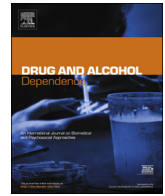




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Short communication

## Causal relationships between substance use and insomnia

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## ABSTRACT

**Background:** Poor sleep quality and insomnia have been associated with the use of tobacco, alcohol, and cannabis, but it is unclear if there is a causal link. In this Mendelian Randomization (MR) study we examine if insomnia causes substance use and/or if substance use causes insomnia.

**Methods:** MR uses summary effect estimates from a genome-wide association study (GWAS) to create a genetic instrumental variable for a proposed 'exposure' variable and then identifies that same genetic instrument in an 'outcome' GWAS. Using GWASs of insomnia, smoking (initiation, heaviness, cessation), alcohol use (drinks per week, dependence), and cannabis initiation, bi-directional causal effects were tested. Multiple sensitivity analyses were applied to assess the robustness of the findings.

**Results:** There was strong evidence for positive causal effects of liability to insomnia on all substance use phenotypes (smoking traits, alcohol dependence, cannabis initiation), except alcohol per week. In the other direction, there was strong evidence that smoking initiation increased insomnia risk (smoking heaviness and cessation could not be tested as exposures). We found no evidence that alcohol use per week, alcohol dependence, or cannabis initiation causally affect insomnia risk.

**Conclusions:** There were unidirectional effects of liability to insomnia on alcohol dependence and cannabis initiation, and bidirectional effects between liability to insomnia and smoking measures. Bidirectional effects between smoking and insomnia might give rise to a vicious circle. Future research should investigate if interventions aimed at insomnia are beneficial for substance use treatment.

### 1. Introduction

Insomnia (trouble falling and/or staying asleep) is associated with substance use, including alcohol, nicotine, and cannabis use. Worldwide, individuals drink on average a glass of alcohol per day. A fifth of US and European adults smoke (World Health Organization (WHO, 2016a), and a quarter to half of them have tried cannabis (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2011). Both insomnia (Bin et al., 2012) and substance use (World Health Organization (WHO, 2016b, 2017, 2018) have serious consequences for health and well-being. Insight into the etiological processes underlying these associations might provide clues for prevention and intervention.

Alcohol, nicotine, and/or cannabis use have been associated with increased prevalence of insomnia (Angarita et al., 2016; Sabanayagam and Shankar, 2011). These comorbidities may reflect overlapping genetic etiology and/or causal relationships. For smoking, previous studies showed a genetic correlation with insomnia (Gibson et al., 2018;

Jansen et al., 2019). As for causal relationships, experimental studies have investigated the acute effects of substance use on insomnia. Alcohol use shortened sleep onset latency, but led to sleep disruptions in the second half of sleep (Ebrahim et al., 2013). Cannabis intake likewise resulted in reduced sleep onset latency, but the effects of cannabis on sleep quality were less clear (Babson et al., 2017). Although smokers often cite its relaxing effects, nicotine intake was found to actually disturb sleep (Irish et al., 2015). Reversed causation -from insomnia to substance use- may also play a role. For example, adolescents with low sleep quality have shown a stronger inclination for later substance use (Hasler et al., 2016), although strong causal inferences cannot be made based on observational designs.

Mendelian Randomization (MR) can be used for causal inference in complex relationships (Lawlor et al., 2008). A previous MR study found that insomnia increased smoking heaviness and decreased chances of cessation and found no effects in the other direction (Gibson et al., 2018). We extend this work by using genetic data from the largest GWASs to date to examine genetic correlations and causal associations

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**Table 1**

Sources of the genome-wide association summary statistics used for the two-sample MR, the number of SNPs in the IVW exposure instrument (being the independent lead SNPs as reported in the source GWAS that were also present in the outcome SNP set, #exposure SNPs), the variance explained in the respective phenotype by these instrument SNPs (Instrument  $R^2$ ), and the genetic correlation of each substance use trait with insomnia ( $r_g$ ) with its associated  $p$ -value. For the computation of  $r_g$  we used the full GWAS summary statistics except for insomnia, where 23andMe participants were excluded.

