Submitted: 02 January, 2024 Accepted: 22 February, 2024 Online Published: 30 August, 2024 DOI:10.22514/jomh.2024.127

ORIGINAL RESEARCH

JOMH Journal of Men's Health

Causal effects of psychiatric traits on the risk of urolithiasis in European and East Asian population: a Mendelian randomization analysis

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Abstract

It has been reported in observation studies that psychiatric traits increase the risk of urolithiasis, but the causal association between them remains to be systematically reveal. Thus, this study aims to estimate the causal effect of psychiatric traits on urinary stones, utilizing Mendelian randomization (MR) analyses. In the study, we collected data of eight psychiatric traits from summary-level genome-wide association studies (GWAS), including attention deficit hyperactivity disorder, bipolar disorder, major depressive disorder (MDD), schizophrenia, insomnia, mood swing, anxiety and neuroticism. FinnGen consortium and BioBank Japan provided the GWAS data of urolithiasis. Three MR methodswere used in the study, in which inverse variance-weighted was employed as the primary analytic tool of causal reference. Furthermore, a meta-analysis combining the results from FinnGen and BioBank Japan was performed. In FinnGen, inverse variance-weighted analysis revealed that mood swing (p = 0.023, odds ratio (OR): 2.272, 95% confidence interval (CI): 1.122–4.600), neuroticism (p = 0.032, OR: 1.086, 95% CI: 1.007–1.171) and MDD (p = 0.014, OR: 1.259, 95% CI: 1.047–1.515) significantly increased the risk of urolithiasis, while schizophrenia (p = 0.026, OR: 0.944, 95% CI: 0.897–0.993) negatively associated with urolithiasis. In BioBank Japan, mood swing (p = 0.015, OR: 3.397, 95% CI: 1.273–9.062), neuroticism (p = 0.041, OR: 1.111, 95% CI: 1.004–1.228) and MDD (p = 0.006, OR: 1.435, 95% CI: 1.107–1.861) were found to have significant causality with urolithiasis. Combining meta-analysis revealed that mood swing (p = 0.001, OR: 2.606, 95% CI: 1.470–4.620), neuroticism (p = 0.003, OR: 1.095, 95% CI: 1.031–1.163) and MDD (p = 0.0003, OR: 1.316, 95% CI: 1.132–1.530) significantly increase the risk of urinary calculus, while schizophrenia (p = 0.04, OR: 0.959, 95% CI: 0.922–0.997) decrease the risk of urinary stones formation to our surprise.

Keywords

Psychiatric traits; Mendelian randomization; Urolithiasis; Causality

1. Introduction

In the domain of urology, urolithiasis represent a prevalent condition with a high recurrence rate, imposing a substantial burden on global health [1]. The incidence of urolithiasis is increasing with each passing year, which can be attributed to lifestyles changes and an ageing population. Urolithiasis has an incidence of 8.8% in the United States [2]. This condition can be induced by many factors, encompassing genetic predispositions [3], dietary habits [4], metabolic conditions [5–7], and environmental factors [3] as the pivotal contributors to their formation.

The emerging evidence gathered from epidemiological investigations suggests a potential relationship between mental health and urolithiasis risks. For example, it has been revealed that the individuals with depression and anxiety are at an elevated risk of urolithiasis [8, 9]. The observational data uncovered that severe depression increases the likelihood of stone formation by 56% [9]. Besides, empirical findings highlight the correlation of inadequate sleep duration and depressive states with an increased propensity for urolithiasis development [6, 10]. Moreover, a case-control study has reported that patients suffering from emotional stress and mood instability are at a higher risk of urinary stones formation [11]. Collectively, these insights lead to the hypothesis that psychiatric disorders may serve as a precipitating factor for urolithiasis. Nevertheless, there are few studies on the association between psychiatric traits and urolithiasis remain scant, especially those based on the East Asian population, underscoring the demand for more robust evidence.

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In this study, Mendelian randomization (MR) was employed as an analytical paradigm to delineate causality. Through a large-scale genome-wide association study (GWAS), instrumental variables (IVs) which were in the form of single-nucleotide polymorphisms (SNPs) strongly related to exposure, were introduced into the MR analysis to elucidate causality between exposure and outcome [12]. Different from conventional observational methodology, MR is more resistant to confounding factors and the influence of reverse causation, owing to the inherent stability and random allocation of genetic variants [13]. In this research, GWAS summary statistics served as instruments for estimating the causal effect of 8 psychiatric traits on urolithiasis, including attention deficit hyperactivity disorder (ADHD), bipolar disorder (BPD), insomnia, major depressive disorder (MDD), mood swing, schizophrenia, anxiety and neuroticism, on urolithiasis. Moreover, two-sample MR analyses were conducted, which can maximize statistical power and precision.

2. Method

2.1 Study design

To ensure the validity of the causal inference, the IVs employed should meet three critical criteria: Firstly, genetic IVs should be strongly correlated with the exposure studied; Secondly, genetic IVs should be independent of any potential confounders related to urolithiasis; Lastly, genetic IVs should affect the outcome (urolithiasis) solely through exposure [14]. The methodological framework of the study is illustrated in Fig. 1. From publicly accessible datasets, GWAS summary statistics were gathered for exposures (8 psychiatric traits) and outcomes (urolithiasis). This process involved rigorous filtering to identify valid IVs, which were then retained for further analyses. After harmonizing the selected IVs of exposure with GWAS summary statistics for urolithiasis from two distinct ethnic datasets, namely the FinnGen consortium and BioBank Japan, a two-sample MR analysis was conducted respectively. Subsequently, a meta-analysis of the FinnGen and BioBank Japan findings was performed, to further estimate the potential causal effects of psychiatric traits.

