

## RESEARCH ARTICLE

# Investigating genetic correlation and causality between nicotine dependence and ADHD in a broader psychiatric context

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## Abstract

People with attention-deficit/hyperactivity disorder (ADHD) or other psychiatric disorders show high rates of nicotine dependence (ND). This comorbidity might be (partly) explained by shared genetic factors. Genetic correlations between ND and ADHD (or other psychiatric disorders) have not yet been estimated. A significant genetic correlation might indicate genetic overlap, but could also reflect a causal relationship. In the present study we investigated the genetic correlation (with LD score regression analyses) between ND and ADHD, as well as between ND and other major psychiatric conditions (major depressive disorder, schizophrenia, anxiety, bipolar disorder, autism spectrum, anorexia nervosa, and antisocial behavior) based on the summary statistics of large Genome Wide Association studies. We explored the causal nature of the relationship between ND and ADHD using two-sample Mendelian randomization. We found a high genetic correlation between ND and ADHD ( $r_g = .53$ ,  $p = 1.85 \times 10^{-13}$ ), and to a lesser extent also between ND-major depressive disorder ( $r_g = .42$ ,  $p = 3.6 \times 10^{-11}$ ) and ND-schizophrenia ( $r_g = .18$ ,  $p = 1.1 \times 10^{-3}$ ). We did not find evidence for a causal relationship from liability for ADHD to ND (which could be due to a lack of power). The strong genetic correlations might reflect different phenotypic manifestations of (partly) shared underlying genetic vulnerabilities. Combined with the lack of evidence for a causal relationship from liability for ADHD to ND, these findings stress the importance to further investigate the underlying genetic vulnerability explaining co-morbidity in psychiatric disorders.

## KEYWORDS

ADHD, causality, genetic correlation, Mendelian randomization, nicotine dependence

## 1 | INTRODUCTION

Use of tobacco is (still) prevalent in the Western world: about 20% of the population (15+ years) in Europe and the United States is a regular smoker (WHO, 2016). This percentage is remarkably higher in people

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with psychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), depression, mood or anxiety disorder, schizophrenia, bipolar disorder, and conduct disorder (Fergusson, Horwood, & Ridder, 2007; Grant, Hasin, Chou, Stinson, & Dawson, 2004; Medeiros, Lafer, Kapczynski, Miranda-Scippa, & Almeida, 2018; Parker, Sigmon, & Villanti, 2019; Pereiro et al., 2013). However, for instance anorexia nervosa and autism were not associated with increased prevalence of smoking (Mangerud, Bjerkeset, Holmen, Lydersen, & Indredavik, 2014; Solmi et al., 2016).

Smoking and nicotine dependence (ND) showed particularly high comorbidity with ADHD (Kollins, McClernon, & Fuemmeler, 2005; Matthies et al., 2012). ADHD is a common neurodevelopmental condition, with a prevalence of about 3–5% in children and 1–3% in adults (Guilherme, de Lima, Horta, Biederman, & Rohde, 2007; Simon, Czobor, Bálint, Mészáros, & Bitter, 2018). About two thirds of cases with childhood ADHD persist into adulthood (Faraone et al., 2015). A prospective study showed that among participants diagnosed with childhood ADHD, 42% ended up smoking in adulthood, versus 26% among controls of the same age (Lambert & Hartsough, 1998). Other studies demonstrated earlier and faster progression to daily smoking among those with a childhood ADHD diagnosis, as well as greater risk for failed quit attempts (Mitchell et al., 2018), and a higher risk on ND for people with ADHD that persisted into adulthood (Ilbegi et al., 2018).

Previous studies have consistently suggested that comorbidity between smoking/ND and psychiatric disorders such as ADHD can be (partly) explained by common genetic factors (Foo et al., 2018; Nesvåg et al., 2017; van Amsterdam, van der Velde, Schulte, & van den Brink, 2018). With methodological advances in molecular genetics and increased sample sizes in Genome Wide Association studies (GWAS), it has become viable to use summary statistics of large GWAS to estimate genetic correlations between two phenotypes. It has been shown that ADHD is genetically correlated to smoking quantity ( $r_g = .26$ ) and smoking initiation ( $r_g = .22$ ) (Brainstorm et al., 2018), but genetic correlations between ADHD and ND have not yet been estimated.

