Investigating causal pathways between liability to ADHD and substance use, and liability to substance use and ADHD risk, using Mendelian randomization.

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ABSTRACT

Background: Attention-deficit hyperactivity disorder (ADHD) has consistently been associated with substance (ab)use, but the nature of this association is not fully understood. In view of preventive efforts, a vital question is whether there are causal effects, from ADHD to substance use and/or from substance use to ADHD. **Methods:** We applied bidirectional Mendelian randomization using summary-level data from the largest available genome-wide association studies (GWASs) on ADHD, smoking (initiation, cigarettes/day, cessation, and a compound measure of lifetime smoking), alcohol use (drinks/week and alcohol use disorder), cannabis use (initiation and cannabis use disorder (CUD)) and coffee consumption (cups/day). Genetic variants robustly associated with the 'exposure' were selected as instruments and then identified in the 'outcome' GWAS. Effect estimates from individual genetic variants were combined with inverse-variance weighted regression and five sensitivity analyses were applied (weighted median, weighted mode, MR-Egger, generalized summary-data-based MR, and Steiger filtering). **Results:** We found strong evidence that liability to ADHD increases likelihood of smoking initiation and also cigarettes per day among smokers, decreases likelihood of smoking cessation, and increases likelihood of cannabis initiation and CUD. In the other direction, there was evidence that liability to smoking initiation and CUD increase ADHD risk. There was no clear evidence of causal effects between liability to ADHD and alcohol or caffeine consumption. **Conclusions:** We find evidence for causal effects of liability to ADHD on smoking and cannabis use, and of liability to smoking and cannabis use on ADHD risk, indicating bidirectional pathways. Further work is needed to explore causal mechanisms.

Keywords: ADHD, Smoking, Cannabis, Alcohol, Caffeine, Mendelian Randomization.

Introduction

Individuals who have been diagnosed with attention deficit hyperactivity disorder (ADHD) are more likely to be (heavy) substance users compared to those without ADHD[1]. Around 5% of children and adolescents and 2.5% of adults meet the diagnostic criteria for ADHD[2] and genetic studies support that a diagnosis represents the extreme end of a continuum of impulsivity and/or attention problems in the general population[3]. Both ADHD diagnosis and higher levels of impulsivity and attention problems have been associated with higher levels of cigarette smoking[4,5], cannabis use[6,7], alcohol use[6,8] and caffeine consumption[9,10]. The exact nature of these associations is not fully understood, which hampers the development of evidence-based interventions and public health messages.

Several explanations have been posed as to why ADHD and substance use are correlated. First, it may be that there are common risk factors. Twin studies have shown that ADHD and substance use are moderately to highly heritable and that there is evidence for both shared environmental and shared genetic risk factors[11,12]. However, environmental and genetic correlation may also (partly) reflect causal effects of one phenotype on the other. The current literature has mostly focussed on causal effects going from ADHD to substance use. Externalizing symptoms in early adolescence were found to be predictive of onset of smoking and faster progression to daily smoking[4,13–15] and ADHD medication has been shown to reduce early onset smoking and alleviate smoking withdrawal[4]. For alcohol and cannabis the evidence seems less-clear cut, with some studies finding that ADHD symptoms only predicted their use in girls[16,17], and a recent twin study reporting no relation between ADHD symptoms and alcohol or cannabis use involvement[11]. For caffeine, a relatively small longitudinal study (n=144) found reciprocal effects between caffeine consumption and ADHD symptoms during adolescence[9].

There is tentative evidence that there can also be causal effects in the other direction, i.e. substance use leading to an increase in ADHD symptoms[18–20]. In monozygotic twin pairs discordant

for smoking, the smoking twin scored higher on attention problems – a difference which only appeared after smoking was initiated[18,19]. For cannabis use the evidence is mixed. Low to moderate cannabis use in adolescents seems to lead to a small increase in attention and academic problems, which disappears following sustained abstinence[20]. However, there is no indication that cannabis use exacerbates ADHD-related brain alterations[21]. With regards to alcohol use, binge-pattern exposure during development has been shown to cause attention deficits in mice[22], but there is no clear evidence for such effects in humans.

