$, $p < .001$).

3.1. Main effects

Sex, age, and cohort were entered in model 0 (see Supplementary Table S4). Effects of sex were significantly positive for all substances, indicating higher (chance of initiation of) use for males. The association with age was positive for alcohol per week, negative for lifetime cannabis use and not significant for smoking. Younger cohorts were less likely to have smoked and more likely to have used cannabis compared to the cohort born before 1960. The youngest cohort smoked more cigarettes per day than the oldest cohort (although in model 0 this did not survive correction for multiple testing). In model 1–3 there was an indication that the intermediate cohort drank less alcohol than the oldest cohort, but no such effects were observed for the youngest cohort. Variance explained by age, cohort, and sex ranged from 2.4 % for cigarettes per day to 13.6 % for lifetime cannabis use.

The influence of the neighborhood factors on substance use outcomes differed per substance outcome and neighborhood predictor (model 1, Supplementary Table S4). Living in a metropolitan area was associated with higher chances of smoking initiation and higher levels of alcohol consumption, but not with cigarettes per day or cannabis use. Higher SES was related to smoking more cigarettes per day and higher chances of lifetime cannabis use. SES also showed a positive association with smoking initiation, but only in the models that included the genetic predictors (2–3, see Tables 3a and 3b). Variance explained by the neighborhood variables ranged from 0.3 % for smoking initiation to 3.4 % for lifetime cannabis use.

In model 2, the effects of the PGS and genetic covariates were added to the model (Tables 3a and 3b and Supplementary Table S4). The PGS for smoking initiation, cigarettes per day, alcohol per week, and lifetime cannabis use significantly predicted their respective phenotypes, explaining 0.2 % (TAG smoking initiation and GSCAN alcohol per week) to 1.1 % (lifetime cannabis use) of the variance (Tables 3a and 3b).

Table 3a
Results of covariates, neighborhood predictors, genetic predictors, and gene-environment interaction terms (model 3) for the smoking phenotypes using the PGSs based on the GWAS from Tobacco and Genetics Consortium (TAG, 2010), and Liu et al. (GSCAN, 2019). The full results including model 0 (effects of covariates sex, age, and cohort), model 1 (covariates plus neighborhood predictors), and model 2-3 including the parameters for the genetic covariates (batch and 10 PCs) are given in Supplementary Table S4a.