Phenotype	Source	Sample	#exposure SNPs <sup>a</sup>	Instrument $R^2$	$r_g$ , SE ( $p$ )
Insomnia	Jansen et al. (2019)	excl. 23 <sup>nd</sup> Me N = 386,533	248	0.89 %	NA
Smoking initiation	Liu et al. (2019)	excl. UKB* N = 848,460	360	1.16 %	.23, .02 (2.09E-23)
Smoking heaviness	Liu et al. (2019)	excl. UKB N = 143,210	NA <sup>a</sup>	NA <sup>a</sup>	.27, .03 (5.42E-17)
Smoking cessation	Liu et al. (2019)	excl. UKB N = 216,590	NA <sup>a</sup>	NA <sup>a</sup>	.28, .04 (5.56E-12)
Alcohol per week	Liu et al. (2019)	excl. UKB N = 630,154	91	0.59 %	.03, .02 (.029)
Alcohol dependence	Walters et al. (2018)	N = 46,568	8	0.36 %	.29, .07 (1.42E-5)
Cannabis initiation	Pasman et al. (2018)	excl. UKB N = 57,980	32 <sup>b</sup>	1.33 %	.04, .03 (.205)

\* UKB = UK Biobank.

<sup>a</sup> The effect of smoking heaviness and cessation on insomnia could not be tested because the insomnia GWAS could not be stratified on smoking status.

<sup>b</sup>  $p < 1e05$ .

between insomnia and substance use, including alcohol and cannabis use.

## 2. Materials and methods

First, we estimated genetic correlations between insomnia and substance use with LDscore regression (Bulik-Sullivan et al., 2015). Second, we used MR to test for causal effects of insomnia on substance use and vice versa. We used the Two-Sample MR R-package (Hemani et al., 2018) with GWAS summary statistics from non-overlapping samples (Table 1). The rationale behind MR is that genetic variants are randomly distributed in the population and therefore not affected by confounders. This makes them suited as instrumental variables to test causal effects of an 'exposure' on an 'outcome'. Assumptions underlying MR are that the genetic instruments predict the exposure robustly (1) and are not independently associated with confounders (2) or the outcome (3). The latter two assumptions could be violated in case of horizontal pleiotropy (where one genetic variant directly affects multiple traits).

Insomnia cases were people that reported they 'usually' had trouble falling asleep at night or often woke up in the middle of the night; controls 'never/rarely' or 'sometimes' experienced this. Smoking initiation was defined as ever having smoked regularly (yes/no), smoking heaviness as cigarettes smoked per day, smoking cessation as having quit smoking (yes/no), and alcohol per week as the number of standard drinks consumed per week. Alcohol dependence (yes/no) was based on clinician's diagnosis or on a semi-structured interview based on DSM-IV criteria. Cannabis initiation was defined as ever having used cannabis (yes/no). For the genetic instruments we selected independent SNPs that were genome-wide significantly associated with the exposure variable in the source GWAS ( $p < 5E-8$ ; Table 1). For cannabis initiation there were only 2 genome-wide significant variants after excluding the UK Biobank sample, so for this phenotype we included SNPs that reached a 'suggestive' threshold of  $p < 1E-5$ . Smoking heaviness and cessation could not be used as exposures, as the insomnia summary statistics could not be stratified on smoking status. Instrument strength was estimated by summing the variance explained ( $R^2$ ) by each independent instrument SNP in the exposure (Table 1).

The main analysis was an inverse-variance weighted (IVW) meta-analysis of the SNP-outcome association divided by the SNP-exposure association for each SNP. Sensitivity analyses were used to assess the robustness of the IVW findings against violation of the MR assumptions. Weighted median and weighted mode regression correct for effect size outliers that could represent pleiotropic effects (Hartwig et al., 2017). MR-Egger regression provides an intercept that indicates the presence of pleiotropy, and adjusts the regression coefficient for such effects (Bowden et al., 2015). MR-Egger relies on the NO Measurement Error (NOME) assumption, violation of which can be tested with the  $I^2$ -

statistic. When  $I^2$  was between 0.6 and 0.9, simulation extrapolation (SIMEX) was used to correct the MR-Egger for NOME violation; if  $I^2$  was below 0.6 MR-Egger was not reported (Bowden et al., 2016). We also applied Generalised summary-data-based MR (GSMR), which gains statistical power by taking low levels of linkage disequilibrium between the included SNPs into account, and deletes effect size outliers. Using Steiger filtering, MR analyses were repeated excluding SNPs that explained more variance in the outcome than the exposure, and again retaining only SNPs that explained significantly ( $p < .05$ ) more variance in the exposure (to rule out reverse causation; Hemani et al., 2017). Cochran's Q-statistic was used to assess SNP effect heterogeneity (Bowden et al., 2018) and the F-statistic for weak instrument bias (Burgess and Thompson, 2011). Finally, leave-one-out IVW analyses were used to give an indication of disproportional effects of single SNPs (Hemani et al., 2018). Rather than assessing the strength of the statistical evidence by  $p$ -values only, we also consider the effect sizes across the IVW and sensitivity analyses to inform our interpretation.

