

Cigarette smoking and schizophrenia: Mendelian randomisation study

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Background

The link between schizophrenia and cigarette smoking has been well established through observational studies. However, the cause–effect relationship remains unclear.

Aims

We conducted Mendelian randomisation analyses to assess any causal relationship between genetic variants related to four smoking-related traits and the risk of schizophrenia.

Method

We performed a two-sample Mendelian randomisation using summary statistics from genome-wide association studies (GWAS) of smoking-related traits and schizophrenia (7711 cases, 18 327 controls) in East Asian populations. Single nucleotide polymorphisms (SNPs) correlated with smoking behaviours (smoking initiation, smoking cessation, age at smoking initiation and quantity of smoking) were investigated in relation to schizophrenia using the inverse-variance weighted (IVW) method. Further sensitivity analyses, including Mendelian randomisation-Egger (MR-Egger), weighted median estimates and leave-one-out analysis, were used to test the consistency of the results.

Results

The associated SNPs for the four smoking behaviours were not significantly associated with schizophrenia status. Pleiotropy did not inappropriately affect the results.

Conclusions

Cigarette smoking is a complex behaviour in people with schizophrenia. Understanding factors underlying the observed association remains important; however, our findings do not support a causal role of smoking in influencing risk of schizophrenia.

Keywords

Cigarette smoking; schizophrenia; Mendelian randomisation; genome-wide association studies; single nucleotide polymorphism.

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Schizophrenia is a severe mental disorder, affecting approximately 1% of the world population,¹ with a range of heritability estimates from 60 to 80%.² The prevalence of cigarette smoking among people with schizophrenia is recognised to be higher than that in the general population, with around 80% reporting as current smokers in older studies,³ although more recent estimates suggest that the prevalence of smoking in in-patients is nearer 60%.⁴

People with schizophrenia are likely to be heavy smokers, who begin smoking at an earlier age, usually smoke more cigarettes daily and consume larger amounts of cigarettes than the general population.^{5,6} Cigarette smoking is also an important modifiable risk factor for respiratory diseases, metabolic syndrome and cardiovascular disease in this population,⁷ with heavy smoking likely to play at least some role in shorter life expectancies of 10–20 years.⁶

The mechanisms underlying the comorbidity of schizophrenia and smoking are still unclear. It is generally believed that the link between cigarette smoking and schizophrenia can be explained by a self-medication model, with the chemical composition of tobacco alleviating the severity of symptoms or the side-effects of antipsychotics.⁸ However, it is difficult to infer whether the relationship between cigarette smoking and schizophrenia is correlation or causation.⁹

A better understanding of smoking behaviours can be achieved by investigating the genetic architecture of smoking behaviours. In this study, a Mendelian randomisation approach was used to determine the causality between smoking behaviours (smoking initiation, smoking cessation, age at smoking initiation and quantity of smoking (cigarettes per day, CPD) and schizophrenia.

Method

Study design and data sources

The causal relationship between cigarette smoking behaviours and schizophrenia was estimated using a two-sample Mendelian randomisation analysis, which performed analysis of genome-wide associations between exposure and outcome from two traits.^{10,11} For this study, genetic data were obtained from the results of Bio-X Han Chinese populations, drawn from 7711 patients with schizophrenia and 18 327 controls.¹² As described in our previous report, patients with schizophrenia were recruited from the mental health centres in China, diagnosed by two independent psychiatrists according to the DSM-IV criteria. Controls were randomly selected from volunteers from hospitals and the community by excluding volunteers with severe mental disorders.¹² A previously published Japanese genome-wide association study (GWAS) was used to estimate the effect of single-nucleotide polymorphisms (SNPs) associated with the following smoking behaviours: smoking initiation, smoking cessation, age at smoking initiation and quantity of smoking (CPD) (Supplementary Figures and Tables available at <https://doi.org/10.1192/bjp.2020.116>).¹³ The independent variants associated with smoking-related traits below a threshold of $P < 0.00001$ were selected using the PLINK clump command. We used a linkage disequilibrium threshold of $r^2 < 0.001$ based on the 1000 Genomes Project East Asian data. We ultimately examined 31 loci for smoking initiation, 6 for smoking cessation, 7 for age at smoking initiation and 16 for CPD. We thus treated smoking behaviours as the exposure, schizophrenia as the outcome, and SNPs as the instrumental variable.