		Smoking initiation *TAG* (*N* = 6471)		Smoking initiation *GSCAN* (*N* = 6471)		Cigarettes/ day *TAG* (*N* = 3096)		Cigarettes/ day *GSCAN* (*N* = 3096)	
Model		OR (SE)	*p*	OR (SE)	*p*	B (SE)	*p*	B (SE)	*p*
2	Sex[a]	1.39 (0.32)	< .001**	1.44 (0.33)	< .001**	2.41 (0.33)	< .001**	2.49 (0.33)	< .001**
	Age	0.99 (0.01)	.385	1.00 (0.02)	.391	0.02 (0.02)	.407	0.01 (0.02)	.558
	Cohort 1960- < 1980[a]	0.34 (0.15)	< .001**	0.33 (0.15)	< .001**	−0.74 (0.62)	.234	−0.97 (0.61)	.111
	Cohort ≥1980[a]	0.16 (0.12)	< .001**	0.16 (0.12)	< .001**	−2.59 (1.02)	.011*	−2.82 (1.00)	.005**
	Metropolitan factor	0.90 (0.10)	.001**	0.91 (0.10)	.001**	0.28 (0.19)	.142	0.32 (0.19)	.089
	SES factor	1.06 (0.12)	.050*	1.06 (0.12)	.030*	0.67 (0.17)	< .001**	0.71 (0.17)	< .001**
	PGS	1.14 (0.13)	< .001**	1.42 (0.17)	< .001**	0.43 (0.17)	.008**	1.37 (0.17)	< .001**
	Model R^2	.125, Δ = .008[b] (Δ_{PGS} = .004)[b]		.152, Δ = .038[b] (Δ_{PGS} = .004)[b]		.040, Δ = .007 (Δ_{PGS} = .002)		.060, Δ = .027 (Δ_{PGS} = .003)	
3	Sex[a]	1.39 (0.32)	< .001**	1.44 (0.33)	< .001**	2.40 (0.33)	< .001**	2.49 (0.33)	< .001**
	Age	0.99 (0.01)	.388	1.00 (0.01)	.389	0.02 (0.02)	.399	0.01 (0.02)	.591
	Cohort 1960- < 1980[a]	0.34 (0.15)	< .001**	0.33 (0.15)	< .001**	−0.73 (0.62)	.238	−0.99 (0.61)	.103
	Cohort ≥1980[a]	0.16 (0.12)	< .001**	0.16 (0.12)	< .001**	−2.57 (1.02)	.011**	−2.84 (0.99)	.004**
	Metropolitan factor	0.90 (0.10)	< .001**	0.91 (0.10)	.001**	0.28 (0.19)	.148	0.32 (0.19)	.082
	SES factor	1.06 (0.12)	.049*	1.07 (0.12)	.030*	0.67 (0.17)	< .001**	0.72 (0.17)	< .001**
	PGS	1.14 (0.13)	< .001**	1.42 (0.17)	< .001**	0.43 (0.16)	.009**	1.38 (0.17)	< .001**
	PGS* metropolitan	0.98 (0.11)	.567	1.00 (0.12)	.984	0.04 (0.15)	.802	0.31 (0.17)	.068
	PGS*SES	0.98 (0.10)	.582	0.98 (0.11)	.475	0.19 (0.16)	.214	0.23 (0.17)	.172
	Model R^2	.125 (Δ < .001)[b]		.153 (Δ = .001)[b]		.040 (Δ < .001)		.061 (Δ = .001)	

Δ = increase in variance explained compared to the previous model; Δ_{PGS} = additional variance explained (with respect to model 1) by the PGS alone; PC = genetic principal components; PGS = polygenic score for the respective substance use outcome.

[a] Reference category for sex was female and for both cohort variables the reference category was < 1960.

[b] For dichotomous outcomes (smoking and cannabis initiation) the Nagelkerke's Pseudo R^2 is reported.

* < .05; ** < .0125 (significant after Bonferroni correction).

3.2. Gene-environment interaction and correlation

One significant GxE effect was observed (model 3, Tables 3a and 3b), between the alcohol PGS based on Clarke et al. (2017) and the SES factor on alcohol per week. SES did not have a main effect on alcohol use. The slope for low SES (-1 SD) was not significantly different from zero (B = -0.20, p = .179), but the slope for high SES (+1 SD) was (B = 0.27, p = .007), indicating that the PGS only had an effect on alcohol use for individuals with a high SES factor.

There was no significant rGE with the neighborhood variables (Table 4). There was unexpected rGE of sex, age, and cohort with different PGS. The positive rGE between cohort and the GSCAN PGS for alcohol per week survived correction for multiple testing.

4. Discussion

We found a negative association between the metropolitan factor and smoking initiation, indicating that chances of smoking initiation were lower in metropolitan areas. This finding follows patterns of higher smoking prevalence in rural areas as reported in some studies (Li et al., 2009) but contradicts those in others (Idris et al., 2007). Possibly, the urban-rural distinction means something different in different studies. For example, what constitutes a rural area in the Netherlands is quite different from that in countries with a lower population density. For cigarettes per day, in turn, there was a positive association with the metropolitan factor, suggesting that smokers in metropolitan areas smoke on average more cigarettes. Possibly, only individuals with a high vulnerability to becoming addicted start smoking in these areas, so that the average amount of smoked cigarettes becomes higher. Urban stress might contribute to these higher smoking levels (Idris et al., 2007). The SES factor showed small positive associations with both smoking variables, which is opposite to the pattern that is commonly reported (e.g., Chuang et al., 2005). This finding might be spurious or might be due to some unique feature of the research population, such as its relatively high age.

