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Original investigation

Genetic Vulnerability for Smoking and Cannabis Use: Associations With E-Cigarette and Water Pipe Use

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Abstract

Introduction: Cigarette smoking and cannabis use are heritable traits and share, at least in part, a common genetic substrate. In recent years, the prevalence of alternative methods of nicotine intakes, such as electronic cigarette (e-cigarette) and water pipe use, has risen substantially. We tested whether the genetic vulnerability underlying cigarettes smoking and cannabis use explained variability in e-cigarette and water pipe use phenotypes, as these vaping methods are alternatives for smoking tobacco cigarettes and joints.

Methods: On the basis of the summary statistics of the International Cannabis Consortium and the Tobacco and Genetics Consortium, we generated polygenic risk scores (PRSs) for smoking and cannabis use traits, and used these to predict e-cigarette and water pipe use phenotypes in a sample of 5025 individuals from the Netherlands Twin Register.

Results: PRSs for cigarettes per day were positively associated with lifetime e-cigarette use and early initiation of water pipe use, but only in ex-smokers (odds ratio = 1.43, R^2 = 1.56%, p = .011) and never cigarette smokers (odds ratio = 1.35, R^2 = 1.60%, p = .013) respectively.

Conclusions: Most associations of PRSs for cigarette smoking and cannabis use with e-cigarette and water pipe use were not significant, potentially due to a lack of power. The significant associations between genetic liability to smoking heaviness with e-cigarette and water pipe phenotypes are in line with studies indicating a common genetic background for substance-use phenotypes. These associations emerged only in nonsmokers, and future studies should investigate the nature of this observation.

Implications: Our study showed that genetic vulnerability to smoking heaviness is associated with lifetime e-cigarette use and age at initiation of water pipe use. This finding has implications for the current debate on whether alternative smoking methods, such as usage of vaping devices, predispose to smoking initiation and related behaviors.

Introduction

In recent years, the prevalence of use of non-cigarette tobacco products and vaporizers has risen substantially in western countries. Particularly, water pipe (also known as hookah, shisha, or narghile) and electronic cigarettes (e-cigarettes or e-cigs) have become increasingly popular.[1] These two smoking (vaping) methods have very different backgrounds. Water pipe use dates back to around the 18th century[2] and was typically used in middle-eastern countries by adult males during social gatherings. Recently, this habit has also become common among younger people in western countries and across sexes. Nowadays, bars and lounges where one can smoke water pipes can be found in most cities in Europe and the United States. In contrast, e-cigarettes have appeared on the market only in recent times (see Pepper and Eissenberg[1]) and for different reasons. These electronic devices have been marketed as a way to quit (or as a healthier substitute to) smoking conventional cigarettes. Importantly, however, although e-cigarettes are advertised as a method to overcome dependence on conventional cigarettes, mixed findings have been presented in the literature in this regard, with preliminary evidence also suggesting that e-cigarette use may be a gateway for tobacco cigarettes initiation.[3,4]

Despite the difference in timelines and historical background, these two vaping methods are similar in that they both lead to the inhalation of nicotine, along with some intoxicants contained in regular tobacco cigarettes.[5,6] In addition, both methods can be used to consume different types of (psychoactive) substances, such as cannabis, and although for water pipe it is a known practice, this seems to be an emerging trend for e-cigarettes as well.[7]

Twin studies show moderate-to-high heritability estimates for substance use–related phenotypes, which partly share their genetic makeup (for a review see Agrawal et al.[8]). Heritability estimates for smoking initiation and dependence have been estimated to be 44% and 75%, respectively.[9] For lifetime cannabis use and cannabis dependence, heritability estimates are around 45% and 55%, respectively.[10] Twin studies also indicate that shared genetic influences underlie cannabis and tobacco use (r = .31) and, even more consistently, cannabis and tobacco dependence (r = .56).[11] A genetic risk prediction study have further outlined that polygenic risk scores (PRSs) for cigarette smoking are associated with cannabis use, also suggesting shared common genetic factors.[12] Using results from large genetic consortia, substantial genetic correlations between several substance-use phenotypes, including smoking and cannabis use, were found.[13] Particularly notable in this regard was a genetic correlation of .83 between lifetime cannabis use and smoking initiation.

