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ORIGINAL ARTICLE

Understanding the Causal Relationships Between Opioid Dependence and Risk of Mental Disorders: A Comprehensive Two-Sample Mendelian Randomization Study

Yundi Hu[1] · Luheng Qian[1] · Runye Shi[1] · Haojing Duan[2] · Xiaolei Lin[1]

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Abstract
Observational studies have reported positive associations between opioid dependence and major mental disorders. However, the causal relationships and causal mechanisms between opioid dependence and mental disorders remain unknown due to potential confounding bias and reverse causality. In this study, we aim to investigate the causal associations and possible mediating mechanisms between opioid dependence and mental disorders via Mendelian randomization. Comprehensive bidirectional Mendelian randomization (MR) studies were conducted between opioid dependence and major mental disorders, including schizophrenia, bipolar disorder, major depressive disorder, panic disorder, anorexia, obsessive–compulsive disorder, post-traumatic stress disorder, and insomnia. Inverse variance weighted approach was adopted as the primary analytic method with series of sensitivity analyses. Mediation effects of chronic pain along the opioid dependence–mental disorders causal pathway were assessed by multivariate MR and two-step MR. Forward MR identified significant positive causal effects of opioid dependence on insomnia (OR = 1.03, 95% CI = (1.01, 1.05), $p = 0.005$), while reverse MR showed significant positive causal effects of schizophrenia on opioid dependence (OR = 1.20, 95% CI = (1.07, 1.34), $p = 0.002$). No significant causal associations were found between opioid dependence and other mental disorders. Neither opioid dependence on insomnia nor schizophrenia on opioid dependence causal pathway was significantly mediated by chronic pain. Higher risks of genetically predicted opioid dependence may lead to higher risks of insomnia, while higher risks of genetically predicted schizophrenia may lead to higher risks of developing opioid dependence. The majority of causal effects were acted directly rather than via chronic pain.

Keywords Opioid dependence · Mental disorder · Insomnia · Schizophrenia · Mendelian randomization · Causal effect

✉ Xiaolei Lin
xiaoleilin@fudan.edu.cn

[1] School of Data Science, Fudan University, Shanghai, China

[2] Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China

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Opioid use disorder and opioid addiction remain a serious public health crisis in the USA and worldwide, with over 600 million deaths involving opioid overdose over the past two decades (Overdose, 2018). The misuse and addiction to opioids are significant drivers of shortened life expectancy and increased morbidity, including fetal death, infants born with neonatal abstinence syndrome, and transmission of infectious disease via opioid injection (Chang et al., 2019; Dowell et al., 2017; Jones, 2018; Ko et al., 2016; Peters et al., 2016). Originally prescribed for acute pain relief, opioids bind to receptors in the central and peripheral nervous systems to induce intense euphoria and could quickly develop tolerance with severe withdrawal syndromes (Shaheed et al., 2019; Degenhardt et al., 2019). Opioid dependence represents a particular transitional stage from opioid use to misuse, and several risk factors are found to be associated with opioid dependence and addiction, including low socioeconomic status, risk-taking or thrill-seeking behaviors, and history of mental disorders such as depression and anxiety (Han et al., 2015; Han et al., 2017). However, the causal relationships and biological mechanisms between opioid dependence and mental disorders remain largely unknown.

Opioid dependence often co-occurs with mental disorders. According to a national survey on drug use and health, 62% of adults with opioid use disorder in the US had a co-occurring mental illness, and 24% had a serious mental illness (Jones & McCance-Katz, 2019). With potential overlapping neurobiological basis, opioid use disorder and opioid dependence may trigger changes in the brain and increase one's risk for developing mental disorders, and brain changes in people with mental disorders may enhance the rewarding effects of opioids misuse or dependence (Koob, 2020). In addition, patients with diagnosed mental disorders are at higher risk of opioid dependence and overdose, but on the other hand, are more likely to get opioid prescription (Feingold et al., 2018). Therefore, understanding the mechanisms of the co-occurrence and elucidating the causal directions between opioid dependence and mental disorders are of paramount importance to inform preventive strategies.