Alcohol use was higher in metropolitan areas, which may be due to a higher alcohol outlet density (Kuntsche et al., 2008). In contrast to studies showing positive (Galea et al., 2007) or negative (Karriker-Jaffe et al., 2013) association with neighborhood SES, we did not find an effect of our SES factor on alcohol use. This might be due to our use of an aggregate measure of alcohol consumption. One recent study showed that alcohol use *frequency* (how often someone drinks alcohol) was positively genetically correlated with SES measures, whereas alcohol use *quantity* (how much alcohol is consumed per occasion) was genetically negatively correlated with SES, suggesting these phenotypes represent distinct underlying vulnerabilities (Marees et al., 2019). In a similar vein, we only considered alcohol consumption levels ≤70 glasses per week, with most participants showing moderate alcohol use (M = 6.0 glasses per week). Association patterns for measures of more extreme forms of alcohol use might be quite different (Karriker-Jaffe et al., 2018).

For lifetime cannabis use, there was a significant positive effect of the SES factor, which is in line with some previous findings (Galea et al., 2007) but in contrast with a study in cannabis use disorder (Buu et al., 2009). It appears that different cannabis use phenotypes show different associations with SES measures. Indeed, experimentation with cannabis is higher among people with higher education levels (at least in the Netherlands, Centraal Bureau voor de Statistiek (CBS, 2010).

We confirmed that substance use can be predicted by PGS created based on an independent sample, but the PGS explained only 0.2–1.1 % of the variance in their respective phenotype. Variance explained by PGS is often small, because PGS contain the sum of both true effects and error components. Also, their effect depends on the (SNP-based) heritability of the trait, which is somewhat modest in the case of substance use. The PGS in this study were based on discovery GWAS with varying sample sizes. In general, it is expected that PGS based on larger GWAS would be more powerful (Dudbridge, 2013). Therefore, it is remarkable that the use of a larger discovery GWAS (GSCAN) hardly increased the predictive power of the PGS. It must be noted that the PGS were based on partly overlapping discovery samples; results of PGS based on other

Table 3b
Results of covariates, neighborhood predictors, genetic predictors, and gene-environment interaction terms (model 3) for the alcohol phenotypes using the PGSs based on the GWAS from Tobacco and Genetics Consortium (TAG, 2010), and Liu et al. (GSCAN, 2019) and the cannabis phenotype from the International Cannabis Consortium (ICC). The full results including model 0 (effects of covariates sex, age, and cohort, model 1 (covariates plus neighborhood predictors), and model 2-3 including the parameters for the genetic covariates (batch and 10 PCs) are given in Supplementary Table S4b.

		Alcohol/ week *Clarke* (N = 6174)		Alcohol/ week *GSCAN* (N = 6174)		Cannabis initiation *ICC* (N = 5676)	
Model		B (SE)	p	B (SE)	p	OR (SE)	p
2	Sex[a]	4.17 (0.21)	< .001**	4.19 (0.20)	< .001**	1.65 (0.51)	< .001**
	Age	0.06 (0.01)	< .001**	0.05 (0.01)	< .001**	0.96 (0.02)	< .001**
	Cohort 1960- < 1980[a]	−0.90 (0.37)	.017*	−0.96 (0.37)	.010**	1.66 (1.09)	.002**
	Cohort ≥1980[a]	0.36 (0.55)	.516	0.22 (0.55)	.691	1.55 (1.47)	.062
	Metropolitan factor	0.46 (0.11)	< .001**	0.47 (0.11)	< .001**	1.07 (0.16)	.070
	SES factor	0.13 (0.09)	.167	0.12 (0.09)	.177	1.49 (0.23)	< .001**
	PGS	0.52 (0.09)	< .001**	0.78 (0.09)	< .001**	1.26 (0.20)	< .001**
	Model R^2	.130, Δ = .008 (Δ_{PGS} = .006)		.137, Δ = .015) (ΔPGS = .002)		.189, Δ = .019[b] (Δ_{PGS} = .011)[b]	
3	Sex[a]	4.18 (0.21)	< .001**	4.20 (0.20)	< .001**	1.65 (0.51)	< .001**
	Age	0.06 (0.01)	< .001**	0.05 (0.01)	< .001**	0.96 (0.02)	< .001**
	Cohort 1960- < 1980[a]	−0.90 (0.37)	.016*	−0.97 (0.37)	.010*	1.67 (1.10)	.002**
	Cohort ≥1980[a]	0.35 (0.55)	.517	0.22 (0.55)	.684	1.57 (1.49)	.057
	Metropolitan factor	0.46 (0.11)	< .001**	0.47 (0.11)	< .001**	1.06 (0.17)	.113
	SES factor	0.12 (0.09)	.180	0.12 (0.09)	.182	1.49 (0.23)	< .001**
	PGS	0.52 (0.09)	< .001**	0.77 (0.09)	< .001**	1.26 (0.20)	< .001**
	PGS* metropolitan	−0.03 (0.10)	.798	−0.03 (0.09)	.714	1.05 (0.16)	.182
	PGS*SES	0.23 (0.08)	.005**	0.14 (0.08)	.079	1.01 (0.15)	.836
	Model R^2	.137 (Δ < .001)		.137 (Δ < .001)		.190 (Δ = .001)[b]	