Similarly, relatively novel addictive behaviors such as e-cigarette and water pipe use might also be heritable and share genetic factors with cigarette smoking and cannabis use. This seems plausible as current cigarette smoking is the strongest predictor of e-cigarette use, as outlined by a recent meta-analysis.[14] There is also evidence that e-cigarette use is associated with cannabis initiation and water pipe use (both among cigarette smokers and nonsmokers[15,16]). Likewise, consistent evidence has linked water pipe use to both cigarettes and cannabis use.[17–19]

A well-established methodology to investigate shared genetic liability between traits is by creating a PRS for one trait, using the estimated effect sizes from a large discovery sample, and then investigate whether this risk score can predict another trait in an independent target sample.[20,21] PRSs represent the genetic load an individual carries regarding a specific trait. In this study, we aimed to determine to what extent the genetic vulnerability to cigarette smoking and cannabis use accounts for the variability in e-cigarette and water pipe use. To this purpose, we used summary-level data from the International Cannabis Consortium (ICC[22]) and the Tobacco and Genetic Consortium (TAG[23]) to generate PRSs in an independent sample of 5025 individuals registered at the Netherlands Twin Register (NTR). We tested the association of PRSs for smoking initiation, cigarettes per day (CPD), and lifetime cannabis use with e-cigarette and water pipe use characteristics. An association of the genetic liability for cigarette smoking and cannabis use with e-cigarettes and water pipe use traits may indicate that there are common underlying genetic predispositions to smoking and vaping.

Methods

Discovery and Target Samples

Summary statistics were derived from the ICC[22] and TAG[23], which reported summary-level statistics of the genome-wide association (GWA) meta-analyses of cigarette and cannabis use phenotypes, respectively. We used summary statistics of two smoking phenotypes from the TAG[23]: (1) smoking initiation, defined as ever versus never been a regular smoker (having smoked ≥100 cigarettes during lifetime versus having smoked fewer than 100 cigarettes during lifetime), and (2) CPD, operationalized as the average or maximum number of CPD (depending on the cohort). The single nucleotide polymorphism (SNP) effects we used were based on the meta-analytic TAG sample minus the NTR and Genetic Association Information Network samples, resulting in sample size of N = 69 207 for smoking initiation and N =35 173 for CPD. In addition, we used the summary statistics of the GWA meta-analysis for lifetime cannabis use (defined as ever versus never used cannabis during lifetime) of the ICC. The SNP effects we used were based on the meta-analytic ICC sample minus the NTR sample, resulting in a sample size of N = 27 677.

The target sample consisted of people registered at the NTR who participated in the 10th wave of the longitudinal survey study for adult participants and have provided a DNA sample.[24–26] In the 10th survey for adult participants (2013–2014), information regarding cigarette smoking and cannabis use as well as e-cigarette and water pipe use was collected in adult twins and their family members of 18 years and older. TAG and ICC summary statistics are publicly available data; NTR data are available through request via the NTR Web site (http://www.tweelingenregister.org/).

Phenotype Data

Smoking status was based on two questions: “Have you ever smoked?” (with answer categories: no; a few times just to try; yes), and “How often do you smoke now?” (with answer categories: I do not smoke regularly; I have quit smoking; I smoke <1 day/week; I smoke a few days per week but not daily; I smoke daily). Answers on these questions were combined and participants were categorized into never-smokers (never smoked, or a few times to try), ex-smokers (ever smoked, but have quit smoking), or current smokers (non-daily and daily smokers). To assess cannabis use, participants were asked the following question: “Have you ever used cannabis? We are referring to hash, weed, marijuana, a joint or space cake” (with answer categories of no; yes, occasionally; and yes, regularly). Lifetime cannabis use was analyzed as a dichotomous variable and coded as 0 = never users versus 1 = ever users.

