Associations of cigarette smoking with psychiatric disorders: evidence from a two-sample Mendelian randomization study

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We conducted a two-sample Mendelian randomization study to determine the association of smoking initiation with seven psychiatric disorders. We used 353 independent single-nucleotide polymorphisms associated with cigarette smoking initiation as instrumental variables at genome-wide significance threshold (p < 5 × 10⁻⁸) from a recent genome-wide association study in 1,232,091 European-origin participants. Summary-level data for seven psychiatric disorders, including anxiety, bipolar disorder, insomnia, major depressive disorder, posttraumatic stress disorder, suicide attempts, and schizophrenia, was obtained from large genetic consortia and genome-wide association studies. The odds ratios of genetically predicted smoking initiation were 1.96 for suicide attempts (95% CI 1.70, 2.27; p = 4.5 × 10⁻²⁰), 1.69 for post-traumatic stress disorder (95% CI 1.32, 2.16; p = 2.5 × 10⁻⁵), 1.54 for schizophrenia (95% CI 1.35, 1.75; p = 1.6 × 10⁻¹⁰), 1.41 for bipolar disorder (95% CI 1.25, 1.59; p = 1.8 × 10⁻⁸), 1.38 for major depressive disorder (95% CI 1.31, 1.45; p = 2.3 × 10⁻³⁸), 1.20 for insomnia (95% CI 1.14, 1.25; p = 6.0 × 10⁻¹¹) and 1.17 for anxiety (95% CI 0.98, 1.40; p = 0.086). Results of sensitivity analyses were consistent and no horizontal pleiotropy was detected in MR-Egger analysis. However, the associations with suicide attempts, schizophrenia, bipolar disorder, and anxiety might be related to possible reverse causality or weak instrument bias. This study found that cigarette smoking was causally associated with increased risks of a number of psychiatric disorders. The causal effects of smoking on suicide attempts, schizophrenia, bipolar disorder and anxiety needs further research.

Psychiatric disorder, known as mental disorder or mental illness, has become an important health issue due to its high morbidity and mortality risk¹. It was estimated that over 8 percentage of the global population had at least one major mental disorder in 2015² and global disease burden of mental illness ranked the second, accounting for around 11.2% of disability-adjusted life years in 2013³.

Cigarette smoking has been proposed as a risk factor for the majority of psychiatric disorder⁴–⁶. Observational studies have found that cigarette smoking is associated with an increased risk of a number of psychiatric disorders, including suicide, major depressive disorder, and bipolar disorder, etc⁷,⁸. In addition, several meta-analysis of prospective studies revealed a dose–response relationship between smoking and the risk of suicide and schizophrenia⁹–¹². However, whether these observed associations are causal remains unclear since the findings in observational studies are prone to be biased by reverse causality (prevalent nicotine dependence among psychiatric patients, such as schizophrenic patients¹³), residual confounding and misclassification.

Genetic variants can be used as instrumental variables to assess the causal exposure-outcome association, which is known as Mendelian randomization (MR) analysis. This approach can reduce confounding and overcome reverse causality because genetic variants are randomly distributed at conception and cannot be affected by disease status. We conducted a two-sample MR study to investigate whether smoking initiation is causally

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MR can be used to investigate whether exposure (smoking) causes outcomes (psychiatric diseases). Three assumptions are as follows: (1) instrument must be associated with smoking, (2) instrument must not be related with confounders, and (3) instrument must influence the risk of psychiatric diseases only through smoking.

**Methods**

**Study design.** The present MR analysis sets basis at three key assumptions: (1) the genetic variants used as instrumental variables should be tightly associated with smoking; (2) the genetic variants used instrumental variables should not associated with any confounders of the association between smoking and psychiatric disorders, and (3) the genetic variants should only affect the risk of the psychiatric disorders via smoking (Fig. 1). In this study, we included seven major psychiatric disorders, including anxiety, bipolar disorder, insomnia, major depressive disorder, posttraumatic stress disorder, suicide attempts, and schizophrenia, using the summary-level data from publicly available genome-wide association studies (GWAS). Individual studies included in the GWAS datasets had been approved by an ethical review board. No individual-level data were used in the present MR study.