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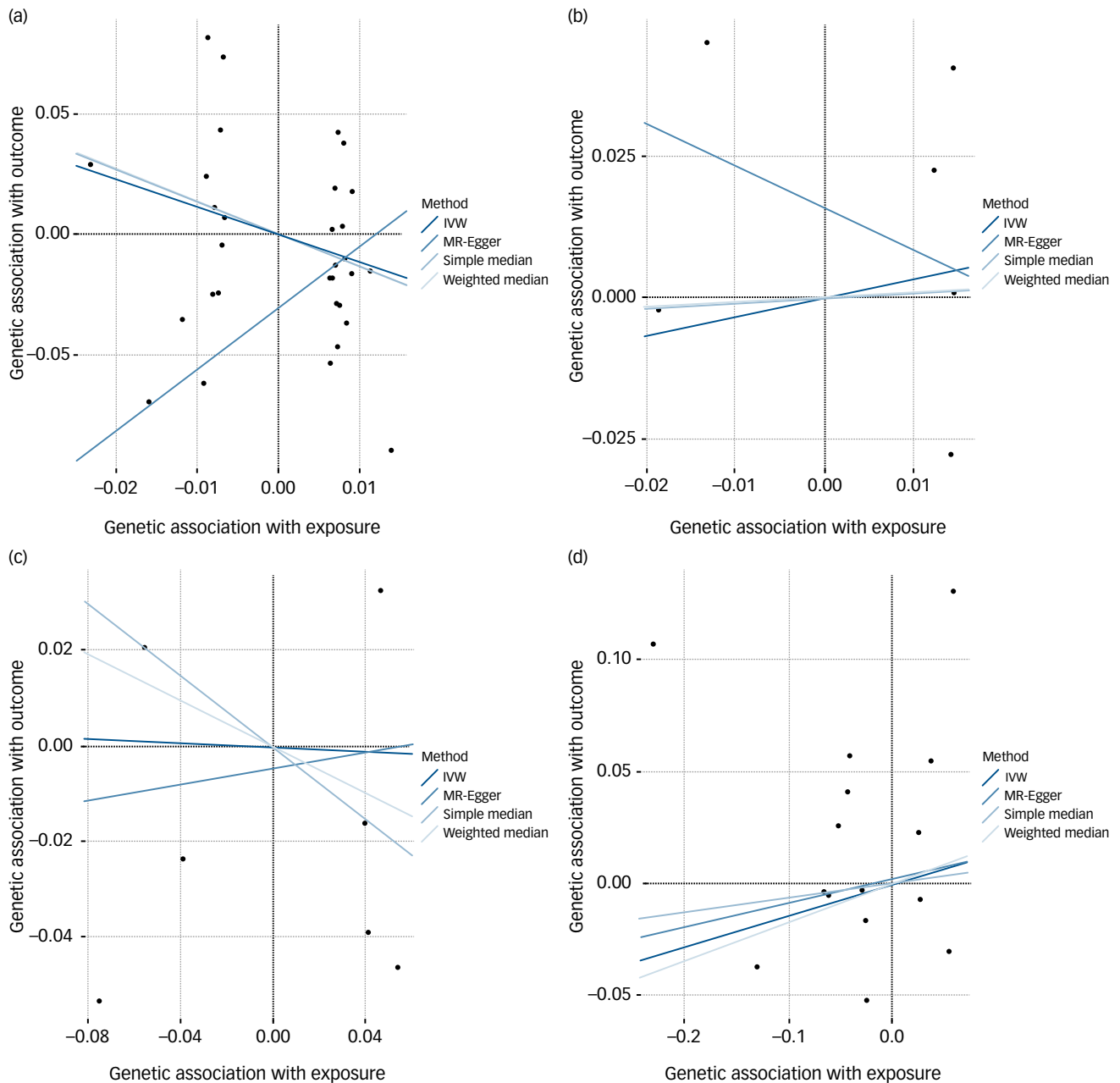


Fig. 1 Scatter plots of Mendelian randomisation regressions for smoking behaviours (exposure) and schizophrenia (outcome). (a) Smoking initiation. (b) Smoking cessation. (c) Age at smoking initiation. (d) Quantity of smoking (cigarettes per day). IVW, inverse-variance weighted standard Mendelian randomisation analysis; MR-Egger, Mendelian randomisation-Egger pleiotropy-adjusted regression.