Several observational studies have reported positive associations between prescription opioid use and common mental health disorders (Davis et al., 2017; Sullivan et al., 2006; Vekaria et al., 2021). However, observational studies are subject to confounding bias and reverse causality, and directions of the causal relationships between opioid dependence and mental disorders cannot be estimated. When randomized clinical trials are not feasible due to ethical and administrative reasons, Mendelian randomization (MR), which uses genetic variants associated with the exposure at genome-wide significance level as unconfounded proxies for the exposure variable, serves as a useful tool for assessing the causal effects and directions between the exposure and outcomes of interest.

In this study, we aim to investigate the causal relationships between opioid dependence and major mental disorders, including major depressive disorder (MDD), schizophrenia (SCZ), bipolar disorder (BIP), panic disorder (PD), anorexia (ANX), obsessive–compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and insomnia, using bidirectional MR design. Summary statistics were obtained from published GWAS of opioid dependence and mental disorders. Causal effects were estimated primarily using the inverse variance weighted method in two-sample MR, with robustness checks for heterogeneity and horizontal pleiotropy and other sensitivity analyses. Causal directions were assessed bidirectionally, by forward MR investigating the effects of opioid dependence on mental disorders, and reverse MR investigating the effect of mental disorders on opioid dependence. Finally, mediation effects of chronic pain along the opioid dependence on mental disorders causal pathway were assessed using multivariate MR and two-step MR methods.

Methods

Study Design

An overview of the study workflow is illustrated in Fig. 1. The study was reported according to Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) guideline (STROBE-MR Checklist) (Skrivankova et al., 2021). All relevant GWAS had obtained ethical permissions from corresponding institutional review boards. Since our study involves only publicly available GWAS summary statistics, no ethical approval was required from the institutional review board.

Data Source

Summary statistics were obtained from the GWAS of opioid dependence (1303 cases and 455,045 controls) (Jiang et al., 2021), MDD (135,458 cases and 344,901 controls) (Wray et al., 2018), SCZ (53,386 cases and 77,258 controls) (Trubetskoy et al., 2022), BIP (41,917 cases and 371,549 controls) (Mullins et al., 2021), PD (2147 cases and 7760 controls) (Forstner et al., 2021), ANX (16,992 cases and 55,525 controls) (Watson et al., 2019), PTSD (23,212 cases and 151,447 controls) (Nievergelt et al.,

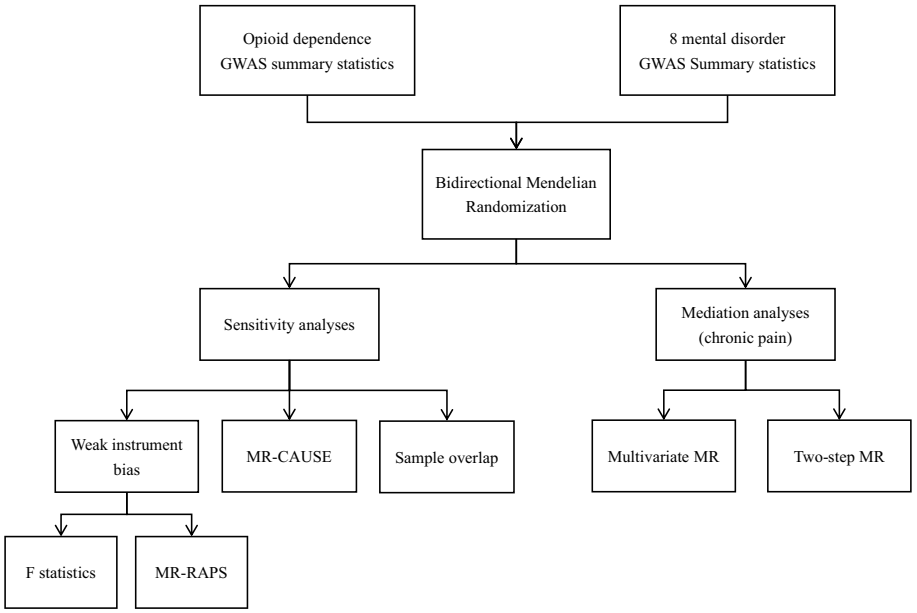

Fig. 1 Flowchart of the overall study design. Eight mental disorders include schizophrenia (SCZ), bipolar disorder (BIP), major depressive disorder (MDD), panic disorder (PD), anorexia (ANX), obsessive–compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and insomnia. Assumption of Mendelian randomization (MR) include the following: (1) instrumental variables are strongly associated with exposures (i.e., the relevance assumption); (2) instrumental variables should not be associated with confounders (i.e., the independence assumption); (3) instrumental variables should influence the outcomes only through the exposures (i.e., the exclusion restriction assumption). GWAS, genome-wide association study; CAUSE, causal analysis using summary effect; RAPS, robust adjusted profile score; MR, Mendelian randomization