Questions regarding e-cigarette use and water pipe use were “Have you ever tried one of the following substances, devices, etc.

('yes' or 'no')?", followed by a list including e-cigarettes (with nicotine) and water pipe. If the question was answered affirmatively, the follow-up questions were "at what age for the first time?" and "have you used it in the past year?" (yes or no), and if used in the past year, "how many times?" Phenotypes investigated in this study were lifetime e-cigarette and water pipe use as well as age at initiation of water pipe use (ie, age at which respondent used water pipe for the first time). "Age at initiation" for e-cigarette was not included in the analysis as this product is on the market only for a few years. We also did not include the variable "used in past year" (yes vs. no) for both e-cigarette and water pipe, because it paralleled/overlapped largely with responses on the lifetime use item. The variables "frequency of use in past year" for both e-cigarettes and water pipe were excluded, as the sample sizes for these variables were too small (N = 129 and N = 182, respectively). A flowchart of available data is depicted in Supplementary Figure 1. Complete genotypic data for subjects with water pipe and/or e-cigarette traits and covariates were available for N = 5025 individuals.

Of the total sample, 66.2% individuals were female and the age range was 18–88 years (M = 45, SD = 16). Age at first water pipe was reported by 771 participants, but five individuals reported to have used before they were 10 years old and were set as missing. After individuals were excluded, age at initiation ranged from 11 to 63 years. Age at water pipe use was subsequently split by its median (Mdn = 20) as to reflect early (1) versus late onset (0) water pipe initiation. Also, information on current and past cigarette smoking and on cannabis use was available (see Treur et al.[26]). Sample sizes for all variables are shown in Table 1, and an overview of the mean and median ages per subgroup is presented in Supplementary Table 1.

Polygenic Risk Scores

SNP data were available from genome-wide SNP arrays, collected within the NTR through several projects between 2004 and 2008.[27,28] Genotyping was performed across different platforms, that is, the Perlegen-Affymetrix, Affymetrix 6.0, Illumina 660, and 1M.[29] After pre-imputation quality control (QC, see Abdellaoui et al.[28]), data were cross-platform imputed against a Dutch reference set (Genome of the Netherlands, GONL) so that the SNPs missing per platform could be inferred.[30,31] Stringent post-imputation quality thresholds were used.[32] Only SNPs with an imputation quality score above 0.95 were retained; SNPs were removed if they had a minor allele frequency less than 0.05 or deviated from Hardy–Weinberg equilibrium with p less than .001. Individuals were excluded if their genotype missing rate was greater than 10%, if they had excess genome-wide homozygosity, or if they were of non-Dutch ancestry.[32] All SNPs that survived QC (N = 1 224 793) were used to construct polygenic scores. Detailed information on DNA collection, genotyping, genetic QC, and imputation is available elsewhere.[27,28]

We used SNP effect sizes from the summary statistics to generate PRS for smoking initiation, CPD, and lifetime cannabis use. PRSs were calculated using LDpred,[33] a Bayesian approach that has been shown to have increased predictive accuracy compared to other methods. LDpred computes SNP weights based on their effect size estimates, their linkage disequilibrium (LD) with other SNPs (determined using a reference panel), and the degree of polygenicity of the trait, quantified as the expected fraction of causal markers contributing to the trait. The reference panel used to determine linkage disequilibrium structure consisted of European populations of the 1000 Genomes project. Multiple LDpred risk scores were calculated to optimize prediction accuracy; here we employed eight different

Table 1. Overview of the Number of Users of Alternative Tobacco Products in the Study Sample. For Each Row, the Number of Current Smokers, the Number of Ever-Smokers, and the Number of Cannabis Users Both in Cases (Coded as 0) and Controls (Coded as 1) Are Shown in the Last Six Columns