**Instrumental variable selection.** For smoking initiation, we selected 378 single-nucleotide polymorphisms (SNPs) as instrumental variables at the genome-wide significance threshold \( p < 5 \times 10^{-8} \) from a GWAS in 1,232,091 European-origin participants. We excluded SNPs with linkage disequilibrium (\( R^2 > 0.1 \)), leaving 353 independent instrumental variables for smoking initiation. Genetic principle components, population stratification and relatedness of participants were adjusted for in the GWAS. Cigarette initiation was defined as smoking every day for at least a month, smoking more than 100 cigarettes over total life or smoking regularly. Detailed information about SNPs is shown in Supplementary Table 1.

**Source of outcomes.** Summary-level genetic data for seven psychiatric disorders were obtained from large-scale GWAS or genetic consortia. Descriptions of outcome sources, such as the number of controls and cases, population structure and dataset source, are presented in Table 1. The definitions of included disorders are listed in Supplementary Table 2.

**Statistical analyses.** The random-effects inverse-variance weighted method was used as the main analysis due to the most precise estimation it can provide. However, because the inverse-variance weighted method is sensitive to invalid instrumental variables and pleiotropy, several sensitivity analyses were additionally performed, including weighted median, MR Egger, MR-Egger-SIMEX and MR-PRESSO. The weighted median approach can provide a consistent estimate if more than 50% of weight comes from valid instrumental variables. The MR-Egger regression is a technique to detect and correct for horizontal pleiotropy albeit with low power. MR-Egger-SIMEX can provide estimation with adjustment for dilution of the MR-Egger estimate using the simulation extrapolation (SIMEX) method, as a supplementary tool for MR-Egger when \( I^2 < 90\% \). The MR pleiotropy residual sum and outlier (MR-PRESSO) method can generate empirical distribution of causal esti-
Table 1. Characteristics of included genome-wide association studies for smoking initiation and psychiatric disorders. CNCR, Center for Neurogenomics and Cognitive Research; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use; SNP, single-nucleotide polymorphism. a The number represents the number of total population in the GWAS analysis for smoking initiation. b The number of all SNPs reaching the genome-wide significance level for smoking initiation is 378, leaving 353 SNPs proposed as instrumental variables after LD exclusion (R$^2 > 0.1$). c We assumed that the used SNPs for smoking initiation in the analysis of each outcome explained around 2% phenotypic variance. Power calculation was based on a web-tool: https://cnsgenomics.com/shiny/mRnd/.

| Exposure/outcome | Cases, No | Controls, No | Population | Used SNPs, No. | Power | Source | Consortium |
|------------------|-----------|--------------|------------|----------------|-------|--------|------------|
| Smoking initiation | NA        | 1,232,091*   | European   | NA             | NA    | Liu et al.14 | GSCAN |
| Anxiety          | 7,016     | 14,745       | European   | 348            | 0.45  | Otowa et al.15 | Psychiatric Genomics Consortium |
| Bipolar disorder | 20,352    | 31,358       | European   | 352            | 1.00  | Stahl et al.16 | Psychiatric Genomics Consortium |
| Insomnia         | 397,959   | 933,051      | European   | 344            | 1.00  | Jansen et al.17 | CNCR |
| Major depressive disorder | 170,756 | 329,443       | European | 347            | 1.00  | Stahl et al.18 | UK Biobank |
| Posttraumatic stress disorder | 30,000 | 170,000       | Mix        | 351            | 1.00  | Niervegelt et al.19 | Psychiatric Genomics Consortium |
| Suicide attempts | 6,024     | 44,240       | European   | 304            | 1.00  | Erlangsen et al.20 | iPSYCH |
| Schizophrenia    | 33,426    | 54,065       | European   | 350            | 1.00  | Psychiatric Genomics Consortium12 | Psychiatric Genomics Consortium |

Results

The associations between cigarette smoking initiation and psychiatric disorders are shown in Fig. 2. Genetically predicted smoking initiation was associated with higher odds of all seven included psychiatric disorders. The odds ratios (ORs) of psychiatric disorders with 95% confidence intervals (CIs) represent the increase of one standard deviation in the prevalence of smoking initiation. The power was calculated based on a web-tool: https://cns.genomics.com/shiny/mRnd/.