Ethical approval

This study had obtained the ethical approval of the Ethics Committee of Human Genetic Resources at the Bio-X Institutes of Shanghai Jiao Tong University. Our study is compliant with the guidance of the Ministry of Science and Technology (MOST) for the review and approval of human genetic resources. Written informed consent was obtained from all participants.

Genetic pleiotropic assessment

Mendelian randomisation-Egger (MR-Egger) regression, which is usually performed to examine for publication bias in meta-analysis, has a strong ability to resist multiplicity of directions under the assumption of instrument strength independent of direct effect (InSIDE).¹⁴ We used this method to assess the hypothesis and

detect pleiotropic effects of targeted genes.^{14,15} We used funnel plots to provide symmetrical visual inspection. Any deviation may indicate potential pleiotropy of genetic instrumental variables.¹⁶ The regression slope of MR-Egger was also used to estimate the causal effect of poly-validity. It would be considered sufficient if the chosen SNPs could explain the proportional difference.¹⁴ InSIDE indicated that the SNPs' estimate of exposure effects must be independent of their direct impact on the outcome. Even if the selected SNP is weak, MR-Egger tends to provide reliable causal estimation.¹⁴

Mendelian randomisation estimates

We weighted the estimated impact of each SNP on schizophrenia and on smoking behaviours using the inverse variance weighted (IVW) method. This weighted linear regression model can aggregate and