2019), OCD (2688 cases and 7037 controls) (Arnold et al., 2018), insomnia (593,724 cases and 1771,286 controls) (Watanabe et al., 2022), and chronic pain (152 cases and 456,196 controls) (Jiang et al., 2021). All participants included in the analyses were of European ancestry. Opioid dependence, insomnia, and chronic pain's GWAS are from UK Biobank (UKB), and other 7 mental disorders' GWAS are from Psychiatric Genomics Consortium (PGC). Detailed description of data sources is provided in Table 1. Table S17 showed the baseline characteristic of cohorts in UKB. Table S18—Table S24 showed the country, cases number, and controls number of each PGC cohort.

Since weak instrument bias and inflation of Type I error rate could result from partially overlapped samples of the exposure and outcome GWAS (Burgess et al., 2016), we additionally checked the sample overlap between participants in the GWAS of opioid dependence and those in the GWAS of mental disorders. Since GWAS of insomnia involved participants from the UK Biobank, we additionally assessed the amount of bias using sensitivity analysis to account for sample overlap with opioid dependence. GWAS of the remaining mental disorders involve cohorts from the Psychiatric Genomics Consortium and did not have sample overlap with opioid dependence.

Selection of Genetic Instruments

For opioid dependence, a p value threshold of 1e-5 was used for selecting instrumental SNPs since no enough valid instrumental SNPs could be obtained using p value threshold of 5e-8 or 5e-6. SNPs were then clumped by linkage disequilibrium (LD) < 0.001 within a 100 kb window for independence. When instrumental SNPs were not present in outcome GWAS, we used SNPs in outcome GWAS with high LD (> 0.8) to replace. Palindromic SNPs with intermediate allele frequencies were removed. This resulted in 9 valid instrumental SNPs for opioid dependence (Table S5). Although using relatively relaxed p value thresholds could increase the statistical power by using larger numbers of genetic instruments, it could potentially lead to weak instrument bias (Pierce & Burgess, 2013). Therefore, we further tested the strength of association between these 9 instrumental SNPs and phenotypic opioid dependence using F statistics, where an F value greater than 10 indicates strong association between instrumental SNPs and phenotypic opioid dependence (Pierce et al., 2011). Robust adjusted profile score MR (MR-RAPS) was also conducted to test weak instrument bias (SCORE, 2018).

Similarly in the reverse MR, instrumental SNPs were identified for each mental disorder. Following the suggestions of previous studies, a p value threshold 5e-8 of was used to select instrumental SNPs for SCZ, BIP, and ANX, while a threshold of 5e-6 was used for MDD, PD, PTSD, OCD, and insomnia due to insufficient number of instrumental SNPs under more stringent p value thresholds (Gage et al., 2018; Choi et al., 2019; Rosoff et al., 2021). After clumping by LD, we obtained 43, 146, 51, 13, 6, 19, 13, and 13 instrumental SNPs for MDD, SCZ, BIP, PD, ANX, PTSD, OCD, and insomnia, respectively. Detailed information about individual instrumental SNP for each mental disorder were provided in Table S6-S13. Again, the strength of association between instrumental SNPs and each mental disorder when using relaxed p value threshold was assessed by F statistics and MR-RAPS.

Table 1 Description of the data sources (GWAS summary statistics) included in this study

Phenotype	Diagnostics	GWAS sample (European Ancestry)			Consortium / cohorts	Publication journal	PubMed ID
		Cases	Controls				
Opioid dependence	ICD-10, ICD-9	1,303	455,045		UKB	Nature Genetics	34737426
Insomnia	Self-reported	593,724		1,771,286	UKB	Nature Genetics	35835914
Anorexia	DSM-III-R, DSM-IV, ICD-8, ICD-9, or ICD-10	16,992		55,525	PGC	Nature Genetics	31308545
Bipolar disorder	DSM-IV, ICD-10, or ICD-9	41,917		371,549	PGC	Nature Genetics	34002096
Major depressive disorder	DSM-IV, ICD-10, or ICD-9	135,458		344,901	PGC	Nature Genetics	29700475
Obsessive–compulsive disorder	Self-reported	2,688		7,037	PGC	Molecular Psychiatry	28761083
Panic disorder	DSM-IV, ICD-10, or ICD-9	2,147		7,760	PGC	Molecular Psychiatry	31712720
Post-traumatic stress disorder	DSM-III-R, DSM-IV, DSM-5	23,212		151,447	PGC	Nature Communications	31,594,949
Schizophrenia	DSM-IV, ICD-10	53,386		77,258	PGC	Nature	35396580
Chronic pain	ICD-10, ICD-9	152		456,196	UKB	Nature Genetics	34737426