	Variable	N	No. of cases (%)	No. of current smokers in cases (%)	No. of current smokers in controls (%)	No. of ever-smokers in cases (%)	No. of ever-smokers in controls (%)	No. of ever cannabis users in cases (%)	No. of ever cannabis users in controls (%)
1	Lifetime e-cigarette use (0 = never, 1 = ever use)	4138	194 (4.7)	134 (70.5)	404 (10.5)	169 (88.9)	1320 (34.2)	130 (67.0)	1098 (27.9)
2	Lifetime water pipe use (0 = never, 1 = ever use)	4142	818 (19.7)	177 (22.4)	357 (10.9)	340 (43.0)	1145 (35.1)	505 (62.0)	724 (21.8)
3	Age at initiation of water pipe use (0 > 19, 1 ≤ 19 years)	766	301 (39.3)	76 (26.5)	94 (20.0)	127 (44.3)	188 (41.5)	210 (70.5)	263 (56.7)
4	Lifetime smoking (0 = never, 1 = ever)	4837	1934 (40.0)	610 (31.5)	—	—	—	728 (37.8)	525 (18.2)
5	Current vs. nonsmokers (0 = nonsmokers, 1 = smokers)	4837	610 (12.6)	—	—	—	1324 (31.3)	308 (50.8)	945 (22.5)
6	Lifetime cannabis use (0 = never, 1 = ever)	4989	1301 (26.1)	308 (24.6)	298 (8.4)	728 (58.1)	1196 (33.6)	—	—

Table 2. Associations of Polygenic Risk Scores for Smoking Initiation (Fraction 0.1), Cigarettes Per Day (Fraction 0.01), and Lifetime Cannabis Use (Fraction 0.1), With E-Cigarette/Water Pipe Use Phenotypes for the Total Sample, and for the Sample Stratified for Exposure vs Unexposure to the Covariate of Interest (ie, Ever vs. Never-Smokers, Current vs. Ex- vs. Never-Smokers, and Ever vs. Never Cannabis Users)

	Total sample			Exposed			Unexposed		
	N	Odds ratio	*p*	*N*	Odds ratio	*p*	*N*	Odds ratio	*p*
PRS smoking initiation					Ever-smokers			Never-smokers	
Lifetime e-cigarette use	4050	0.98	.839	1489	1.00	.981	2561	0.81	.390
Lifetime water pipe use	4052	0.96	.418	1485	0.93	.316	2567	1.00	.992
Age at initiation water pipe use	740	1.03	.771	315	1.00	.998	425	1.03	.809
PRS CPD					Current smokers			Nonsmokers (ex-/never-smokers)	
Lifetime e-cigarette use	4050	1.20	**.022**	538	1.17	.136	951/2561	1.43/1.03	**.011***/.888
Lifetime water pipe use	4052	0.96	.438	534	0.98	.844	951/2567	0.94/0.96	.505/.450
Age at initiation water pipe use	740	1.16	.098	170	0.84	.379	145/425	1.10/1.35	.638/**.013***
PRS lifetime cannabis use					Ever cannabis users			Never cannabis users	
Lifetime e-cigarette use	4128	1.14	.139	1228	1.08	.456	2900	1.21	.184
Lifetime water pipe use	4132	0.97	.552	1229	1.03	.611	2903	0.92	.245
Age at initiation water pipe use	762	1.10	.234	473	1.13	.249	289	1.17	.262

CPD = cigarettes per day, PRS = polygenic risk scores.
Bold: $p < .05$; *$p < .017$ (Bonferroni correction 0.05/3)

fractions for causal markers (0.0001, 0.0003, 0.001, 0.003, 0.03, 0.01, 0.1, and 1), representing the expected degree of polygenicity in the trait (eg, 0.01 = 1%). The computed PRSs were standardized.