It is difficult to fully unravel the nature of the association between ADHD and substance use with observational data because of bias due to (unmeasured) confounding and reverse causality (i.e., the outcome affecting the exposure)[23]. Mendelian randomization (MR) is a method to infer causality which has recently gained much popularity. MR uses genetic variants robustly associated with an exposure variable as an instrument to test causal effects on an outcome variable[24,25]. Recent genome-wide association studies (GWASs) have identified genetic variants for both ADHD and substance use[26–30]. Because genes are transmitted from parents to offspring randomly, genetic variants that are inherited for a trait (e.g. ADHD) should not be associated with confounders such as social-economic status. By using genetic variants as instrumental variables it is therefore possible to obtain a less biased causal estimate. Three important assumptions underlying MR are that the genetic variants used as instruments: 1) strongly predict the exposure variable, 2) are independent of confounding variables, and 3) do not affect the outcome through an independent pathway, other than its possible causal effect via the exposure. A potential threat to MR is horizontal pleiotropy, where the genetic variants used as an instrument affect vulnerability to multiple phenotypes. This could lead to violation of MR assumptions 2 and 3. To assess whether MR assumptions may have been violated, various sensitivity analyses are available[25,31].

So far, one MR study found evidence for a causal influence of alcohol use on attention problems and aggression in adolescents (but not on delinquency, anxiety, or depression)[32]. Two

other studies provided evidence that liability to ADHD as well as higher extraversion causally lead to smoking initiation[33,34]. Finally, a recent MR study found that liability to ADHD leads to a higher risk of cannabis initiation[35]. Existing MR studies are limited in that they tested unidirectional effects only, had a narrow focus on one specific substance use behaviour, and/or had limited statistical power. Therefore, we performed bidirectional MR using summary-level data of the largest available GWASs, investigating causal effects between liability to ADHD and a broad spectrum of substance use phenotypes (smoking behaviour, alcohol use and abuse, cannabis use and abuse and caffeine consumption). We applied five different sensitivity analyses more robust to potential violation of the MR assumptions, each with their own assumptions. Throughout the manuscript, we refer to *'liability to'* a particular exposure (e.g. liability to ADHD). This is because the exposure estimates and the outcome estimates for our analyses come from separate samples, and it is not possible to determine whether or not the individuals in the outcome sample have actually experienced a particular exposure (e.g. an ADHD diagnosis).

Methods and Materials

Data

Summary-level data of large GWASs were obtained for ADHD (n=55,374[26]), smoking (initiation, n=1,232,091; cigarettes per day, n=337,334; cessation, n=547,219[28]; lifetime smoking, n=463,003[36]), alcohol use (drinks per week, n=941,280[28]; alcohol use disorder (AUDIT total score: Alcohol Use Disorders Identification Test), n=121,630[30]), cannabis use (initiation, n=162,082[27]; cannabis use disorder (CUD), n=51,372[37]) and caffeine consumption (cups of coffee per day, n=91,462[29]). When smoking initiation, cigarettes per day, smoking cessation or alcohol drinks per week was the outcome in the MR analysis, data of 23andMe were excluded, resulting in sample sizes of n=632,783, n=263,954, n=312,821 and n= 537,341, respectively.

Lifetime smoking is a compound variable that captures smoking initiation, duration, heaviness and cessation, across mid- to late adulthood. As ADHD onset is expected to occur (long) before mid- to late adulthood, this variable was not appropriate to use as an exposure and it was only used as an outcome. In addition, cigarettes per day and smoking cessation could only be used as outcomes because the GWASs these are based on were only performed in (former) smokers.

To test for causal effects of liability to ADHD on substance use, summary statistics from the complete ADHD GWAS containing child, adolescent, and adult data were used. To test for causal effects of substance use on ADHD, only adult data (ADHD diagnosed >18 years) were used (*n*=15,548) to ensure a plausible temporal sequence of a potential causal effect – i.e. substance use cannot logically have a causal effect on ADHD diagnosed in childhood.

There was no sample overlap of the ADHD GWAS with the smoking, alcohol and caffeine GWASs. Between the ADHD and the cannabis initiation GWAS there was very minimal overlap (<3%) while between ADHD and CUD there was quite extensive overlap (for the ADHD to CUD analysis; 46.6% of the ADHD sample was also in the CUD sample and 50.3% of the CUD sample was also in the ADHD sample, for the CUD to ADHD analyses; 91.2% of the ADHD sample was also in the CUD sample and 27.7% of the cannabis sample was also in the ADHD sample). Finally, it should be noted that in the GWAS for CUD, the association analyses were corrected for the presence of schizophrenia, bipolar disorder, autism spectrum disorder, major depressive disorder, and ADHD, which were prevalent both among individuals in the control group and CUD cases[26].