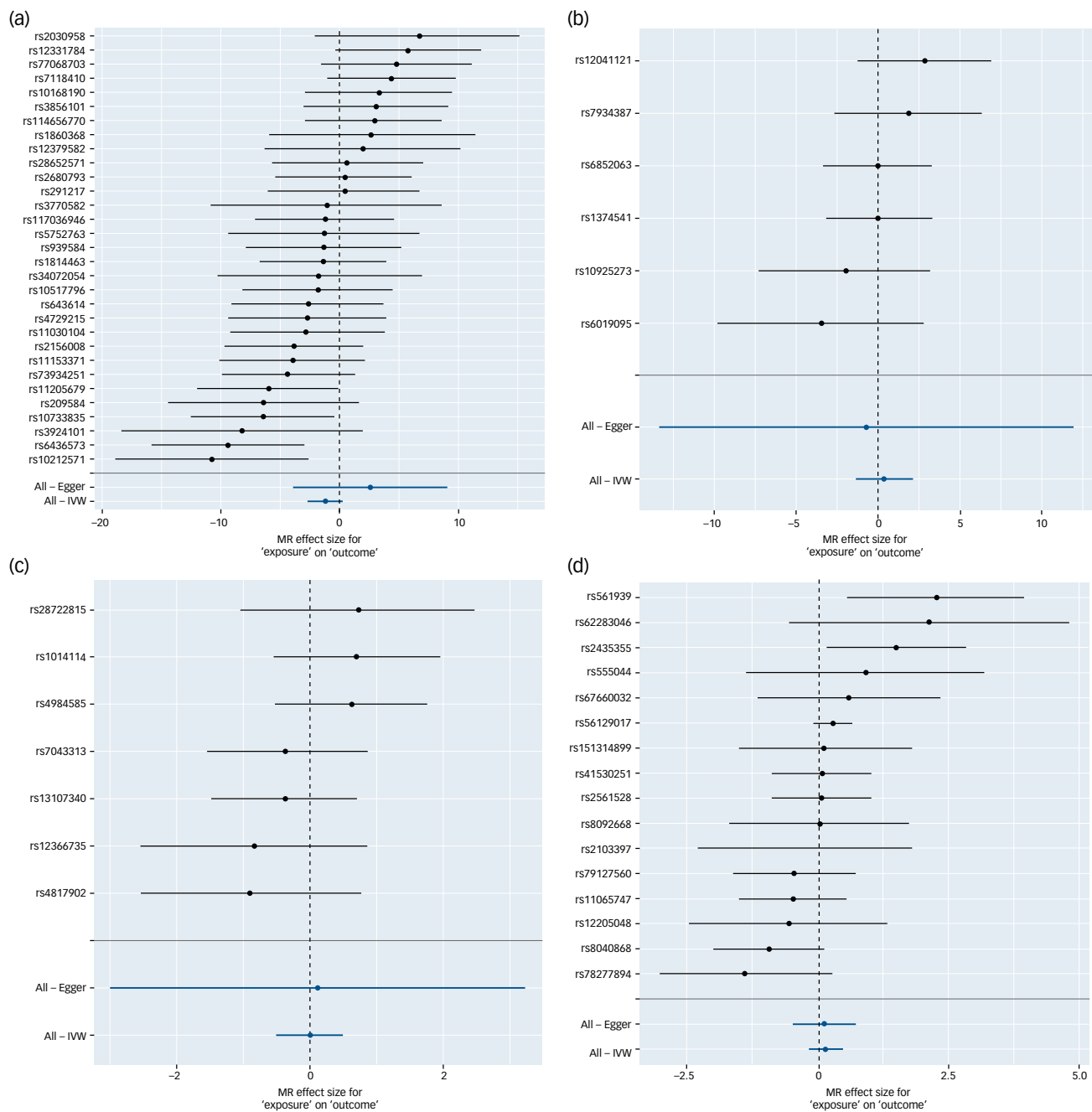


Fig. 2 Forest plots of the single nucleotide polymorphism (SNP) ratio estimates and Mendelian randomisation estimates (using Egger and inverse-variance weighted (IVW) models) for the instrument variable set for analysis of smoking behaviours (exposure) on schizophrenia (outcome). (a) Smoking initiation. (b) Smoking cessation. (c) Age at smoking initiation. (d) Quantity of smoking (cigarettes per day). The solid lines represent 95% CI.

minimise the sum of the variances. And each random variable is inversely proportional to its variance.¹⁷ Fixed- or random-effects meta-analysis models were pooled to estimate the impact of gene-associated smoking behaviours on schizophrenia risk.^{18,19}

R version 3.4.0 and MendelianRandomisation 0.4.2, both for Windows, were used for all statistical analyses.²⁰ The weighted median method was used to supplement the MR-Egger, in order to obtain a more reliable estimation of the causal effect.

Sensitivity analyses

To rule out the possibility that the Mendelian randomisation studies were affected by these SNPs, we performed sensitivity analyses.

A leave-one-out analysis was also performed to see whether there were any SNP-driven associations.

Results

We compared standard IVW analysis with MR-Egger analysis for potential horizontal multidirectional correction to demonstrate the relationship between the effect of SNPs on exposures (the four smoking behaviours) and of SNPs on the outcome (schizophrenia status), which further confirmed the results of zero multiplicity.

Results are displayed in Figs 1 and 2, Tables 1 and 2, Supplementary Figures 1–3 and Supplementary Tables 1–6. In

Table 1 Results of Mendelian randomisation (MR) analyses and sensitivity analyses for the effect of quantity of smoking (cigarettes per day) on schizophrenia status

Method	OR	95% CI	P
Simple median	1.067	0.674–1.687	0.782
Weighted median	1.186	0.845–1.664	0.323
Inverse-variance weighted	1.150	0.832–1.590	0.397
MR-Egger	1.113	0.602–2.056	0.734
(Intercept)	1.002	0.969–1.038	0.899

summary, no significant associations were found with schizophrenia status for the 31 smoking initiation-associated SNPs (IVW estimate of odds ratio OR = 0.318, 95% CI 0.073–1.394, $P = 0.129$), for the 6 smoking cessation-associated SNPs (OR = 1.397, 95% CI 0.259–7.538, $P = 0.698$), for the 7 age at smoking initiation-associated SNPs (OR = 0.976, 95% CI 0.589–1.619, $P = 0.927$) or for the 16 CPD-related SNPs (OR = 1.150, 95% CI 0.832–1.590, $P = 0.397$).

After multiple testing correction, none of the assessed genetic risk variables was individually associated with schizophrenia. MR-Egger regression analysis indicated no statistical significance, indicating that genetic pleiotropy did not give rise to causal bias. The leave-one-out analyses showed that most of the associated signals were not driven by a single genetic marker (Supplementary Fig. 3).