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We had 100% power in all analyses, except for analysis of anxiety with a power of 45%. In the MR Steiger directionality test, the variance explained by included SNPs is larger in schizophrenia, bipolar disorder and anxiety compared with smoking initiation, suggesting that these observed associations might not be directionally causal. In addition, we found the weak instrument bias might exist in the associations for anxiety, bipolar disorder, suicide attempts and schizophrenia (F statistic < 10). Figure 3 shows the scatter plots for all analyzed associations. The causal associations of smoking with depression and insomnia appeared to be stable given a stronger effect on outcome comparted with exposure. However, other associations might be risked by reverse causation or weak instrument bias, which is also partly revealed in MR Steiger directionality tes. In the reserve MR analysis for depression, the liability to depression was associated with an increased risk of smoking initiation (OR = 1.11; 95% CI 1.02–1.22; p = 0.016). The result remained consistent in the weighted median method, but not in MR-Egger regression (Supplementary Table 4).

### Table 2. Association of genetically predicted smoking initiation with psychiatric disorder in sensitivity analysis.

| Psychiatric disorder | Weighted median OR | 95% CI | p | MR-PRESSO OR | 95% CI | p | MR-Egger OR | 95% CI | p | MR-Egger (SIMEX) OR | 95% CI | p | F_{GV} | p for pleiotropy |
|----------------------|--------------------|--------|---|---------------|--------|---|-------------|--------|---|-------------------|--------|---|--------|----------------|
| Suicide attempts     | 1.99               | 1.63, 2.46 | 2.1 × 10^{-12} | 1.97 | 1.70, 2.27 | 7.1 × 10^{-14} | 1.42 | 0.78, 2.61 | 0.310 | 1.63 | 0.79, 3.40 | 0.188 | 61% | 0.29 |
| Post-traumatic stress disorder | 1.79 | 1.24, 2.57 | 0.002 | 1.70 | 1.32, 2.16 | 3.1 × 10^{-3} | 1.55 | 0.54, 4.45 | 0.419 | 1.90 | 0.33, 10.8 | 0.468 | 59% | 0.86 |
| Schizophrenia        | 1.42               | 1.24, 1.61 | 2.3 × 10^{-7} | 1.55 | 1.38, 1.73 | 5.9 × 10^{-13} | 2.20 | 1.25, 3.92 | 0.007 | 3.32 | 1.20, 9.14 | 0.021 | 58% | 0.20 |
| Bipolar disorder     | 1.54               | 1.34, 1.76 | 1.3 × 10^{-18} | 1.49 | 1.34, 1.67 | 4.1 × 10^{-12} | 1.79 | 1.07, 3.02 | 0.027 | 2.23 | 0.96, 5.13 | 0.062 | 59% | 0.35 |
| Major depressive disorder | 1.38 | 1.31, 1.44 | 6.4 × 10^{-18} | 1.40 | 1.34, 1.46 | 3.4 × 10^{-12} | 1.19 | 0.97, 1.47 | 0.101 | 1.28 | 0.93, 1.75 | 0.125 | 59% | 0.15 |
| Insomnia             | 1.22               | 1.16, 1.29 | 9.1 × 10^{-14} | 1.20 | 1.14, 1.25 | 1.6 × 10^{-13} | 1.08 | 0.89, 1.32 | 0.420 | 1.13 | 0.76, 1.67 | 0.557 | 60% | 0.32 |
| Anxiety              | 1.17               | 0.90, 1.51 | 0.234 | 1.17 | 0.98, 1.40 | 0.086 | 1.25 | 0.55, 2.80 | 0.597 | 1.32 | 0.42, 4.15 | 0.627 | 55% | 0.88 |

**Figure 2.** Associations of genetically predicted smoking initiation with psychiatric disorders using inverse-variance weighted model. CI indicates confidence interval; OR, odds ratio; SNPs, single-nucleotide polymorphisms. Estimates were estimated using the mrrobust package in Stata/SE 15.0 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