ICD International Classification of Diseases, *DSM* The Diagnostic and Statistical Manual of Mental Disorders, *UKB* UK Biobank, *PGC* Psychiatric Genomics Consortium

Statistical Analyses

For forward MR, univariate two-sample MR was performed between opioid dependence and each mental disorder, with Bonferroni correction for multiple comparisons. Inverse variance weighted MR was used as the primary analytic approach when heterogeneity and horizontal pleiotropy did not exist. Cochran Q statistic and MR pleiotropy residual sum and outlier (MR-PRESSO) / MR-Egger tests were used to assess heterogeneity and horizontal pleiotropy, respectively (Burgess & Thompson, 2017; Huedo-Medina et al., 2006; Verbanck et al., 2018). In case of heterogeneity, results from weighted median method (which only requires 50% of the weight to come from valid genetic instruments) were adopted, and in case of horizontal pleiotropy, results from MR-Egger regression models (which gives consistent estimates when 100% of the genetic instruments were invalid) were adopted. We also conducted leave-one-SNP-out analysis to check whether results were driven by individual genetic instrument. For reverse MR, univariate two-sample MR was performed between each mental disorder and opioid dependence following the same analytic strategy. MR-CAUSE analysis, which accounts for both correlated and uncorrelated pleiotropy between exposure and outcome variables, was conducted as a sensitivity analysis when significant causal effect was obtained between opioid dependence and mental disorders.

Mediation effects of chronic pain along the mental disorder on opioid dependence causal pathway was evaluated using both multivariate MR and two-step MR analysis (Carter et al., 2021). Specifically, to estimate the mediation effects of chronic pain along the mental disorder on opioid dependence causal pathway, both mental disorder and chronic pain were included as the exposure variables in multivariate MR, while effects of mental disorder on chronic pain and effects of chronic pain on opioid dependence were successively estimated and multiplied in two-step MR analysis.

Causal effects between opioid dependence and mental disorders are quantified by odds ratio (ORs), which represent the risk for mental disorders per one unit increase in log odds of opioid dependence (forward MR), or the risk for opioid dependence per one unit increase in log odds of mental disorders (reverse MR). Both point estimates and 95% confidence intervals (CI) were reported. For consistent estimation of the effects and directions between opioid dependence and mental disorders, only results with consistent magnitude and direction across multiple MR analytic strategies are considered. Bonferroni corrected p value threshold $< 0.05/8$ (across 8 mental disorders) was used for statistical significance. All two-sample MR analyses were performed using the "TwoSampleMR" and "MRPRESSO" package in R (version 4.0.3).

Results

Causal Effects of Opioid Dependence on Mental Disorders

As shown in Fig. 2, using 9 valid instrumental SNPs strongly associated with opioid dependence, univariate forward MR analysis showed significant positive causal effects of opioid dependence on insomnia via inverse variance weighted approach (OR = 1.03, 95% CI = (1.01, 1.05), $p = 0.0053$). Specifically, higher probabilities of opioid dependence were causally related to higher risks of insomnia. Cochran's Q statistics did not show evidence of heterogeneity ($p = 0.26$), and neither MR-PRESSO nor MR-Egger test