Statistical Analysis

Prediction analyses were carried out using generalized estimation equations with a logit link function. To account for familial relatedness, this method uses an exchangeable covariance matrix, allowing for correlated residuals between family members.[34] Analyses were run using robust standard errors for the parameter estimates. Sex, age, and 10 genetic principal components were included as covariates in all analyses. Principal components were included to correct for effects of population stratification. Depending on which PRS we analyzed (smoking initiation, CPD, or lifetime cannabis use) the corresponding phenotypic trait was controlled for in analyses: either ever versus never cigarette smokers, current cigarette smokers versus ex-smokers versus never-smokers, or ever versus never cannabis use, respectively. Subsequently, analyses were carried out separately for these groups in order to test whether genetic liability was differentially expressed. Estimates of the explained variance (Nagelkerke's pseudo-R^2) were obtained from logistic regressions by subtracting the pseudo-R^2 estimates of the model with covariates only from those including PRSs. Analyses were performed in SPSS version 22.

Results

Prevalence

Approximately 5% of the sample reported to have used e-cigarettes in their lifetime, whereas up to 20% reported to have tried water pipe at least once (Table 1). The mean age of first water pipe use was 24.0 years (SD 9.6, Mdn = 20). The mean age of first e-cigarettes use was much higher (35.4, SD = 13.1, Mdn = 34, mean age when completing the survey 37.3 [SD = 13.3]) because e-cigarettes have been only available on the market for a limited number of years. In 76.8% of the e-cigarette users, the difference between their age at first use and their current age is 2 years or less.

The prevalence of lifetime e-cigarette and water pipe use was higher in current cigarette smokers (25% and 33%, respectively) than in ex-smokers (4% and 17%) and never-smokers (1% and 17%). Likewise, lifetime cannabis users were more likely to have ever tried e-cigarettes (11%) and water pipe (41%) compared to never cannabis users (2% and 11% respectively). Of the total sample, 1.9% of individuals had used both e-cigarette and water pipe at least once in their life.

Associations of PRSs With Their Corresponding Traits

Associations of the PRSs with the corresponding traits (eg, PRSs for smoking initiation with smoking initiation) were tested to find the fraction with the highest prediction accuracy (ie, highest variance explained), which would then be used in our main analyses (see Vilhjálmsson et al.[33]). PRSs for smoking initiation were significantly associated with smoking initiation at all fractions above 0.001 with the highest variability accounted for by the 0.1 fraction (as well as the 1 fraction, because they were 100% correlated). Likewise, PRSs for CPD were significantly associated with smoking heaviness (CPD) at all fractions above 0.0001, with the highest variability explained by the 0.01 fraction. Finally, the PRSs for lifetime cannabis use showed significant associations with lifetime cannabis use at all fractions above 0.0003, with the highest variability accounted for by the 0.1 fraction (as well as the 1 fraction). Supplementary Figure 2 in Supplementary Material depicts variance explained by all PRSs. Later (Table 2) we report association tests for PRSs based on the 0.1 fraction for smoking initiation and lifetime cannabis use, and on the 0.01 fraction for CPD, as these showed the highest predictive accuracy with the corresponding traits. Bivariate correlations between these PRSs fractions showed significant positive associations between PRS for smoking initiation and PRS CPD ($r = .03$, $p < .05$), and between PRS for smoking initiation and PRS for lifetime cannabis use ($r = .09$, $p < .0001$), but not between PRS CPD and PRS for lifetime cannabis use ($r = -.01$, $p > .05$).

Association of PRS for Smoking Initiation With E-Cigarette and Water Pipe Use

No significant associations were evident between PRS for smoking initiation (fraction 0.1) and any of the three phenotypes considered (Table 2). This null finding was also consistent across other fractions