Δ = increase in variance explained compared to the previous model; Δ_{PGS} = additional variance explained (with respect to model 1) by the PGS alone; PC = genetic principal components; PGS = polygenic score for the respective substance use outcome.

[a] Reference category for sex was female and for both cohort variables the reference category was < 1960.

[b] For dichotomous outcomes (smoking and cannabis initiation) the Nagelkerke's Pseudo R^2 is reported.

* < .05; ** < .0125 (significant after Bonferroni correction).

Table 4

a Gene-environment correlation tests with the polygenic scores as outcome and the neighborhood characteristics and covariates as predictors. PGS based on TAG (2010) and GSCAN (2019) for the smoking phenotypes, Clarke (2017) and GSCAN (2019) for alcohol, and ICC (2018) for cannabis. Covariates sex, age, cohort, batch, and PCs were included (parameter estimates for batch variables and principal components are given in Supplementary Table S5). Explained variance is given for the two neighborhood variables (Neigh R^2), the genetic covariates (Gen R^2), and the total model (incl. sex, age and cohort; Model R^2).

		Sex[a]	Age	Cohort2[a]	Cohort3[a]	Metro	SES fac	Neigh R^2	Gen R^2	Model R^2
PGS smoking initiation *TAG* (*N* = 6471)	**B (SE)**	−0.01(0.03)	> -0.01 (< 0.01)	−0.13 (0.05)	−0.16 (0.08)	−0.02 (0.01)	−0.01 (0.01)	< .001	.070	.071
	p	.843	.016*	.015*	.049*	.197	.515			
PGS smoking initiation *GSCAN* (*N* = 6471)	**B (SE)**	−0.06 (0.03)	> -0.01 (< 0.01)	−0.10 (0.06)	−0.16 (0.09)	−0.03 (0.01)	−0.02 (0.01)	.001	.005	.007
	p	.031*	.258	.089	.076	.066	.150			
PGS cigarettes/ day *TAG* (*N* = 3096)	**B (SE)**	−0.08 (0.04)	< 0.01 (< 0.01)	−0.03 (0.08)	0.05 (0.14)	< 0.01 (0.02)	< 0.01 (0.02)	< .001	.009	.009
	p	.039*	.919	.751	.697	.894	.923			
PGS cigarettes/ day *GSCAN* (*N* = 3096)	**B (SE)**	−0.09 (0.04)	0.01 (< 0.01)	0.16 (0.08)	0.19 (0.14)	−0.03 (0.02)	−0.03 (0.02)	< .001	.009	.009
	p	.025*	.104	.034*	.172	.170	.088			
PGS alcohol/ week *Clarke* (*N* = 6174)	**B (SE)**	0.03 (0.03)	< 0.01 (< 0.01)	0.04 (0.06)	0.07 (0.09)	0.02 (0.01)	−0.03 (0.01)	.001	.007	.008
	p	.364	.466	.546	.457	.130	.069			
PGS alcohol/ week *GSCAN* (*N* = 6174)	**B (SE)**	−0.01 (0.03)	0.01 (< 0.01)	0.11 (0.06)	0.23 (0.09)	< 0.01 (0.01)	−0.01 (0.01)	.001	.007	.008
	p	.673	.016*	.068	.010**	.940	.379			
PGS cannabis initiation *ICC* (*N* = 5676)	**B (SE)**	−0.01 (0.03)	> -0.01 (< 0.01)	−0.04 (0.09)	−0.09 (0.09)	0.01 (0.01)	0.01 (0.02)	< .001	.004	.004
	p	.704	.254	.496	.316	.481	.753			