We had 100% power in all analyses, except for analysis of anxiety with a power of 45%. In the MR Steiger directionality test, the variance explained by included SNPs is larger in schizophrenia, bipolar disorder and anxiety compared with smoking initiation, suggesting that these observed associations might not be directionally causal. In addition, we found the weak instrument bias might exist in the associations for anxiety, bipolar disorder, suicide attempts and schizophrenia (F statistic < 10). Figure 3 shows the scatter plots for all analyzed associations. The causal associations of smoking with depression and insomnia appeared to be stable given a stronger effect on outcome compared with exposure. However, other associations might be risked by reverse causation or weak instrument bias, which is also partly revealed in MR Steiger directionality tes. In the reserve MR analysis for depression, the liability to depression was associated with an increased risk of smoking initiation (OR = 1.11; 95% CI 1.02–1.22; p = 0.016). The result remained consistent in the weighted median method, but not in MR-Egger regression (Supplementary Table 4).

**Discussion**

The findings of the present two-sample MR study demonstrated positive associations of smoking initiation with six psychiatric disorders, including suicide attempts, post-traumatic stress disorder, schizophrenia, bipolar disorder, major depressive disorder, and insomnia. There was a suggestive positive association between smoking initiation and anxiety. However, the associations for suicide attempts, schizophrenia, bipolar disorder and anxiety could not be determined due to possible reverse causality or weak instrument bias. There was a reverse association between the liability to depression and increased risk of smoking initiation.

Observational studies have revealed that smoking initiation and other smoking-related traits were associated with overall and specific psychiatric disorders, which is supported by the results of the present MR study. Findings of meta-analyses of cohort, case–control and/or cross-sectional studies have shown that smoking is associated with an increased risk of suicide attempts, post-traumatic stress disorder, schizophrenia and major depressive disorder as well as bipolar disorder. Several prospective studies also found an elevated risk of insomnia among smokers, especially among heavy smokers. Observational findings of the association between smoking and anxiety are inconsistent in terms of the directions of the associations. A previous MR study...
reported no association between smoking heaviness and anxiety, but that study relied on a single instrumental variable for smoking\(^4\). The present MR study, which exploited 348 SNPs as instrumental variables, detected a possible modest positive association between smoking initiation and anxiety but had inadequate power.

Figure 3. Scatter plots of the associations of smoking initiation with seven psychiatric diseases. The Scatter plots were constructed using TwoSampleMR package\(^3\) in R Software 3.6.0 (R Core Team. R Foundation for Statistical Computing. Vienna, Austria. 2019. https://www.R-project.org). Betas (SEs) and p values were 0.68 (0.07) and \(4.6 \times 10^{-20}\) in inverse-variance weighted (IVW), 0.65 (0.10) and \(1.8 \times 10^{-19}\) in weighted median (WM), 0.35 (0.31) and 0.256 in MR-Egger for suicide attempts; 0.53 (0.12) and \(2.2 \times 10^{-3}\) in IVW, 0.56 (0.18) and \(2.2 \times 10^{-3}\) in WM, 0.49 (0.54) and 0.366 in MR-Egger for post-traumatic stress disorder; 0.43 (0.07) and \(1.7 \times 10^{-10}\) in IVW, 0.32 (0.07) and 9.5 \times 10^{-7}\) in WM, 0.77 (0.29) and 0.008 in MR-Egger for schizophrenia; 0.34 (0.06) and 2.0 \times 10^{-4}\) in IVW, 0.40 (0.07) and 2.0 \times 10^{-4}\) in WM, 0.56 (0.26) and 0.035 in MR-Egger for bipolar disorder; 0.32 (0.02) and \(1.8 \times 10^{-18}\) in IVW, 0.29 (0.02) and \(1.5 \times 10^{-3}\) in WM, 0.18 (0.11) and 0.091 in MR-Egger for major depressive disorder; 0.18 (0.02) and \(6.2 \times 10^{-14}\) in IVW, 0.19 (0.03) and \(4.8 \times 10^{-12}\) in WM, 0.08 (0.10) and 0.430 in MR-Egger for insomnia; and 0.16 (0.09) and 0.085 in IVW, 0.16 (0.13) and 0.229 in WM, 0.22 (0.41) and 0.598 in MR-Egger for anxiety.
The associations of smoking with depression, schizophrenia, suicide ideation and bipolar disorder have been revealed in previous MR studies. The present study was based on more recent GWASs and comprehensively investigated the causal associations between smoking initiation and psychiatric traits. We confirmed established causal associations for depression, schizophrenia, suicide ideation and bipolar disorder. Meanwhile, we found some novelty associations for insomnia, post-traumatic stress disorder and a possible association for anxiety. However, it should be cautious to interpret causal associations of smoking initiation with suicide attempts, schizophrenia, bipolar disorder and anxiety due to the limitation of instrumental variables used. More studies are needed to explore these association in a causal fashion.