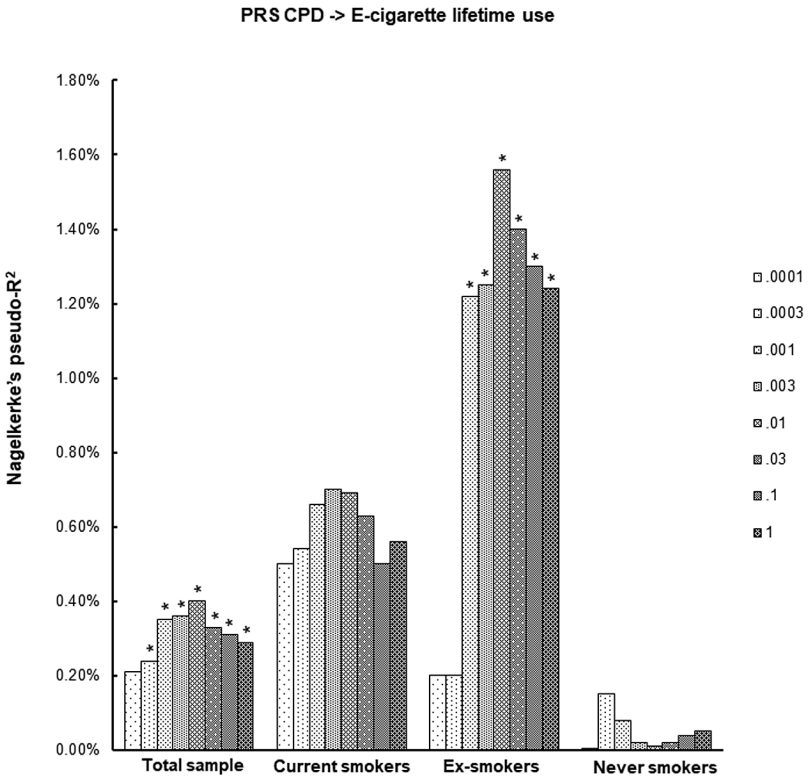

Figure 1. Associations of polygenic risk scores (PRSs) for cigarettes per day (CPD) with lifetime e-cigarette use in the total sample ($N = 4050$) and stratified for current smokers ($N = 538$) vs. ex-smokers ($N = 951$) vs. never-smokers ($N = 2561$). Polygenic scores were calculated for eight different fractions of causal markers, ranging from 0.0001 to 1. *$p < .05$.

(Supplementary Tables 2–4). This was true also when the sample was stratified for lifetime cigarette smoking (ie, ever vs. never cigarette smoking).

Association of PRS for CPD With E-Cigarette and Water Pipe Use

We found positive associations between PRS for CPD and lifetime e-cigarette use, indicating that individuals with a higher genetic predisposition for smoking more CPD were more likely to have ever tried e-cigarettes (fraction 0.01: odds ratio [OR] = 1.20, $R^2 = 0.40\%$, $p = .022$; see Table 2). This trend was observed for all the fractions above 0.0003 ($.022 < p < .042$, Figure 1; Supplementary Table 5), with the risk scores explaining a maximum of 0.40% of the variance in lifetime e-cigarette use. When the sample was stratified for current versus ex-smokers versus never (cigarette) smokers, this association seemed to be only significant in ex-smokers (OR = 1.43, $R^2 = 1.56\%$, $p = .011$) and not in current smokers (OR = 1.17, $R^2 = 0.69\%$, $p = .136$) nor in never-smokers (OR = 1.03, $R^2 < 0.01\%$, $p = .888$).

No significant associations were observed between PRS for CPD (fraction 0.01) and lifetime water pipe use or age at initiation of water pipe use (Table 2 and Supplementary Tables 6 and 7). However, when the sample was stratified for current versus ex- versus never (cigarette) smokers, a positive association emerged between PRS for CPD and age at initiation of water pipe in never-smokers only (OR = 1.35, $R^2 = 1.60\%$, $p = .013$, Table 2). The results across all fractions (see Supplementary Table 7 and Figure 2) indicate that the PRS explained up to 1.90% of the variance in age at initiation of water pipe use.