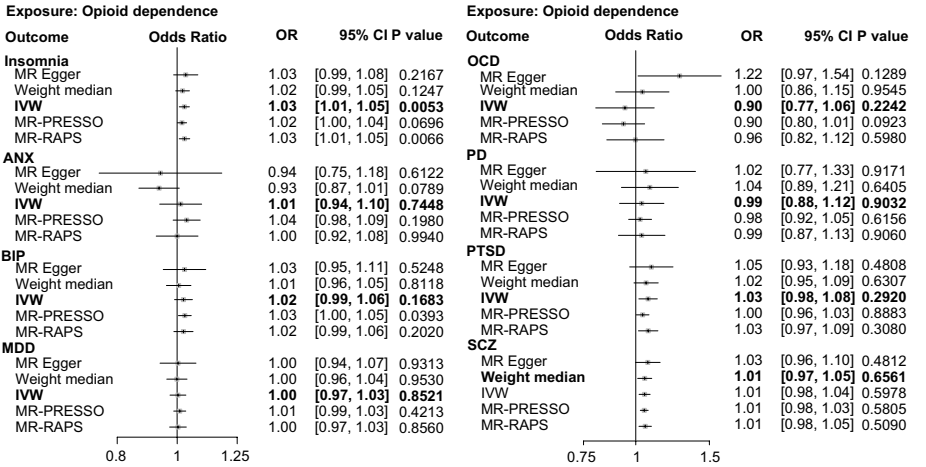

Fig. 2 Causal effects of opioid dependence on mental disorders assessed by forward MR. Boxes represent point estimates of the causal effects, and error bars represent 95% confidence intervals. Methods in bold represent appropriate MR analytical approach after testing for assumptions of heterogeneity and horizontal pleiotropy. OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted; PRESSO, pleiotropy residual sum and outlier; RAPS, robust adjusted profile score; ANX, anorexia; BIP, bipolar disorder; MDD, major depressive disorder; OCD, obsessive–compulsive disorder; PD, panic disorder; PTSD, post-traumatic stress disorder; SCZ, schizophrenia

intercept tests showed evidence of horizontal pleiotropy ($p = 0.61$ for MR-PRESSO, $p = 0.81$ for MR-Egger). Scatter plot and funnel plot are shown in Figure S1 and Figure S2. *F* statistics showed strong association between genetic instruments of opioid dependence and phenotypic opioid dependence (*F* value = 11,338). Results from the MR-CAUSE model suggested that causal model of opioid dependence on insomnia outperformed both the null and sharing model (Table 2).

Table 2 Sensitivity analyses for the causal effect of opioid dependence on insomnia, and for the causal effect of schizophrenia on opioid dependence via MR-CAUSE

Model 1[a]	Model 2[a]	Δ ELPD[b]	SE Δ ELPD	*Z* score	*p* value
Opioid dependence → insomnia					
Null	Sharing	−0.59	0.53	−1.10	0.14
Null	Causal	−2.38	2.50	−0.95	0.17
Sharing	Causal	−1.79	2.02	−0.89	0.19
Schizophrenia → opioid dependence					
Null	Sharing	−1.79	1.63	−1.10	0.14
Null	Causal	−2.52	2.82	−0.89	0.19
Sharing	Causal	−0.72	1.53	−0.47	0.32

CAUSE causal analysis using summary effect, *ELPD* expected log pointwise posterior density, *SE* standard error

[a]Model 1 and Model 2 are the corresponding models being compared

[b]Δ ELPD measures the difference between model fit, where negative value indicates better fitting for model 2 than model 1

Since the GWAS sample of insomnia involved UK Biobank participants and overlapped with opioid dependence, we assessed the risk of bias using sensitivity analysis. No significant risk of bias or inflation of Type I error was observed for the causal effects of opioid dependence on insomnia (bias < 0.001, regardless of overlap proportion, Table S14). Further, causal effects of opioid dependence on insomnia were consistent in terms of directions and magnitude across multiple MR approaches. Leave-one-SNP-out analyses did not show that results were driven by individual SNPs (Table S3).

Causal Effects of Mental Disorders on Opioid Dependence

Having observed significant causal effects of opioid dependence on insomnia, we conducted reverse MR analysis investigating the causal effects of mental disorders on opioid dependence. As shown in Fig. 3, using 146 valid instrumental SNPs, univariate MR analysis showed significant positive effects of schizophrenia on opioid dependence (OR = 1.20, 95% CI = (1.07, 1.34), $p = 0.002$) via inverse variance weighted approach. Specifically, higher risks of genetically predicted schizophrenia would lead to higher chances of developing opioid dependence. Cochran's Q statistics did not show any evidence of heterogeneity ($p = 0.23$), and neither MR-PRESSO / MR-Egger test intercept tests showed evidence of horizontal pleiotropy ($p = 0.22$ for MR-PRESSO, $p = 0.45$ for MR-Egger). Scatter plot and funnel plot are shown in Figure S3 and Figure S4. F statistics showed strong association between genetic instruments of schizophrenia and phenotypic schizophrenia (F value = 295).