Cohort2 = born between 1960- < 1980, Cohort3 = born ≥ 1980; Gen = genetic covariates (batch and genetic principal components); PGS = polygenic score; Metro = metropolitan factor; SES = socioeconomic status factor.

[a] Reference category for sex was female and for both cohort variables the reference category was cohort1 (born before < 1960).

* p < .05, **p < .0125 (significant after Bonferroni correction).

independent samples might be different. This suggests that future GWAS should not focus solely on increasing sample sizes, but should for example also focus on using homogeneous, reliable phenotype measures (Dudbridge, 2013; Manolio et al., 2009; Wainschtein et al., 2019).

There was an interaction between the PGS based on Clarke et al. (2017) and SES on alcohol use, such that genetic risk only came to expression when neighborhood SES was high. As there was no main effect of SES it is difficult to interpret this finding. Assuming that high SES generally acts as a risk factor for alcohol use (Galea et al., 2007), our GxE finding is in line with diathesis-stress or differential susceptibility frameworks, stating that individuals that are already at risk genetically will react more strongly to environmental risk (Belsky and Pluess, 2009). The only previous study that used PGS to test GxE with neighborhood factors in substance use found indications for GxE in the same direction (Meyers et al., 2013).

However, it needs to be pointed out that this was only one of the 14 tested interactions, and it explained a very small amount of variance in alcohol use (less than 0.1 %). The same interaction did not reach significance when using the GSCAN PGS. This difficulty detecting GxE might be due to the fact that only SNPs that had a main effect on substance use in the GWAS ended up in the PGS, whereas potentially more relevant SNPs for GxE may be those that have an effect on differential susceptibility rather than on substance use per se (Fox and Beevers, 2016). It is also a possibility that GxE effects are different in other (earlier) developmental periods than during one's late forties, which was the average age of our sample (Kendler et al., 2011; Samek et al., 2017). Although we controlled for age and cohort effects, we deemed sample size insufficient to test such three-way interactions. For main and two-way GxE effects power seemed reasonable: assuming an effect size of $f^2 = 0.005$, power was estimated to range between 66–98 % (see Supplementary Table S6), but it is possible that true effects are even smaller. If that is so, GxE might not be as important in the etiology of substance use as has traditionally been predicted. Indeed, a recent review of studies that used polygenic measures of genetic risk showed that the evidence for GxE in substance use is still weak (Pasman et al., 2019). More studies will be needed to establish the robustness of GxE effects in this context.