Discussion

Smoking rates in people with schizophrenia are well-recognised to be substantially higher than those in the general population, but the causal relationship between smoking and schizophrenia still remains controversial. Previous GWASs of schizophrenia have identified more than 100 common risk variants,^{12,21} and a GWAS of four smoking behaviours among 165 436 Japanese individuals identified three loci (EPHX2–CLU, RET and CUX2–ALDH2) associated with CPD, three loci (DLC1, CXCL12–TMEM72–AS1 and GALR1–SALL3) associated with smoking initiation and one locus (LINC01793–MIR4432HG) associated with age at smoking initiation.¹³ Drawing on these known associations with cigarette smoking behaviours, we therefore applied a two-sample

Mendelian randomisation methodological approach using genetic instrumental variables on schizophrenia as an outcome.

The causal relationship, self-medication and shared diathesis hypotheses

There are three main hypotheses for high smoking rates in people with schizophrenia: (a) the causal relationship hypothesis, (b) the self-medication hypothesis and (c) the shared diathesis hypothesis. The self-medication hypothesis postulates that patients can alleviate clinical symptoms or gain relief from treatment-related side-effects by smoking. Smoking is also found to be associated with poorer cognitive performance compared with non-smoking status.²² However, the processes underlying the smoking–schizophrenia association may be much more complex. One study found that smoking might be the independent factor increasing the risk for schizophrenia,²³ and others have reported that tobacco smoking might give rise to an increased risk of psychosis and/or an earlier onset.^{24,25} A prospective dose–response relationship was found between smoking and risk for schizophrenia in Swedish cohorts.²⁶ Another two-sample bi-directional Mendelian randomisation study found no evidence for pleiotropy in the causal effect of smoking initiation on schizophrenia risk when the potential impact of pleiotropy was minimised.²⁷ Furthermore, two previous Mendelian randomisation studies have also assessed causality in associations between the use of cannabis and the risk of schizophrenia.^{28,29} Cannabis use is markedly linked with cigarette smoking in some countries, and it can confound the causal relationship. Our results in a Han Chinese population suggest that the causal relationship hypothesis is not an underlying explanation. Specifically, no causal effects relating to smoking initiation, smoking cessation, age at smoking initiation or quantity of smoking were identified for schizophrenia as an outcome. In addition, none of the intercept estimates from the MR-Egger method significantly deviated from zero, and no evidence of heterogeneity or outlier pleiotropy was observed. The prevalence of smoking is significantly different between men and women in many East Asian countries. One potential explanation is that pregnancy affects the prevalence of smoking. In China, pregnant women hardly smoke, while their partners often quit smoking or do not smoke around them during pregnancy.³⁰

Recent genetic studies have identified several loci associated with smoking and schizophrenia, and shared familial/genetic risk factors have been found to contribute to the association.²⁶ The

Table 2 Associations of individual single nucleotide polymorphisms (SNPs) (used as Mendelian randomisation instruments) with quantity of smoking (cigarettes per day, CPD) and schizophrenia

CPD SNP	Chromosome	Position (base pair)	Alleles ^a	CPD results		Schizophrenia results	
				P	β^b	P	β^b
rs561939	1	37333860	A/C	8.26E–07	0.057	0.009	0.130
rs62283046	3	174891789	A/G	6.25E–06	–0.024	0.119	–0.052
rs67660032	3	194831870	C/T	5.24E–06	–0.026	0.508	–0.015
rs151314899	5	56076308	T/A	2.30E–06	–0.028	0.900	–0.003
rs12205048	6	70190978	G/A	9.39E–06	0.053	0.562	0.030
rs79127560	7	21001372	T/A	4.45E–06	–0.228	0.434	0.107
rs78277894	8	27429192	G/A	5.63E–13	–0.040	0.086	0.057
rs2435355	10	43624833	T/C	3.62E–08	0.036	0.028	0.055
rs555044	12	335922	C/A	2.30E–06	0.025	0.436	0.023
rs2103397	12	6835485	G/A	6.36E–06	0.028	0.820	–0.007
rs11065747	12	111326666	G/T	3.41E–14	–0.053	0.359	0.026
rs8040868	15	78911181	T/C	2.49E–15	–0.043	0.077	0.041
rs8092668	18	57783111	A/G	5.01E–06	–0.032	0.960	–0.001
rs2561528	19	41226415	G/C	3.44E–21	–0.065	0.904	–0.004
rs41530251	19	41316355	T/C	5.34E–25	–0.060	0.882	–0.004
rs56129017	19	41416948	C/T	2.18E–96	–0.131	0.137	–0.036

a. Alleles are shown as other allele/effect allele.

b. Effect sizes for the effect allele.