Results of the MR-CAUSE analysis suggested that causal model of schizophrenia on opioid dependence outperformed both the null and sharing model (Table 2). Further, causal

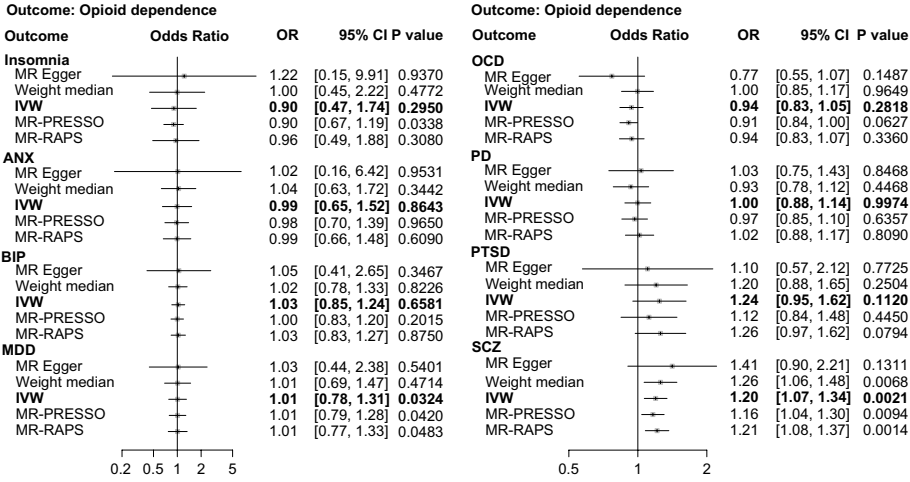

Fig. 3 Causal effects of mental disorders on opioid dependence assessed by reverse MR. Boxes represent point estimates of the causal effects, and error bars represent 95% confidence intervals. Methods in bold represent appropriate MR analytical approach after testing for assumptions of heterogeneity and horizontal pleiotropy. OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted; PRESSO, pleiotropy residual sum and outlier; RAPS, robust adjusted profile score; ANX, anorexia; BIP, bipolar disorder; MDD, major depressive disorder; OCD, obsessive–compulsive disorder; PD, panic disorder; PTSD, post-traumatic stress disorder; SCZ, schizophrenia

effects of schizophrenia on opioid dependence were consistent in terms of directions and magnitude across multiple MR approaches. Leave-one-SNP-out analyses did not show that results were driven by any individual SNPs (Table S4).

In addition to schizophrenia, we observed nominal significant causal effects of MDD (OR = 1.33, 95% CI = (1.02, 1.72), $p = 0.0323$) on opioid dependence using 43 valid instrumental SNPs. Specifically, higher risks of genetically predicted MDD would lead to higher risks of opioid dependence at nominal significant level. However, these results became non-significant after Bonferroni correction for multiple comparisons.

Mediating Effects of Chronic Pain Along the Opioid Dependence on Mental Disorder Causal Pathway

To investigate whether causal effects of opioid dependence on insomnia and causal effects of schizophrenia on opioid dependence are mediated by chronic pain, we conducted both multivariate MR and two-step MR analyses. As shown in Table 3, both multivariate MR and two-step MR analyses suggest that opioid dependence effect insomnia via the direct pathway and independent of chronic pain. What is more, genetically predicted risk of schizophrenia impacts opioid dependence via a direct route independent of chronic pain. Detailed results of total effects, direct effects, and indirect effects can be found in Table S15 and Table S16.