Different mechanisms play a role in smoking initiation, smoking quantity, and ND. Initiation is thought to be mainly associated with impulse control and high novelty/sensation seeking. Specific impulsivity-related traits differentially relate to smoking status and severity of nicotine dependence (Kale, Stautz, & Cooper, 2018). Heaviness of smoking and ND are also influenced by the response to nicotine (e.g., through variation in nicotinic acetylcholine receptors in the brain and variation in dopamine release in response to nicotine intake) (Gorwood, Le Strat, & Ramoz, 2017). ND might be mainly driven by compulsive use of cigarettes, aiming to reduce negative affect, craving and stress (Uhl, Koob, & Cable, 2019). The observational correlation between number of cigarettes per day and ND (measured with Fagerström Test for Nicotine Dependence score, without the question on cigarettes per day) ranges between .50 and .60 (Vink, Willemssen, Beem, & Boomsma, 2005), indicating that although these are overlapping phenotypes they are not identical. It could thus be speculated that the genetic correlation of ND with

ADHD (or other psychiatric disorders) might be different than for smoking initiation or quantity.

A significant genetic correlation between two phenotypes, like smoking and ADHD, might indicate genetic overlap, but it could also reflect a causal relationship—corresponding to horizontal or vertical pleiotropy, respectively (Paaby & Rockman, 2013; Schadt et al., 2005). Horizontal (independent) pleiotropy means that the same genetic variants influence vulnerability for multiple phenotypes (e.g., ND and ADHD), while vertical (reactive) pleiotropy means that genetic variants influence vulnerability for one phenotype, and that phenotype in turn causes another phenotype (Paaby & Rockman, 2013; Schadt et al., 2005). Evidence for a causal relationship can be explored with Mendelian randomization (MR). This method uses genetic variants robustly associated with an exposure (e.g., ADHD) and as instrument, or proxy, to test causal effects on an outcome (e.g., nicotine dependence). Because genes are transmitted from parents to offspring randomly, and genetic variation is fixed at birth, MR is less affected by potential bias from confounding or reverse causality when compared with conventional epidemiological approaches (Lawlor, Harbord, Sterne, Timpson, & Davey Smith, 2008).

A previous study applying MR with summary-level data of large GWAS suggested causal effects between ADHD and smoking behavior (Treur et al., 2019). The study found strong evidence that liability to ADHD leads to higher likelihood of smoking initiation, more cigarettes per day among smokers, and lower likelihood of smoking cessation. However, this study did not look at ND.

In the current study we: (a) investigate the genetic correlation between ND and ADHD; (b) investigate the genetic correlation between ND and other major psychiatric conditions, including depression, anxiety disorder, schizophrenia, bipolar disorder, anorexia nervosa, antisocial behavior, and autism spectrum disorder for comparison. Lastly (c), we explore the causal nature of the relationship between ADHD and ND through MR. Exploring these relationships will shed light on the underlying mechanisms explaining the high phenotypic co-morbidity.

## 2 | METHODS

### 2.1 | Genetic correlations

Using summary statistics of the largest available GWA studies for ND (Hancock et al., 2018) ( $N = 28,677$ ) and ADHD (Demontis et al., 2019) ( $N = 55,374$ ) we calculated genetic correlations with cross-trait LD-Score regression (Bulik-Sullivan et al., 2015), using the European subset of 1,000 Genomes reference data (Delaneau et al., 2014). In this procedure reference population LD scores are regressed on the test statistics of pairs of GWA studies. The resulting estimate represents the genetic covariation between the pairs of GWA traits based on all polygenic effects captured by SNPs.

As a comparison we also calculated the genetic correlations between ND and other psychiatric traits [MDD (Wray et al., 2018), Schizophrenia (Schizophrenia Working Group of the Psychiatric

Genomics et al., 2014), Bipolar Disorder (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium et al., 2018), Autism Spectrum (Grove et al., 2019), Anorexia Nervosa (Duncan et al., 2017), Anxiety (Otowa et al., 2016), and antisocial behavior (Tielbeek et al., 2017)] with the same method. To correct for multiple testing we used a  $p$ -value threshold of  $0.05/6$  tests = .008.