Main analysis

To assess causal effects of liability to ADHD on substance use, we identified single nucleotide polymorphisms (SNPs) that reached genome-wide significance (*p*<5e-08) in the ADHD GWAS to use as genetic instruments. These same SNPs were then identified in the substance use GWASs. To assess causal effects in the other direction, we identified genome-wide significant SNPs in the

different substance use GWASs as genetic instruments, and then identified those different sets of SNPs in the ADHD GWAS. For CUD only, we additionally created a genetic instrument with SNPs reaching the 'suggestive' significance threshold of p<1e-05, since only one locus reached genome-wide significance and multiple SNPs are needed for sensitivity analyses. For all relationships, the causal effect was computed as SNP-outcome association / SNP-exposure association, after which the effect estimates of the individual SNPs were combined with inverse variance weighted regression (IVW)[25].

Sensitivity analyses

Five MR sensitivity methods were applied to test the robustness of the main IVW findings. First, we performed weighted median regression, which can provide an unbiased estimate of the causal effect, even if up to 50% of the weight of the genetic instrument comes from invalid instruments[38]. Second, we applied weighted mode regression which provides unbiased results as long as the causal effect estimate that is most common among the included SNPs is consistent with the true causal effect[39]. Third, MR-Egger regression was performed, which provides an unbiased estimate of the causal effect provided that the strength of the genetic instrument (association between the SNP and the exposure) does not correlate with the effect that same instrument has on the outcome. This is called the 'InSIDE assumption' (instrument strength independent of direct effect) and it is a weaker assumption than the assumption of no pleiotropy[40]. MR-Egger does rely on the NOME (NO Measurement Error) assumption, however, and if this is violated its results may be biased. Violation of the NOME assumption can be assessed by the I^2 statistic, ranging between 0 and 1. An I^2 value below 0.9 indicates considerable risk of bias, which may still be corrected for with MR-Egger simulation extrapolation (SIMEX)[41]. An I^2 value below 0.6 means that MR-Egger results (even with SIMEX correction) are unreliable. We report MR-Egger results when I^2 >0.9, MR-Egger SIMEX results when I^2 = 0.6-0.9 and we do not report MR-Egger results when I^2 <0.6[41]. Fourth, generalised

summary-data-based Mendelian randomization (GSMR) was conducted[42]. This method achieves higher statistical power than other MR methods by taking into account linkage disequilibrium (LD) between the included SNPs. GSMR includes a filtering step which identifies and removes SNPs that are outliers (HEIDI filtering). MR-Egger and GSMR were applied only when the genetic instruments contained a sufficient number of SNPs (≥10). Fifth and final, we applied Steiger filtering which computes the amount of variance each SNP explains in the exposure and in the outcome variable. In case of a true causal effect of the exposure on the outcome, it would be expected that a SNP used as an instrument is more predictive of the exposure than the outcome. If not – i.e. the SNP is more predictive of the outcome than the exposure – it might imply reverse causation[43]. Steiger filtering was used to exclude all SNPs that were more predictive of the outcome than the exposure, after which MR analyses were repeated. For the relationship from liability to CUD to ADHD risk only, we applied MR using robust adjusted profile score (MR-RAPS) to deal with the increased potential of weak instrument bias resulting from the relaxed *p*-value threshold of $p<1e\text{-}05$[44].

For an additional indication of the robustness of our findings we inspected the Cochran's Q statistic, which provides an estimate of heterogeneity between the effects of the individual genetic variants[45]. We also performed leave-one-out analyses, repeating the main IVW analysis after removing each of the SNPs one at a time and inspecting whether the overall estimate changes[46].

Results

We found strong evidence for causal effects of liability to ADHD on smoking initiation (IVW beta = 0.07, p = 1.7e-05), cigarettes smoked per day (IVW beta = 0.04, p = 0.006), smoking cessation (IVW beta = -0.03, p = 0.005) and lifetime smoking (IVW beta = 0.07, p = 1.4e-07). The weighted median and weighted mode sensitivity analyses confirmed these findings, albeit with slightly weaker statistical evidence for the latter (**Table 1**). For smoking initiation, MR-Egger did not show clear evidence for a causal effect. Given that MR-Egger generally has lower power than the other