## 3. Results

There were moderate genetic correlations between the insomnia GWAS and all substance use GWASs except alcohol per week (small overlap) and cannabis initiation (no significant overlap; Table 1).

### 3.1. Insomnia to substance use

The IVW analyses showed strong evidence for causal effects of liability to insomnia on all substance use traits except alcohol use per week (Table 2). For all analyses except insomnia-on-cannabis initiation there was evidence for SNP-effect heterogeneity, although leave-one-out analyses did not show the effects were driven by a single SNP (Figures S1-S6). The insomnia instrument had low explained variance, but did not suffer from weak instrument bias ( $F > 10$ ).  $I^2$ ,  $F$ , and  $Q$  statistics are presented in Table S1. The effect of insomnia on substance use retained similar effect sizes across the weighted mode, median, and GSMR analyses (although effect estimates became less precise). MR-Egger results were not reported because the  $I^2$  statistic was below 0.6. For smoking and alcohol use per week outcomes the proportion of SNPs that explained more variance in the outcome than in insomnia varied from 5.4–20.6 % (Table S2). The Steiger-filtered IVW with those SNPs excluded showed only slightly attenuated effect sizes. However, when retaining only SNPs that significantly explained more variance in insomnia than in the outcome, strong evidence remained only for an effect on smoking initiation. For alcohol dependence (36.0 %) and cannabis initiation (25.4 %) large proportions of SNPs explained more variance in the outcome than in the exposure. Filtering those out led to substantial attenuation of effects (Table 2).

**Table 2**  
Results for the MR analyses with the IVW representing the main analysis and the remaining representing the results for the sensitivity analyses.