## 2.2 | Mendelian randomization

We performed MR analysis with summary-level data of the largest available GWASs, testing causal effects of liability to ADHD (Demontis et al., 2019) on nicotine dependence (Hancock et al., 2018). MR is an example of instrumental variable analysis. Genetic variants are used as proxies (i.e., instrumental variables) for exposure. For a genetic variant to be a valid instrumental variable, it must satisfy three conditions: (a) the genetic variant must be associated with the exposure of interest (i.e., the behavior being studied); (b) the genetic variant must be independent of any confounders of the exposure–outcome relationship being studied; and (c) the genetic variant should only affect the outcome through the exposure of interest (Katikireddi, Green, Taylor, Davey Smith, & Munafò, 2018). To satisfy Condition “a” we have used the summary-level data of the largest available GWASs. It must be noted that although significantly associated, these SNPs explain only a small proportion of the total variance. For Condition “b” it is expected

**TABLE 1** Genetic correlations between nicotine dependence ( $N = 38,602$ ) and psychiatric phenotypes

	N cases/N controls	$r_g$ (SE)	$p$
ADHD	20,183 / 35,191	<b>.53</b> (.07)	<i>1.85x10<sup>-13</sup></i>
MDD	59,851 / 113,154	<b>.42</b> (.06)	<i>3.6x10<sup>-11</sup></i>
Anxiety disorder	18,186	.37 (.17)	.031
Antisocial behavior	25,781	.21 (.19)	.266
Schizophrenia	36,989/113,075	<b>.18</b> (.05)	.001
Bipolar disorder	20,129/21,524	<b>.13</b> (.06)	.022
Autism spectrum	18,381/27,969	.08 (.10)	.443
Anorexia nervosa	3,495/10,982	.02 (.06)	.720

Note: In each cell:  $r_g$  (genetic correlation) with SE, and  $p$ -value (italic). Correlations with a  $p$  value  $<.05$  are depicted in **bold**. Correlations that survived correction for multiple testing (Bonferroni correction,  $p < .00625$ ) are depicted in **bold and underlined**.  $N$  cases/control represent the number of cases/number of controls in the GWA studies or the total  $N$  for continuous phenotypes.

**TABLE 2** Two sample, bidirectional Mendelian randomization from liability to ADHD to nicotine dependence

Exposure	Outcome	$n$ SNPs	IVW			Weighted median			Weighted mode			GSMR		
			Beta	SE	$p$	Beta	SE	$p$	Beta	SE	$p$	Beta	SE	$p$
ADHD	ND	9	0.001	0.03	.956	−0.013	0.04	.722	−0.023	0.05	.634	−0.001	0.03	.957
ADHD	ND	82	0.005	0.01	.654	0.004	0.02	.782	0.027	0.04	.519	−0.003	0.01	.775

Abbreviations: GSMR, generalized summary-data-based Mendelian randomization; IVW, variance weighted regression.

that any specific allele should be distributed randomly across the population (based on Mendel's first and second law) assuming there is no assortative mating. Condition “c” cannot be tested directly, but sensitivity tests can help to explore potential bias (see below).

Two genetic instruments were created for liability to ADHD: one including all SNPs that were genome-wide significantly ( $p$ -value  $5e-08$ ) associated with ADHD diagnosis and one including SNPs that reached a more lenient, suggestive,  $p$ -value threshold of  $1e-05$ . These sets of SNPs were then identified in the nicotine dependence GWAS. Effect estimates of the individual SNPs were combined with Inverse Variance Weighted Regression (IVW). Three sensitivity analyses were performed to assess the robustness of the IVW findings and if these assumptions would be violated: weighted median, weighted mode regression, and Generalized Summary-data-based Mendelian Randomization (GSMR). Weighted mode and weighted median regression are more robust against weak instruments. Weighted median regression can provide an unbiased causal estimate when no more than 50% of the weight of the genetic instrument that is used comes from invalid instruments (Bowden, Davey Smith, Haycock, & Burgess, 2016; Lawlor et al., 2008). Weighted mode regression provides an unbiased causal estimate if the causal effect estimate that is most common among all of the included SNPs is consistent with the true causal effect (Bowden et al., 2016). Finally, we performed GSMR, which includes a filtering step that excludes SNPs suspected to have horizontally pleiotropic effects (HEIDI filtering) (Zhu et al., 2018). This method generally has higher statistical power because it takes into account very small amounts of LD between the genetic variants included in a given instrument. GSMR also.