methods, it may have been underpowered to reject the causal null hypothesis[40]. The Egger intercept did not indicate horizontal pleiotropy (intercept = 0.01, p = 0.41, **Supplementary Table 2**). For cigarettes smoked per day and smoking cessation MR-Egger also did not confirm the IVW findings, with weak evidence for horizontal pleiotropy (Egger intercept= 0.01, p = 0.068 and 0.01, p = 0.089, respectively). GSMR could not be performed because there were too few SNPs (<10). Steiger filtering showed that – with the exception of one SNP in the ADHD risk to smoking initiation analysis – all SNPs were more predictive of the exposure than of the outcome. Cochran's Q statistic indicated strong evidence for heterogeneity of the effects of the included variants for the ADHD liability to smoking initiation and ADHD liability to lifetime smoking analyses (**Supplementary Table 3**; Q = 34.44, p = 7.5e-05 and Q = 47.73, p = 2.9e-07, respectively), while leave-one-out analyses gave no indication that the overall causal effect was driven by a particular SNP (**Supplementary Figure 1**).

There was also evidence that liability to ADHD causally increases risk of cannabis use (initiation IVW beta = 1.13, p = 0.010 and CUD IVW beta = 1.35, p = 0.012). Weighted median, weighted mode and GSMR confirmed these findings, but with (slightly) weaker statistical evidence. MR-Egger analyses were not reported due to low I^2 values (**Supplementary Table 4**). Steiger filtering did not identify any SNPs more predictive of the outcome than of the exposure. There was weak evidence for heterogeneity in SNP effects for the ADHD liability to cannabis initiation analysis (Q = 15.90, p = 0.069), and less with respect to ADHD liability to CUD analysis (Q = 12.11, p = 0.36). Leave-one-out analyses did not show any individual SNPs driving the overall effect.

There was no clear evidence for a causal effect of liability to ADHD on alcohol drinks per week, alcohol use disorder or coffee consumption. It is interesting to note, however, that when we repeated these analyses using alcohol intake *frequency* as the outcome measure in UK Biobank – one of the cohorts included in the much larger GWAS sample the main analyses were based on – there was more evidence for a causal effect reflecting increased risk (IVW beta = 0.22, p = 0.013,

Supplemental Table 5). This is in line with recent findings of opposite patterns of genetic associations for quantity versus frequency of alcohol consumption[47].

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In the other direction, strong evidence was found for causal effects of liability to smoking initiation on ADHD risk (IVW OR = 3.72, p = 2.9e-51). Weighted median, weighted mode, MR-Egger, and GSMR sensitivity analyses indicated similarly strong evidence, albeit with smaller effect sizes (**Table 2**). The Egger intercept did not indicate horizontal pleiotropy (intercept = 0.01, p = 0.37). It should be noted, however, that for this relationship the I^2 value was on the lower limit of reliability – 0.60 (**Supplementary Table 4**) – indicating that MR-Egger was not optimally reliable. Furthermore, Steiger filtering revealed that only 265 of the 346 smoking initiation SNPs (77%) were 'valid' instruments, i.e. that they were more predictive of the exposure, smoking, than of the outcome, ADHD. When repeating the IVW and sensitivity analyses with the valid SNPs only, the evidence for a causal effect was still strong, but effect sizes were attenuated (**Supplementary Table 6**). Cochran's Q statistic provided no clear evidence for heterogeneity for the liability to smoking initiation to ADHD risk analysis (Q = 373.84, p = 0.14) and leave-one-out analyses did not indicate that the overall effects were driven by a single SNP.

For cannabis use initiation there was no clear evidence for a causal effect on ADHD risk (IVW OR = 1.46, p = 0.10), while for CUD evidence was quite strong, reflecting increased risk (OR one-SNP instrument = 1.47, p = 0.001, OR 22-SNP instrument = 1.13, p = 0.004). For the 22-SNP instrument, weighted median, weighted mode, and GSMR showed a similar direction and strength of effect with weaker statistical evidence. This was also true for MR-RAPS, which was performed to account for possible weak instrument bias from the relaxed p-value threshold (OR = 1.13, p = 0.005). MR-Egger

results did not confirm a causal effect (OR = 0.87, p = 0.23) with weak evidence for horizontal pleiotropy (intercept = 1.06, p = 0.094). Steiger filtering did not identify any SNPs more predictive of the outcome than of the exposure and there was no clear evidence for heterogeneity from Cochran's Q statistic. Leave-one-out analyses indicated that SNP rs56372821 – the single genome-wide significant SNP for CUD – had a considerably stronger effect than the others. When this SNP was excluded the IVW OR was 1.10 (p = 0.031).