Association of PRS for Lifetime Cannabis Use With E-Cigarette and Water Pipe Use

No significant associations were evident between the PRS (fraction 0.1) for lifetime cannabis use and any of the phenotypes considered, even when the sample was stratified for lifetime cannabis use (ie, ever vs. never cannabis use; Table 2). However, when considering the lowest fractions (fraction 0.001 and smaller, see Supplementary Table 8), a significant positive association with early initiation of water pipe was evident in the total sample. This, indicated that the higher the genetic predisposition to lifetime cannabis use, the more likely an individual was to start using water pipe at an early age, with the strongest association at fraction 0.0003 (OR = 1.21, $R^2 = 0.85\%$, $p = .018$). When analyses were stratified for lifetime cannabis use, the association only held for those who never used cannabis (fraction 0.0003, OR = 1.50, $p = .008$), with up to 2.89% of variance explained by the lowest PRSs fractions. See also Supplementary Tables 9 and 10 for results across all fractions and Supplementary Tables 11–19 for descriptive statistics of the PRSs per groups.

Discussion

In this study, we examined whether the genetic liability underlying cigarette smoking and cannabis use explained variability in e-cigarette and water pipe use. Only the genetic liability for number of CPD was significantly associated with lifetime e-cigarette use and with early water pipe initiation. This finding is in line with other studies indicating a common genetic background for substance-use phenotypes[8] and consistent with evidence suggesting that different smoking methods tend to co-occur. However, we did not find

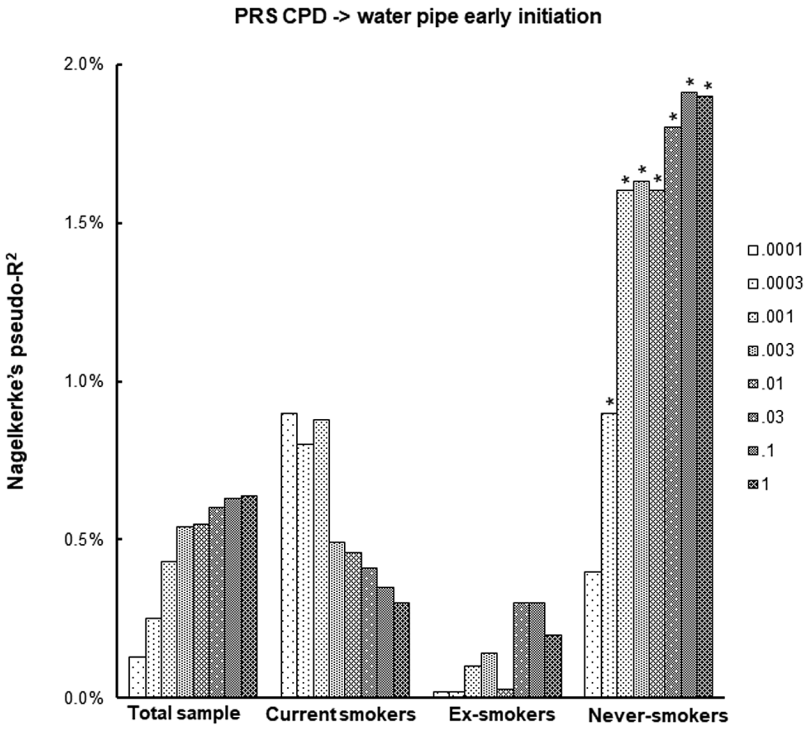

Figure 2. Associations of polygenic risk scores (PRSs) for cigarettes per day (CPD) with age at initiation of water pipe use in the total sample (N = 740) and stratified for current smokers (N = 170) vs. ex-smokers (N = 145) vs. never-smokers (N = 425). Polygenic scores were calculated for eight different fractions of causal markers, ranging from 0.0001 to 1. *p < .05.

significant associations between genetic vulnerability for smoking initiation or cannabis use with the use of e-cigarettes. Interestingly, the association between the PRS for CPD with alternative smoking methods seems to hold only in ex-smokers for e-cigarettes and only in never smokers for early water pipe initiation. The explanation for this observation is unclear. We could speculate that these associations might in fact underlie an overall vulnerability for addictive, smoking-related, behaviors. Although in (tobacco cigarette) smokers this predisposition leads to smoking more CPD (compared to individuals with a low genetic predisposition for CPD), in nonsmokers such genetic liability may find its expression in alternative smoking methods (ie, use of e-cigarettes in ex-smokers and early initiation of water pipe use in never-smokers). The same pattern was also observed in never cannabis users with a higher genetic vulnerability for cannabis use having higher odds to use water pipe, although only for the smallest PRSs fractions. Both cigarettes and the alternatives (e-cigarettes, water pipe) often contain nicotine, and from large genetic studies to cigarette smoking, it is clear that genetic variation in nicotine acetylcholine receptors is strongly associated with the number of CPD.[23] This set of genes could also be involved in addictive, smoking-related behaviors such as e-cigarette or water pipe use.