Psychiatric Genomics Consortium (PGC) conducted a series of GWASs of schizophrenia,²¹ and they reported that variants in the nicotinic acetylcholine receptor *CHRNA5-A3-B4* gene cluster were associated.³¹ Not only that, variants within this gene cluster were also identified as strongly associated with number of cigarettes smoked per day (CPD). This might mean that there is a common genetic architecture shared between smoking and schizophrenia.^{32,33} However, our findings just address the causal relationship hypothesis, and further research is needed to investigate the shared diathesis hypothesis.

Limitations

Our research has some limitations. First, the lack of stratification on smoking status may dilute any causal effect. Second, the analyses were focused on a Han Chinese population and generalisability cannot be assumed. Third, the sample size and the number of variants for analysis were relatively small.

Implications for further research

As we found no significant associations indicating a causal relationship between smoking and schizophrenia, at least in the population sampled, further research is needed to investigate other potential mechanisms. Understanding the relationship between cigarette smoking and schizophrenia is critical, not least because of the substantial health disparities that may result from this risky behaviour.

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First received 3 Jan 2020, final revision 6 May 2020, accepted 15 May 2020

Data availability

GWAS summary statistics of schizophrenia and smoking behaviours are publicly available online (Bio-X at <http://gwas.bio-x.cn/>; and JENGER at <http://jenger.riken.jp/en/>). The data that support the findings of this study are available within the article and its supplementary files.

Acknowledgements

We thank all the patients and healthy controls participating in this study and the psychiatrists for their help in the recruitment and diagnosis.

Author contributions

J.C., Y.S. and Z.L. were the overall principal investigators who were responsible for study design and oversaw the entire study. Y.X. supervised the diagnosis of patients and participant recruitment. R.C., S.X., N.L., C.G., C.W., Q.Z. and Y.Z. coordinated and carried out the study. Z.L. performed analyses. J.C., N.L., Y.L., R.S. and Z.L. interpreted the results. Y.L. and R.S. supervised the experiments and data analyses. The manuscript was drafted by J.C. under the supervision of R.S., Y.X., Y.S. and Z.L. All authors critically reviewed the article and approved the final manuscript.

Funding

This work was supported by the National Key R&D Programme of China (grant numbers 2016YFC1306900, 2017YFC0908105, 2019YFA0905400), the Natural Science Foundation of China (grant numbers 81701321, 81871055, 81421061, 31571012, 81501154, 81871051), the 973 Programme (grant number 2015CB559100), Taishan Scholar Programme of Shandong Province (Z.L., grant number tsqn201812153), the Natural Science Foundation of Shandong Province (grant number ZR2019YQ14), the Programme of Shanghai Subject Chief Scientist (Y. S., grant number 15XD1502200), the National Programme for Support of Top-Notch Young Professionals (Y.S.), Shanghai Key Laboratory of Psychotic Disorders (grant number 13dz2260500), the National Institute for Health Research (NIHR) Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King's College London (R.S.), Shanghai Hospital Development Centre (grant numbers SHDC12017X12, SHDC12016115), the Specialised Construction Project of Integrated Chinese and Western Medicine of Shanghai General Hospitals (grant number ZHYY-ZXYJHZ-2-201709), Shanghai Youth Top-Notch Talent Support Programme (J.C.), Shanghai Mental Health Centre (J.C., grant number 2016-fx-02), Shanghai Municipal Commission of Science and Technology (grant numbers 17JC1402900, 17490712200, 18DZ2260200), Shanghai Municipal Health Commission (grant numbers ZK2015B01, 201540114), Shanghai Municipal Science and Technology Major Project (grant number 2018SHZDZX05), Scientific Research and Development Fund of Shanghai Jiao Tong University (grant number 19X150010012), the Innovative Research Team of High-Level Local Universities in Shanghai and Shanghai Clinical Research Centre for Mental Health (grant number 19MC1911100).

Declaration of interest

None.

ICMJE forms are in the supplementary material, available online at <https://doi.org/10.1192/bjp.2020.116>.

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Supplementary material

Supplementary material is available online at <http://doi.org/10.1192/bjp.2020.116>.

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