There was no clear evidence for a causal effect of liability to alcohol use or coffee consumption on ADHD risk.

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Discussion

With Mendelian randomization analyses using summary-level data, we found strong evidence for causal effects of liability to ADHD on substance use risk, such that it increases the odds of initiating smoking, smoking more cigarettes per day and finding it more difficult to quit, as well as that it increases the odds of initiating cannabis use and developing a cannabis use disorder. In the other direction we also found some evidence that liability to smoking initiation and cannabis use disorder causally increase (adult) ADHD risk. There was no clear evidence of causal effects from liability to ADHD to alcohol or caffeine consumption, or from alcohol or caffeine consumption to ADHD risk.

Our findings complement and confirm a large body of observational literature suggesting that individuals diagnosed with ADHD are at a higher odds of initiating smoking, transitioning into regular smoking and being less able to quit[4]. We also provide evidence for a causal, increasing effect of liability to ADHD on risk of cannabis (ab)use, for which the literature has so far been inconclusive[11,16,17]. While previous observational studies may have been biased by (unmeasured)

confounding, our approach of using genetic variants as instrumental variables is more robust to confounding and reverse causality. We were not able to identify the exact mechanism of causation, but it seems likely that higher levels of impulsivity lead individuals with ADHD to try out cigarettes or cannabis without considering their possible negative consequences[4,49–51]. Another potential mechanism is 'self-medication', whereby a substance is used because of its (real or perceived) positive effects on ADHD symptomatology[52,53].

Interestingly, there was also evidence for causal effects of liability to smoking initiation and cannabis use disorder on ADHD risk. This is in line with previous literature indicating that smoking can have detrimental, long-term effects on attention[18] and that (heavy) cannabis use can decrease attention performance[20]. It has been hypothesized that nicotine inhaled through cigarette smoke can affect the developing prefrontal cortex – involved in attention and impulse control – during adolescence[54,55]. In rats, exposure to nicotine during adolescence decreased attentional performance with effects lasting into adulthood[56]. It is important to note however, that the evidence we found for causal effects of smoking and cannabis use on ADHD risk was less convincing than it was in the other direction. First of all, we were not able to test causal effects of smoking heaviness or smoking cessation on ADHD. Since the GWAS studies on cigarettes per day and smoking cessation were performed in (former) smokers only, our MR analyses would have had to account for that by stratifying the ADHD GWAS sample on smoking status, which was not possible due to a lack of information on smoking status of the analysed individuals. Second, a considerable portion (23%) of the SNPs used as an instrument for smoking initiation were in fact more predictive of the outcome, ADHD, implying reverse causation. There is also extensive research showing that genetic influences on smoking initiation are mediated via impulsivity-related traits[4]. Another important point is that for the analyses of substance use to ADHD, we used adult-onset ADHD as the outcome (i.e., cases where the diagnosis was made >18 years). This strengthened our approach by ensuring the appropriate temporal sequence for a causal effect in this direction, which was not done in a previous MR study on ADHD and cannabis[35]. However, it might be that individuals with adult-onset ADHD differ from

those who were diagnosed during childhood. A recent study assessed the neurodevelopmental profile of late-onset ADHD and found that the majority were probably misclassified at a younger age. Moreover, those with genuine late-onset ADHD did not have a typical profile of neurodevelopmental impairment[57]. Our results should therefore be replicated looking at other, continuous measures of ADHD symptoms in adulthood. Preferably these would be more 'proximal' measures of attention problems and impulsivity, obtained through cognitive performance tasks or (functional) brain imaging.

We found no clear evidence of causal effects between liability to ADHD and alcohol use or between ADHD or between liability of ADHD and caffeine consumption – two relationships where current evidence is inconclusive. Given the very large and powerful genetic data sets that our analyses are based on, our findings are a strong indication that liability to ADHD does not causally increase alcohol consumption, the risk of developing alcohol dependence or caffeine consumption. This is an important finding as it implies that observational associations of ADHD with alcohol and caffeine use are due to shared underlying risk factors.