The observed associations could also reflect a more general personality trait, such as impulsivity, risk-taking behavior, or sensation-seeking, which are often associated with substance-use and addictive behavior.[35–39] Other behavioral traits, for example gambling, risky sexual behavior, and mental health traits (conduct disorder, antisocial behavior), are likely also related to this "personality profile," which may have a common genetic basis. For example, the *CADM2* gene is associated with lifetime cannabis use[40] but is also associated with risk behavior,[41] alcohol use,[42]and personality.[43] Other mechanisms may also play a role, such as epigenetic factors or environmental factors.

Variance explained by the PRSs was generally low (varying from 0.37% to 2.89%), but consistent with other PRS studies of addictive phenotypes.[12,44,45] Explained variance is expected to increase as GWAS sample sizes grow. No associations were found for the PRS for smoking initiation with any of the outcome variables, with the exception of a single significant association at fraction 0.001, which may be a false positive. These overall nonsignificant associations for the PRS for smoking initiation are in line with previous findings in a partly overlapping sample,[12] in which the PRS for smoking initiation was not a good predictor of other substance-use phenotypes.

Previous research indicated that exposure to cigarette smoking or cannabis might causally influence e-cigarette or water pipe use,[14,17] with some studies also pointing to reverse causation (eg, e-cigarette use leading to cigarettes smoking, see also Bunnell et al.[3] and Fielder et al.[18]). It is likely that our findings represent both (environmental) causality and shared genetic liability. On the one hand, we found associations between genetic vulnerability to CPD and e-cigarette use in ex-smokers, which seems to suggest a causal link between smoking and e-cigarette use. On the other hand, the association of PRSs for CPD with age at initiation of water pipe use in never-smokers seems to indicate a shared genetic architecture underlying these traits.

Several limitations should be taken into account when considering these results. First, in some instances statistical power may have been limited (especially after stratifying for smoking status or lifetime cannabis use), which may explain the many null findings in our article. Power analyses for the nine main analyses are provided in the Supplementary Material. Estimated statistical power varied considerably between the different discovery and target traits (due to differences in sample size, and prevalence rates of case–control traits) and was also largely dependent on the estimated genetic correlation between the discovery and target trait as well as the SNP-based

heritability estimates of these traits. For this reason, we also had to exclude continuous measures of frequency of use in the past year, as the sample size for these variables precluded power for meaningful statistical testing. Second, we generated PRSs using summary-level data from the TAG and ICC meta-analyses, which are the largest GWA meta-analyses for smoking and cannabis phenotypes to date. However, increased accuracy in the estimation of SNPs effect sizes may be derived by even larger discovery sets in the future.[46] Overall, larger discovery sets, better phenotyping, and novel statistical methods may help overcoming the present limitations.

This is the first study exploring whether genetic vulnerability underlying cigarette smoking and cannabis use might explain variability in e-cigarette and water pipe phenotypes. The majority of associations of PRSs for cigarette smoking and cannabis use with e-cigarette and water pipe use were not significant. The significant associations are in line with studies indicating a common genetic background for substance-use phenotypes. Future studies should investigate the etiology of this observation. Given the exploratory nature of this study, the present findings must be considered as preliminary rather than conclusive.

Supplementary Material

Supplementary data are available at *Nicotine and Tobacco Research* online

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Declaration of Interests

No competing interests from part of the first author or any of the co-authors are noted. The authors had full access to all of the relevant data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. The sponsors of this study did not exert any editorial influence over the written text.

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