Discussion

In this study, we comprehensively investigated the causal relationships between opioid dependence and multiple mental disorders using bidirectional MR design. Despite high genetic correlation and strong pleiotropy between various mental disorders (Amare et al., 2020; Cardno & Owen, 2014), our results suggested a high degree of variability regarding their causal patterns with opioid dependence. Our analyses provide statistical evidence for a positive causal effect of opioid dependence on insomnia, and a positive causal effect of schizophrenia on opioid dependence. By dissecting the total effects of schizophrenia on opioid dependence (and of opioid dependence on insomnia), we also found that the

Table 3 Mediation effects of chronic pain on the opioid dependence on insomnia and schizophrenia on opioid dependence causal pathways

Causal pathway	Total effect	Direct effect	Mediation effect	*p* value (mediation effect)
Opioid dependence → insomnia				
MVMR	0.0266	0.0246	2.0×10^{-3}	0.8777
Two-step MR		0.0267	-4.0×10^{-5}	0.8737
Schizophrenia → opioid dependence				
MVMR	0.1790	0.1857	-6.7×10^{-3}	0.9351
Two-step MR		0.1791	-6.1×10^{-5}	0.9855

SE standard error, *MVMR* multivariate Mendelian randomization

majority of causal effects are acted directly from schizophrenia to opioid dependence (and from opioid dependence to insomnia), compared to those mediated through chronic pain.

Associations between opioid use and sleep disorders have been reported in many literatures, suggesting that both are linked to brain regions involved in reward processing. Opioids intake could increase daytime sleepiness and decrease sleep latency, while disrupting night sleep and augmenting night awakening due to acute withdrawal effects (Roth, 2009; Schierenbeck et al., 2008). Studies also showed dose-dependent effects of opioids on total sleep, sleep efficiency, and sleep disruptions (Kay et al., 1981; Moore & Kelz, 2009). While the initiation and continuation of opioid use have been known to reduce rapid eye movement (REM) sleep without inducing sleep arousal, chronic use and addiction to opioids were found to elevate REM sleep with pronounced alteration in slow-wave sleep, wakefulness, and arousal (Wang & Teichtahl, 2007; Shaw et al., 2005; Hartwell et al., 2014). In addition to chronic use of opioids, acute opioid withdrawal could also contribute to sleep disturbances by elonging sleep latency and decreasing total sleep and REM sleep time (Schierenbeck et al., 2008), which act as risk factors for substance relapse (Hartwell et al., 2014; Morgan et al., 2010; Asaad et al., 2011; Dijkstra et al., 2008; Haack et al., 2020).

Consistent with many observational studies, we found positive causal effects of opioid dependence on insomnia (Battle, 2013; Dolsen & Harvey, 2017; Serdarevic et al., 2017; Tran et al., 2009). A randomized controlled trial showed that using buprenorphine, which has been approved for prescription opioid detoxification since 2002, 2 patients with a 4-week buprenorphine taper demonstrated remarkable sleep improvement (Dunn et al., 2015). On the contrary, a prospective longitudinal study led by Nordmann et al. showed that methadone maintenance treatment had no effect on sleep disturbance, suggesting that sleep disturbances are not a cause r obstacle to the initiation or continuation of methadone maintenance treatment (Nordmann et al., 2016). All these findings support our conclusion that there exists positive causal effect of opioid dependence on insomnia, not the other way around. Considering the complicated relationships between substance addiction and sleep and great amount of confounding bias from observational studies, there has been no published study investigating or claiming the causal relationships between opioid dependence and insomnia. Our findings thus stand as strong evidence with important therapeutic implications on sleep disturbances.

Epidemiologic studies have shown that rates of substance abuse remained higher in patients with psychological disorders than in the general population (Regier et al., 1990). Although studies found lower prevalence of opioid abuse among patients with schizophrenia compared to those with major depressive disorders and bipolar disorder (Chiappelli et al., 2018; Farrell et al., 2002), substantial evidence suggested that co-occurring opioid use disorder in schizophrenia patients was associated with worsened clinical outcomes, treatment non-compliance, and poor overall quality of life (Sayers et al., 2005; Li et al., 2020; Clark et al., 2019; Watkins et al., 2019; Hjorthøj et al., 2018; Shekhar, 2019). A meta-analysis of placebo-controlled clinical trials of opioid antagonists (such as naloxone, naltrexone, nalmefene, and buprenorphine) in schizophrenia patients showed that opioid antagonists are associated with a significant reduction in the positive, negative, total, and general symptoms of schizophrenia (Clark et al., 2020).