Important strengths of this study include the very large sample sizes that the analyses are based on, the variety of different substance use phenotypes that were included, and the use of multiple sensitivity analyses that each rely on distinctly different assumptions. However, there are also limitations to consider. First, the genetic instruments used in MR may vary in power, i.e. the amount of variance in the exposure variable that they explain (R^2). Better-powered instruments are more likely to pick up on a potential causal effect, which in theory could explain why there was evidence for causality for some relationships (e.g. smoking to ADHD), but not for others (e.g. alcohol to ADHD). While the instruments that we used varied in power, the differences were modest – for ADHD all SNPs included in the instrumental variable combined explained 0.5-0.7% of the variance, for smoking initiation 2.4%, for cannabis initiation 0.2%, for cannabis use dependency 0.1% with 1 SNP and 1.1% with 22 SNPs, for alcohol drinks per week 1.1%, for alcohol use disorder 0.3%, and for

caffeine consumption 0.6% (the formula to compute these numbers is described elsewhere[27]). We were not able to apply all sensitivity analyses to all the tested relationships, due to an insufficient number of SNPs for some of the instruments. When even larger GWASs will become available, identifying more SNPs, we will be able to examine these relationships better. For the relationship between ADHD and cannabis use disorder, there was substantial sample overlap between the GWAS datasets used, which may have biased those MR results towards the observational association (false-positive). In addition, the fact that the cannabis use disorder GWAS corrected for ADHD as a covariate could also have introduced bias – the effect of risk ADHD on cannabis use disorder might be underestimated (because the outcome has been corrected for the exposure) while the effect of cannabis use disorder on ADHD might be overestimated[25]. Finally, the multiple testing burden should be taken into account when interpreting our findings, although it is unlikely that this would change our conclusions given the strong statistical evidence.

To inform preventive efforts, future work should focus on determining the exact mechanisms through which causal effects from liability to ADHD to smoking and cannabis use are mediated. Maybe more importantly, our finding that smoking and cannabis use disorder might causally increase ADHD should be followed-up with different research methods and a wider range of measures of ADHD symptoms. Such 'triangulation'[58] will be essential to provide conclusive evidence on this, potentially highly impactful, finding. For the relationships where there was no indication of any causal effects – liability to ADHD and alcohol and caffeine use – it seems that the best approach for prevention is to identify shared risk factors that are modifiable, so as to decrease liability to ADHD as well as alcohol and caffeine use.

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Disclosures

None of the authors have anything to declare.

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Table 1. Results of the Mendelian randomization analyses using summary level data from liability to ADHD to substance use risk including IVW estimates and four sensitivity analyses: weighted median, weighted mode, MR-Egger, and GSMR (generalized summary-data-based Mendelian randomization).

Exposure	Outcome	IVW					Weighted median				Weighted mode				MR-Egger				GSMR				
		n SNPs	beta	*SE*	OR	*p*	beta	*SE*	OR	*p*	beta	*SE*	OR	*p*	beta	*SE*	OR	*p*	*n* SNPs*	beta	*SE*	OR	*p*
ADHD	Smoking initiation	10	0.07	0.02		1.7e-05	0.05	0.01		4.2e-05	0.05	0.01		0.010	0.01	0.07		0.937	8	*n.a.*	*n.a.*		*n.a.*
ADHD	Cigarettes / day	10	0.04	0.01		0.006	0.05	0.02		0.004	0.05	0.03		0.089	-0.11	0.07		0.127	8	*n.a.*	*n.a.*		*n.a.*
ADHD	Smoking cessation	11	-0.03	0.01		0.005	-0.03	0.01		0.026	-0.03	0.02		0.215	0.06	0.05		0.255	9	*n.a.*	*n.a.*		*n.a.*
ADHD	Lifetime smoking	10	0.10	0.02		8.8e-08	0.09	0.02		1.6e-09	0.10	0.02		0.003	*n.a.*	*n.a.*		*n.a.*	9	*n.a.*	*n.a.*		*n.a.*
ADHD	Alcoholic drinks / week	10	-0.01	0.02		0.741	0.02	0.01		0.150	0.02	0.01		0.153	0.08	0.01		0.468	7	*n.a.*	*n.a.*		*n.a.*
ADHD	Alcohol use disorder	10	0.01	0.01		0.234	0.00	0.01		0.729	0.00	0.01		0.815	*n.a.*	*n.a.*		*n.a.*	8	*n.a.*	*n.a.*		*n.a.*
ADHD	Cannabis initiation	10	0.12	0.05	1.13	0.010	0.17	0.06	1.19	0.001	0.19	0.11	1.21	0.107	*n.a.*	*n.a.*	*n.a.*	*n.a.*	10	0.25	0.09	1.28	0.004
ADHD	CUD	12	0.30	0.12	1.35	0.012	0.32	0.16	1.37	0.054	0.21	0.26	1.23	0.442	*n.a.*	*n.a.*	*n.a.*	*n.a.*	10	0.55	0.29	1.73	0.055
ADHD	Cups of coffee / day	9	0.03	0.03		0.322	0.04	0.04		0.331	0.05	0.07		0.458	*n.a.*	*n.a.*		*n.a.*	9	*n.a.*	*n.a.*		*n.a.*