	insom > smok init	insom > smok heav	insom > smok ces	insom > alc week	insom > alc dep	insom > can init	smok init > insom	alc week > insom	alc dep > insom	can init > insom
<b>IVW</b>	205	204	205	205	203	201	316	78	5	28
<b>N<sub>SNPs</sub></b>	0.13 (0.02)	0.11 (0.02)	-0.08 (0.02)	-0.01 (4.29E-3)	0.16 (0.04)	0.18 (0.06)	0.11 (0.03)	0.12 (0.13)	0.05 (0.05)	7.43E-4 (0.01)
<b>beta (SE)</b>	NA	NA	NA	NA	1.18 (0.09)	1.20 (0.14)	0.11 (0.06)	1.13 (0.25)	1.05 (0.09)	1.00 (0.02)
<b>OR (SE)</b>	1.58E-12	1.67E-12	6.37E-8	115	5.43E-5	.003	3.68E-5	.349	.292	.937
<b>p-value</b>	205	204	205	205	203	201	316	78	5	28
<b>N<sub>SNPs</sub></b>	0.08 (0.02)	0.08 (0.02)	-0.07 (0.02)	-0.01 (4.95E-3)	0.19 (0.06)	0.16 (0.09)	0.11 (0.04)	0.09 (0.19)	0.04 (0.06)	-2.47E-3 (0.01)
<b>beta (SE)</b>	NA	NA	NA	NA	1.21 (0.14)	1.17 (0.19)	1.11 (0.08)	1.10 (0.34)	1.05 (0.11)	1.00 (0.03)
<b>OR (SE)</b>	3.70E-7	1.41E-5	6.42E-4	.263	1.64E-3	.086	3.79E-3	.624	.456	.866
<b>p-value</b>	204	204	205	205	203	201	316	78	5	28
<b>N<sub>SNPs</sub></b>	0.10 (0.03)	0.07 (0.04)	-0.08 (0.04)	-0.01 (9.80E-3)	0.28 (0.13)	0.20 (0.18)	0.10 (0.11)	0.09 (0.46)	0.04 (0.08)	3.25E-3 (0.01)
<b>beta (SE)</b>	NA	NA	NA	NA	1.32 (0.29)	1.22 (0.35)	1.11 (0.21)	1.10 (0.65)	1.04 (0.15)	1.00 (0.03)
<b>OR (SE)</b>	4.15E-4	.060	.059	.470	.031	.246	.354	.843	.634	.816
<b>p-value</b>	194	200	201	200	202	200	306	71	28	28
<b>N<sub>SNPs</sub></b>	0.11 (0.01)	0.09 (0.01)	-0.07 (0.01)	-0.01 (3.15E-3)	0.13 (0.04)	0.16 (0.06)	0.11 (0.02)	0.10 (0.13)	0.02 (0.04)	-3.70E-3 (8.60E-3)
<b>beta (SE)</b>	NA	NA	NA	NA	1.14 (0.04)	1.17 (0.07)	1.12 (0.03)	1.11 (0.13)	1.02 (3.76E-3)	1.00 (0.01)
<b>OR (SE)</b>	5.00E-26	4.08E-14	2.92E-7	.076	8.85E-4	.012	3.29E-5	.424	.703	.671
<b>p-value</b>	181	169	194	191	130	150	305	69	5	28
<b>N<sub>SNPs</sub></b>	0.11 (0.02)	0.09 (0.01)	-0.08	-0.01 (3.84E-3)	0.08 (0.04)	0.13 (0.06)	0.10 (0.03)	0.11 (0.13)	0.05 (0.05)	7.43E-4 (0.01)
<b>beta (SE)</b>	NA	NA	NA	NA	1.09 (0.04)	1.14 (0.07)	1.10 (0.06)	1.12 (0.25)	1.05 (0.09)	1.00 (0.02)
<b>OR (SE)</b>	9.02E-12	1.09E-11	4.49E-8	.091	.055	.046	2.92E-4	.388	.292	.937
<b>p-value</b>	74	28	60	90	0	1	143	30	5	28
<b>N<sub>SNPs</sub></b>	0.07 (0.01)	0.03 (0.02)	-0.03 (0.02)	-3.02E-3 (3.58E-3)	0.02 (0.03)	0.02 (0.03)	0.02 (0.03)	0.11 (0.13)	0.05 (0.05)	7.43E-4
<b>beta (SE)</b>	NA	NA	NA	NA	1.02 (0.07)	1.02 (0.07)	1.02 (0.07)	1.12 (0.25)	1.05 (0.09)	1.00 (0.02)
<b>OR (SE)</b>	5.65E-07	0.134	0.052	0.398	0.641	0.641	0.641	0.388	0.292	0.937
<b>p-value</b>										

Odds ratios are given for binary outcomes (note that smoking initiation and cessation were not binary because in the summary statistics they were rescaled to SD units).

Abbreviations: insominitis; smok init/smoking initiation; smok heav/smoking heaviness; smok ces/smoking cessation; alc week/alc use per week; alc dep/alc dependence; can init/cannabis initiation; IVWinverse variance weighted meta-analysis; ORodds ratio; GSMRgeneralised summary-data-based Mendelian randomization; NSNPs number of SNPs that was retained in the analyses after filtering for high LD, palindromic, and ambiguous SNPs, with additional HEIDI filtering in the GSMR and filtering for pleiotropic SNPs in the Steiger analyses.

<sup>a</sup> MR-Egger was not reported because I<sup>2</sup> was below 0.6.

<sup>b</sup> SIMEX-corrected MR-Egger is reported because I<sup>2</sup> was > .06 and < .09.

<sup>c</sup> GSMR was not performed for the alcohol dependence to insominitis analysis as there were too few SNPs.

<sup>d</sup> The IVW after Steiger filtering, i.e. after filtering out all SNPs that explained more variance in the outcome than in the exposure; see also Table S2.

<sup>e</sup> The IVW after keeping only those SNPs that explained more variance in the exposure than in the outcome; see also Table S2.

### 3.2. Substance use to insomnia

The IVW analyses showed a causal effect of smoking initiation on insomnia risk, and no effects of other traits. In the weighted median, mode, and GSMR sensitivity analyses the effect size of smoking initiation was roughly equal, although statistical evidence was slightly weaker (substantially weaker in the weighted mode). Smoking initiation-on-insomnia was the only analysis with sufficiently high  $I^2$  to allow for MR-Egger intercept interpretation, showing no evidence for pleiotropy ( $p = .347$ ), although the MR-Egger estimate was substantially attenuated. Less than 4% of the instrument SNPs explained more variance in insomnia outcome than in smoking initiation (Table S2). Filtering those out hardly changed results, although retaining only SNPs that explained significantly more variance in the exposure did attenuate the effects (Table 2). There was no evidence for heterogeneity or weak instrument bias (Table S1, Figures S7-S10).