Numerous hypotheses have been proposed to explain the possible mechanisms through which schizophrenia interplay with substance use. The cumulative risk factor model posits that individuals with schizophrenia have increased propensity to develop substance abuse due to the accumulation of cognitive, social, educational, and vocational deficits (Mueser et al., 1990), while the self-medication hypothesis suggests that patients with schizophrenia

develop substance abuse to lessen the schizophrenic symptoms or side effects related to antipsychotic treatments (Khantzian, 1997). Psaman et al. also revealed new risk loci of lifetime cannabis use and showed evidence for a causal positive influence of schizophrenia risk on cannabis use (Pasman et al., 2018). Our findings of a positive causal effect of schizophrenia on opioid dependence support the primary addiction hypothesis (also called reward deficiency model), which argues that shared neuropathology of schizophrenia and substance addiction involving dopaminergic and glutamatergic regulation of the mesolimbic pathway leads to higher risks of comorbid schizophrenia and substance addiction (Chambers et al., 2001). Results from epidemiologic studies demonstrated inconsistent conclusions regarding the direction of causal effects between psychotic disorders and substance use (Abdel-Baki et al., 2017; Barkus, 2016; Gage & Munafò, 2015; Kendler et al., 2015). Our findings thus provide an evidence-based conclusion that genetic determinants of schizophrenia, especially within neural circuits related to reward processing, place patients at increased vulnerability to opioid dependence. Further, people with substance use disorders often experience comorbid chronic physical health conditions including chronic pain, cancer, and cardiovascular diseases (Garland et al., 2013; Schulte & Hser, 2013). An estimated 10% of chronic pain patients reported misuse of prescription opioids (Garland et al., 2013). Although chronic pain and related emotional distress could increase the risk of opioid dependence via dysregulating the reward circuitry, our results suggested that the majority causal effects of schizophrenia (and of opioid dependence) are likely to be implemented directly on the mesolimbic system via shared genetic architecture.

Unlike observational investigations, our study avoids potential confounding bias by utilizing a two-sample Mendelian randomization design that relies on summary statistics obtained from large-scale population cohorts. Multiple sensitivity analyses were conducted to robustly check the assumptions required for Mendelian randomization and ensure the validity of both the analytical approaches and results. To our knowledge, this is the first study comprehensively investigating the causal relationships between opioid dependence and major mental disorders. With that being said, we also need to acknowledge potential limitations of the study. Firstly, although we evaluated the associational strength of instrumental SNPs with opioid dependence using F statistics and replicated the MR analyses using MR-RAPS, the use of a relatively relaxed p value threshold in selecting the instrumental SNPs for opioid dependence could lead to weak instrumental bias. Secondly, GWAS of opioid dependence, OCD, and PD have relatively small sample sizes, which could lead to decreased statistical power in detecting a meaningful significant signal. Future research involving larger population cohorts are needed to elucidate the causal relationships between opioid dependence and OCD/PD. Thirdly, participant samples overlapped between GWAS of opioid dependence and insomnia, which could potentially lead to weak instruments bias and inflation of Type I error rate. However, results from sensitivity analyses suggest that both bias and inflation of Type I error rate should be kept at relatively negligible level. Finally, since our analyses are restricted to GWAS samples of European ancestry, our conclusions cannot be genialized to the general populations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11469-024-01315-y.

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Author Contribution XL contributed to the conception and design of the study. YH and LQ participated in the assessments and data extraction processes. YH, RS, and HD performed the statistical analyses. XL and YH discussed the results and wrote the original draft of the manuscript. XL performed the review and

editing. XL supervised the project and contributed to the funding acquisition. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the finalized manuscript.

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Data Availability The GWAS summary data of opioid dependence is available at https://www.ebi.ac.uk/gwas/studies/GCST90043725. The GWAS summary data of 8 mental disorders are available at https://figshare.com/articles/dataset/an2019/14671980; https://figshare.com/articles/dataset/bip2021_noUKBB/22564402; https://figshare.com/articles/dataset/MDD2_MDD2018_GWAS_sumstats_w_o_UKBB/21655784; https://figshare.com/articles/dataset/ocd2018/14672103; https://figshare.com/articles/dataset/panic2019/16602218; https://figshare.com/articles/dataset/ptsd2019/14672133; https://figshare.com/articles/dataset/scz2022/19426775; https://research.23andme.com/collaborate/#publication. The GWAS summary data of chronic pain is available at https://www.ebi.ac.uk/gwas/studies/GCST90043740. Ethics statement All relevant GWAS had obtained ethical permissions from corresponding institutional review boards. Since our study involves only publicly available GWAS summary statistics, no ethical approval was required from the institutional review board.

Declarations

Conflict of Interest The authors declare no competing interests.

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