n SNPs = number of SNPs included in the genetic instrument. SE = standard error of the beta. CUD = substance use disorder. Note that the dichotomous variables smoking initiation and smoking cessation were rescaled in the original GWAS such that its unit is a standard deviation increase in prevalence[48]. For MR-Egger; when I^2 was 0.6-0.9, a SIMEX correction was applied, while estimates were not reported at all when I^2 was <0.6. *n.a:* the number of SNPs available for the analysis was too low, or, in the case of MR-Egger, I^2 was <0.6. *Number of SNPs left after the HEIDI filtering step which is part of GSMR.

Table 2. Results of the Mendelian randomization analyses using summary level data from liability to substance use to *adult* ADHD risk (diagnosis received after age 18) including IVW estimates and four sensitivity analyses: weighted median, weighted mode, MR-Egger, and GSMR (generalized summary-level-data based Mendelian randomization).

Exposure	Outcome	IVW					Weighted median				Weighted mode				MR-Egger				GSMR				
		n SNPs	beta	*SE*	OR	*p*	beta	*SE*	OR	*p*	beta	*SE*	OR	*p*	beta	*SE*	OR	*p*	*n* SNPs*	beta	*SE*	OR	*p*
Smoking initiation	ADHD	346	1.31	0.09	3.72	2.9e-51	1.18	0.12	3.26	5.0e-22	1.04	0.45	2.84	0.021	1.00	0.31	2.72	0.001	330	0.90	0.06	2.46	1.3e-44
Alcohol / week	ADHD	90	0.01	0.29	1.01	0.975	0.01	0.43	1.01	0.978	-0.17	0.54	0.84	0.747	-0.46	0.61	0.63	0.444	80	0.06	0.22	1.06	0.787
AUDIT total score	ADHD	7	0.59	1.32	1.81	0.655	0.52	1.64	1.68	0.752	0.78	2.21	2.18	0.736	*n.a.*	*n.a.*	*n.a.*	*n.a.*	7	*n.a.*	*n.a.*	*n.a.*	*n.a.*
Cannabis initiation	ADHD	5	0.38	0.23	1.46	0.103	0.48	0.24	1.62	0.044	0.57	0.30	1.77	0.132	*n.a.*	*n.a.*	*n.a.*	*n.a.*	5	*n.a.*	*n.a.*	*n.a.*	*n.a.*
CUD (threshold $p<5\times10^{-8}$)	ADHD	1	0.39	0.12	1.47	0.001	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	*n.a.*	1	*n.a.*	*n.a.*	*n.a.*	*n.a.*
CUD (threshold $p<1\times10^{-5}$)	ADHD	22	0.12	0.04	1.13	0.004	0.13	0.06	1.14	0.027	0.14	0.12	1.15	0.261	-0.14	0.11	0.87	0.232	19	0.57	0.22	1.76	0.010
Coffee / day	ADHD	4	-0.01	0.21	0.99	0.969	-0.01	0.16	0.99	0.923	0.01	0.19	1.01	0.951	*n.a.*	*n.a.*	*n.a.*	*n.a.*	4	*n.a.*	*n.a.*	*n.a.*	*n.a.*

n SNPs = number of SNPs included in the genetic instrument**.** SE = standard error of the beta. CUD = substance use disorder. Note that the dichotomous variable smoking initiation was rescaled in the original GWAS such that its unit is a standard deviation increase in prevalence[48]. For MR-Egger; when I^2 was 0.6-0.9, a SIMEX correction was applied, while estimates were not reported at all when I^2 was <0.6. *n.a:* the number of SNPs available for the analysis was too low, or, in the case of MR-Egger, I^2 was <0.6. *Number of SNPs left after the HEIDI filtering step which is part of GSMR.