## 4. Discussion

There were moderate genetic correlations between insomnia and smoking traits and alcohol dependence, such that insomnia was genetically associated with higher levels of substance use. The genetic correlation with alcohol per week was small but significant, and there was no significant correlation with cannabis initiation.

Overall, we found more evidence for causal effects from liability to insomnia to substance use than vice versa. MR results suggest that insomnia leads to heavier smoking, increased chances of smoking initiation, alcohol dependence, and cannabis initiation, and decreased chances of smoking cessation. The finding that insomnia caused heavier smoking and lowers chances of smoking cessation confirms results from Jansen et al. (2019) and Gibson et al. (2018) on smoking. As a possible interpretation, a desire to smoke may be induced by sleep deprivation (Hamidovic and de Wit, 2009). The causal effects of insomnia on alcohol use may be interpreted in light of a self-medication framework, as alcohol has somnolent properties (Goodhines et al., 2019). For cannabis the same reasoning might apply, although this interpretation seems more likely for a measure of cannabis use frequency rather than lifetime use. While we found an effect of insomnia on alcohol dependence, we found no effect on alcohol use. This might be due to the measure of alcohol use in quantity per week, which does not distinguish drinking large quantities in one evening from drinking one glass with dinner daily; the first would impair sleep quality more than the latter. The genetic architecture of drinking frequency seems to differ from that of drinking quantity (Marees et al., 2019).

In the other direction, we found an effect of smoking initiation on insomnia. A previous study testing this relationship did not find this effect, possibly due to lower power (Gibson et al., 2018). The effect of smoking on insomnia might be due to nicotine's stimulant properties (Greenland et al., 1998), although we could not test the effect of smoking heaviness. The absence of an effect of alcohol use and dependence on insomnia is in contrast with experimental literature that suggested a negative effect of alcohol on sleep quality (Ebrahim et al., 2013). Our results might be due to low instrument strength for the alcohol phenotypes. Also, the genetic instruments capture lifetime vulnerability to alcohol use and dependence, which is not directly comparable to the immediate effects of alcohol tested in experiments.

Results were reasonably robust against MR assumption violation. However, the effects of insomnia on alcohol dependence and cannabis initiation were in part driven by pleiotropic SNPs, suggesting caution in interpreting these findings. Although the analysis of smoking initiation on insomnia did not show strong evidence for it, pleiotropy might also play a role in this association. For example, smoking initiation was found to be positively associated with ADHD liability in children that have not started smoking yet, indicating that it might represent something different than only the inclination to smoke (Treur et al., 2019). A limitation might be the use of instruments that explained limited

amounts of variance in their respective phenotype (0.36–1.33 %). Sensitivity analyses correcting for this showed attenuation in effect sizes. Another limitation is that we investigated a simplistic measure of cannabis use (ever vs, never); however, to date no suitable, sufficiently powered GWAS are available on more in-depth cannabis use phenotypes, such as use frequency or quantity. For cannabis initiation we used a more inclusive  $p$ -value threshold, which might have increased chances of pleiotropy. However, filtering out instruments that explained more variance in the exposure than the outcome did not have strong effects on the results.

To summarize, we find genetic overlap between insomnia and substance use, evidence for causal effects from insomnia to most substance use traits, and a causal effect of smoking initiation on insomnia. Future research should focus on underlying mechanisms and potential implications for clinical practice. As has been found previously (Patterson et al., 2017), our results suggest that treatment for substance use and insomnia could be optimized when attention is devoted to both issues.

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None reported.

### Contributors

KJHV and JLT conceived of and designed the study. JAP has conducted the data analyses with help from LK, KJHV and JLT. DJS and JAP have written the manuscript with contributions from LK, KJHV, JMV and JLT. All authors critically reviewed the report, proposed revisions, and approved of the final manuscript.

### Declaration of Competing Interest

None of the authors report conflicts of interest.

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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.2020.108151>.

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