While bidirectional causality between ADHD and ND is possible, we only tested causal effects of liability to ADHD on ND. Testing effects in the other direction is not possible because the GWAS on nicotine dependence was performed in smokers only, and so MR analyses using ADHD as the outcome would have to be stratified on smoking status (Katikireddi et al., 2018). Since we are making use of summary statistics, this cannot be achieved.

## 3 | RESULTS

A significant genetic correlation of  $r_g = .53$  ( $p = 1.85 \times 10^{-13}$ ) was observed between ND and ADHD (Table 1). Other psychiatric disorders that significantly correlated with ND were MDD ( $r_g = .42$ ,  $p = 3.6 \times 10^{-11}$ ) and schizophrenia ( $r_g = .18$ ,  $p = 1.1 \times 10^{-3}$ ). The correlation between ND and bipolar disorder and between ND and

anxiety did not survive correction for multiple testing. The correlations with autism spectrum and anorexia nervosa were not significant.

Using Mendelian randomization, we found no evidence of causal effects of liability to ADHD on ND (Table 2). When using an instrument including SNPs that were associated with ADHD under the  $p$ -value threshold of  $5 \times 10^{-8}$  (9 SNPs) the IVW beta estimate did not significantly deviate from 0, ( $\beta_{IVW} = 0.001$ ,  $p = .956$ ) and neither did it when using an instrument of SNPs under the  $p$ -value threshold  $1 \times 10^{-5}$  (82 SNPs;  $\beta_{IVW} = 0.005$ ,  $p = .654$ ).

## 4 | DISCUSSION

We found a high genetic correlation between ND and ADHD, and to a lesser extent also between ND-MDD and ND-schizophrenia. We did not find evidence for a causal relationship from liability for ADHD to ND. The observed strong genetic correlation ( $r_g = .53$ ) between ND and ADHD might indicate that genetic factors influencing ND and ADHD overlap considerably. It should be noted that this correlation is higher than the previously reported correlations with smoking quantity ( $r_g = .26$ ) and smoking initiation ( $r_g = .22$ ) (Brainstorm et al., 2018). Twin studies have shown that both ADHD and ND are highly heritable, genetic factors account for 76% (Faraone et al., 2005) and 75% (Vink, Willemsen, & Boomsma, 2005), respectively.

Based on results of gene-finding studies for ADHD and ND, there are some candidate genes that might have contributed to the genetic correlation that we observed. Candidate genes include genes from the dopamine neurotransmission pathway involved in reward processing (i.e., DRD4, DRD5, DAT1, and DBH) or nicotine acetylcholine genes (strongly associated with ND, and in some studies associated with ADHD as well, although findings are mixed) (McClernon & Kollins, 2008). Identifying (groups of) genes that are associated with both ADHD and smoking might shed light on the underlying processes that explain the overlap, such as altered reward processing or impulse regulation.

In addition, we also observed significant genetic correlations between ND and other psychiatric phenotypes, namely MDD and schizophrenia, but not between ND and autism spectrum, anorexia nervosa, anxiety, antisocial behavior and bipolar disorder. The nonsignificant results for autism spectrum and anorexia nervosa most likely indicate that there is no genetic overlap between ND and these phenotype. Because there is not much evidence for a phenotypic association (see Section 1) it is logical that there is no genetic overlap. The nonsignificant results for the other disorders could either indicate that the phenotypic association is not explained by genetic overlap (but by environmental factors) or could be explained by a lack of power (caused by somewhat smaller sample size in the GWA MA studies, see Table 1).

Previous studies showed that also other substance use variables (smoking behavior, lifetime cannabis use, and alcohol dependence) are genetically correlated with ADHD: .16 for lifetime cannabis use, .37–.38 for smoking behavior, and .44 for alcohol dependence (Pasman et al., 2018; The Brainstorm Consortium et al., 2018; Walters

et al., 2018). In the same studies, MDD, schizophrenia and bipolar disorder were also genetically correlated with multiple (but not all) substance use variables. Autism spectrum disorder only showed a significant genetic correlation with lifetime cannabis use, and anorexia nervosa was not genetically correlated with any of the substance variables. The magnitude of these correlations (substance use-psychiatric disorders) is comparable with the correlations between the psychiatric disorders (ADHD, MDD, and Schizophrenia) among themselves (The Brainstorm Consortium et al., 2018; Vink & Schellekens, 2018).