A bidirectional association has been observed between smoking and several psychiatric disorders, such as bipolar disorder, schizophrenia and anxiety in observational studies. It has further been shown that individuals with depressive symptoms or past major depressive disorder were less likely to quit smoking compared with smokers without depression. Even though meta-analyses found no psychiatric side-effects, such as depression and bad mood, derived from smoking cessation among general smoking quitters, some studies have detected an increased depression risk among those who attempt to quit unsuccessfully and somatic adverse reactions among individuals with nicotine replacement therapy. Thus, considering mutually detrimental influence between smoking and psychiatric diseases, difficulty of smoking cessation among certain populations and possible side-effects of smoking cessation therapies, reducing smoking initiation at the beginning step is an important public health priority.

Figure 3. (continued)
effective strategy for mental illness prevention. However, a recent study suggested the protective effect of smoking against depression. In our study, we also observed a reverse positive association between depression and smoking initiation, which supported that patients with depressive symptoms were more likely to start cigarette smoking possibly due to a depression-releasing effect derived from smoking. Thus, whether stopping smoking should be recommended among patients with depression needs to be further assessed.

Mechanisms explaining the comorbidity of smoking (nicotine dependence) with psychiatric diseases have been well acknowledged, especially for the prevalent smoking addiction among schizophrenia patients. Experimental and genetic evidence shows that nicotine can normalize several deficits, such as attention deficits, among individuals with certain psychiatric problems via nicotinic acetylcholine receptors. Antidepressant actions via monoamine oxidase inhibition (from unknown components from cigarettes) and nicotine-derived compensation effects of psychiatric medications also rationalize the phenomenon of more smokers among psychiatric patients compared with healthy adults. Although the mechanisms are not clearly clarified about the increased risk of psychiatric diseases among smokers, pathways listed above may play a role. Another possible mechanism linking smoking and psychiatric disorders is the effects of nicotine on the dopamine system. Nicotine has been also proposed to influence the dopamine system through induction of supersensitivity of D2 receptors, which shows associations with the risk of schizophrenia and other psychotic symptoms. In addition, cigarette smoking has been suggested to increase the risk of anxiety by influencing neurotransmitter systems, the immune system, oxidative and nitrogen stress, mitochondrial function, and epigenetic regulation. Given genetic and phenotypic overlapping across major psychiatric disorders, above smoking-caused anxiety-related pathways, may play roles in other specific mental diseases.

There are several advantages of our study. The MR approach minimized reverse causality, residual confounding, and misclassification, which potentially exist in observational studies. Population stratification bias was reduced in this study because SNP selection and summary-level data of psychiatric disorders were merely based on individuals of European descent and population structure was adjusted for in the GWASs. Moreover, the consistency in results across sensitivity analyses and no evidence of horizontal pleiotropy in the MR-Egger analysis indicate that our findings are unlikely biased by horizontal pleiotropy. However, our study has some limitations. The major limitation is the insufficient power to support a significant association between smoking initiation and anxiety, which needs to be verified in future studies. We had weak instrument bias or false causal direction in several analyses, which hindered the causal inference on these associations. In addition, because we only used the data from European-descent individuals, it should be cautious to generalize our findings to other populations.

In conclusion, this MR study provided evidence that smoking initiation is causally associated with an increased risk of a number of psychiatric disorders. However, whether smoking increases the risk of suicide attempts, schizophrenia, bipolar disorder and anxiety warrants future study. Reducing smoking initiation might be an effective strategy to prevent psychiatric disorders, but possibly not among patients with depression.

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**Competing interests**
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**Additional information**

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