There was no strong evidence for gene-environment correlation (rGE), although there were some interesting patterns. First, there was small non-significant rGE between SES and the PGS for alcohol use based on Clarke et al. (2017; $p = .069$), which is potentially relevant as there was also gene-environment interaction (GxE) between these variables in the alcohol use analysis. Secondly, there were some unexpected rGE relationships between the covariates and PGS. Although they did not survive correction for multiple testing, there was a pattern of rGE between age/ cohort and the different smoking PGS. These effects might be due to genetic overlap between smoking phenotypes and educational attainment, as education level was higher in the later cohorts ($\chi^2[16] = 2{,}409$, $p < .001$) and for lower ages (b = -0.60, SD = .07, $p < .001$). It might also be the case that the PGS constituted a better measure for risk for smoking behavior in the older cohorts, as they were largely based on GWAS with earlier born participants (Tobacco and Genetics Consortium, 2010; Liu et al., 2019). The negative rGE between sex and the smoking PGS might be spurious or represent an actual gender difference in the genetic architecture of this trait (Gilks et al., 2014). The only rGE that survived correction for multiple testing was between the GSCAN PGS for alcohol per week and cohort, such that being born in 1980 or later was associated with a higher PGS as compared to being born before 1960. Speculatively, this might be due to decreasing alcohol use in western countries in recent years (World Health Organization, 2018). It might be the case that among younger cohorts only vulnerable individuals consume alcohol, which increases the genetic contribution to this phenotype and would result in higher PGS in this group. Regardless of the interpretation, these findings show that rGE might exist, and that these effects have to be taken into account when studying GxE.

4.1. Conclusions

The current study confirmed that substance use was associated with genetic risk and characteristics of the neighborhood. We found some indication for GxE, such that the effect of genetic risk for substance use could be augmented by environmental risk. Furthermore, there were weak indications of rGE effects. More research into the relationships between neighborhood characteristics and substance use outcomes might help to select stronger neighborhood predictors, increasing the chance to detect GxE effects. Furthermore, more attention should be given to possible rGE effects. Knowledge of gene-environment interplay could help prevent genetic vulnerability from coming to expression, providing clues on which people in which neighborhoods will need intervention the most.

Contributors

JAP and JMV conceived of and designed the study. JAP has conducted the data analyses (under supervision of KJHV and JMV) and wrote the manuscript. KJHV and AA calculated the PGS. JJH and IOF were involved in preparing the genetic data for analysis. GW was involved in data management and data linkage. JMV, AA, KJHV, GW, and DIB critically reviewed the report and proposed revisions. All authors approved of the final manuscript.

Role of funding source

Nothing declared.

Declaration of Competing Interest

No conflict declared.

Acknowledgments

Funding for the NTR research was obtained from the Netherlands Organization for Scientific Research (NWO) and MagW/ZonMW [904-61-090, 985-10-002, 912-10-020, 904-61-193,480-04-004, 463-06-001, 451-04-034, 400-05-717], Addiction-31160008, Middelgroot-911-09-032, Spinozapremie 56-464-14192, Center for Medical Systems Biology (CSMB, NWO Genomics), NBIC/BioAssist/RK [2008.024], Biobanking and Biomolecular Resources Research Infrastructure [BBMRI –NL, 184.021.007]. VU University's Institute for Health and Care Research (EMGO+) and Neuroscience Campus Amsterdam (NCA), University Medical Center Groningen, Leiden University Medical Center; the European Science Foundation [ESF, EU/QLRT-2001-01254], the European Community's Seventh Framework Program [FP7/2007-2013], ENGAGE [HEALTH-F4-2007-201413]; the European Science Council [ERC Advanced, 230374], Rutgers University Cell and DNA Repository [NIMH U24 MH068457-06], the Avera Institute, Sioux Falls, South Dakota (USA) and the National Institutes of Health [NIH, R01D0042157-01A, MH081802, Grand Opportunity grants 1RC2 MH089951 and 1RC2 MH08999]). Part of the genotyping and analyses were funded by the Genetic Association Information Network (GAIN) of the Foundation for the National Institutes of Health. Computing was supported by BiG Grid, the Dutch e-Science Grid, which is financially supported by NWO. Statistical analyses were partly carried out on the LISA Cluster computer hosted by*SURF*sara and financially supported by the Netherlands Organization for Scientific Research [NWO project number 480-05-003]. JAP and JMV were supported by ERC starting Grant 284167: 'Beyond the Genetics of Addiction' (principal investigator JMV). KJHV and AA are supported by the Foundation Volksbond Rotterdam. AA is also supported by ZonMw grant 849200011 from The Netherlands Organisation for Health Research and Development.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drugalcdep.2020.107948.

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