These findings suggest that ND (and other substance use variables) shares a considerable portion of its common variant genetic risk with other psychiatric disorders. In fact, different psychiatric conditions might merely reflect different phenotypic manifestations of (partly) shared underlying genetic vulnerabilities (The Brainstorm Consortium et al., 2018). These findings strengthen the plea for more transdiagnostic approaches for psychiatric disorders and their frequent co-morbidity (Fusar-Poli et al., 2019). A limitation is that a genetic correlation does not reveal which specific genes are involved or which mechanisms underlie this association. Understanding the transdiagnostic mechanisms mediating these relationships between genetic vulnerability and multiple behavioral phenotypes might improve our conceptualization of psychiatric disorders, their frequent comorbidity, and subsequently guide future treatment development.

Genetic correlations might also result from causal relationships, and these processes are not mutually exclusive. In the present study we did not find evidence for a causal relationship from liability for ADHD to ND. This does not concur with a recent MR study (Treur et al., 2019) that looked at the causal relationship between ADHD and other measures of smoking behavior (smoking initiation, cigarettes per day, and smoking cessation). That study was based on summary statistics of a GWAS larger than the ND GWAS, and found evidence for causal effects such that a higher liability to ADHD increased the odds of initiating smoking, lead to smoking more cigarettes per day, and decreased the odds of smoking cessation (Treur et al., 2019). This discrepancy may be explained by a lack of power, due to a smaller sample size of the ND GWA study.

Alternatively, it may be explained by the fact that ND and number of cigarettes per day—while partly overlapping—do not represent the exact same constructs. If ND and cigarettes smoked per day are (in part) different constructs, it could be that ADHD-related phenotypes are associated with these phenotypes in different ways. It could be speculated that genetic liability to ADHD plays a causal role in the impulsive part of smoking behavior (initiation, number of cigarettes), but has less influence on the more compulsive behavior reflected by severity of ND. Future research with larger samples should further investigate the (existence of a) causal relationship between liability to ADHD and ND.

The current study should be interpreted in the light of several (other) limitations. Two-sample MR depends heavily upon the robustness of the instrumental variables. When the genetic variants explain little variance, it may reduce their validity as instrumental variables.

As larger samples become available, the accuracy of SNP effects will increase and more significant SNPs will be detected. This will

hopefully lead to instrumental variables that explain more variance which will make the two-sample MR approaches will become more powerful. Furthermore, for the MR approach to be valid, certain assumptions need to be met (see Section 2). Therefore, we carried out additional sensitivity tests to assess the robustness of our results. A last limitation is that we could only test in the direction from ADHD to ND, and not from ND to ADHD, because we could not stratify the ADHD summary statistics on smoking status. As genetic instruments for ND are by definition only based on data in smokers, we cannot use the GWA ND results as genetic instrument in the ADHD sample (which is based on smokers and nonsmokers). A solution for future research is to stratify the GWA ADHD summary statistics for smokers and nonsmokers separately.

Understanding genetic mechanisms of ADHD-ND comorbidity might have clinical relevance. A recent study showed that the clinical efficacy of methylphenidate (the most frequently used pharmacological treatment in children with ADHD) was influenced by genetic susceptibility of the child (based on several dopamine-related candidate genes) and maternal smoking during pregnancy (Pagerols et al., 2016). Moreover, it has been shown that patients with ADHD-SUD comorbidity might need higher doses of stimulants, compared with patients with ADHD only (Crunelle et al., 2018). It is unknown whether genetic variation is involved. Future studies should further investigate the role of (common) genetic factors and interaction with environmental factors on treatment response.

Taken together, our results indicate shared heritability between ND and the psychiatric disorders: ADHD, MDD, and schizophrenia. The largest genetic overlap was observed between ND and ADHD, suggesting that heritable factors likely predispose to both phenotypes (ADHD and ND). There was no evidence for causal effects of liability to ADHD on ND. These findings underscore the need to take a more transdiagnostic approach to commonly observed comorbidity between psychiatric conditions.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated

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