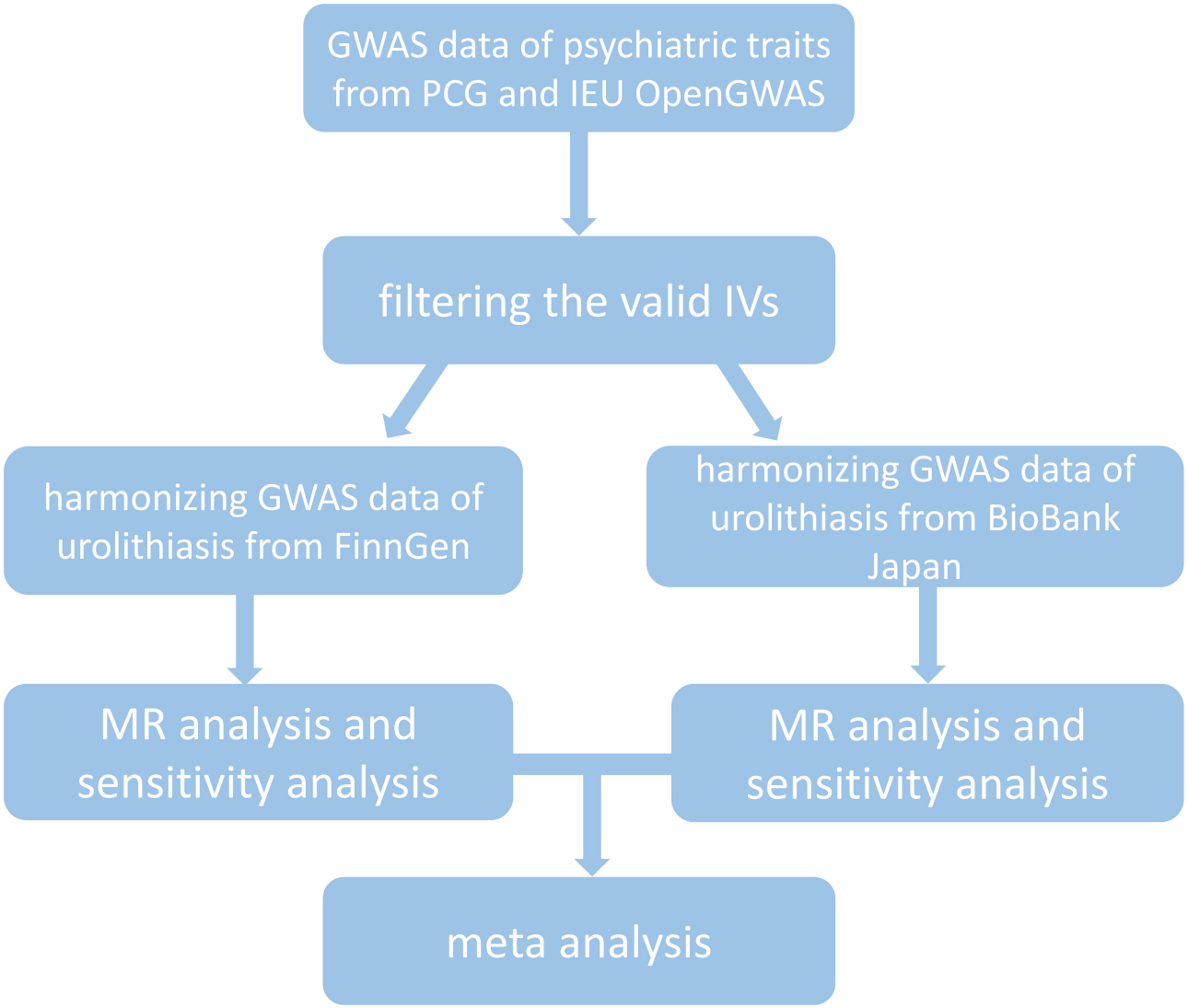

FIGURE 1. Flow chart throughout the study. GWAS: genome-wide association study; PCG: Psychiatric Genomics Consortium; IEU: Integrative Epidemiology Unit; IVs: instrumental variables; MR: Mendelian randomization.

2.2 GWAS for psychiatric traits

GWAS summary statistics of four psychiatric disorders, including ADHD, MDD, schizophrenia and BPD, were sourced from the Psychiatric Genomics Consortium (PGC) under permission. The summary data for ADHD encompassed 12 cohorts from Europe, North America and China, revealing 12 independent loci across 55,347 samples [15]. The study for MDD contains 480,359 individuals, identifying 44 independent and distinct loci [16]. The sample size of schizophrenia study was 320,404, highlighting 289 significant genomic loci [17]. The BPD study comprised 51,710 individuals, with 30 distinct loci identified [18]. Additionally, IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/), developed at Medical Research Council (MRC) Integrative Epidemiology Unit at the University of Bristol [19], was utilized to access summary data for mood swing (451,619 cases), insomnia (336,965 cases), neuroticism (374,323 cases) and anxiety (459,560 cases).

2.3 GWAS for urolithiasis

The summary data for urinary stones were obtained through the latest round of FinnGen dataset [20] and BioBank Japan [21], covering the population with European and Asian ancestries. The baseline characteristics of urolithiasis in FinnGen and Biobank Japan were shown in Table 1. In the FinnGen dataset, urinary calculus was classified under N20 in the 10th revision of the International Classification of Diseases (ICD-10), and as 592 in the 8th and 9th revisions. The ninth release of the FinnGen consortium data included 9713 individuals with urinary stones and 366,693 controls after exclusion of the individuals of high heterozygosity and significant genotype deficiency, and non-European ancestry. The association tests adjusted for the first ten principal components, the age-sex interaction, and the square of age. GWAS data of BioBank Japan consisted of 212,453 adult subjects of East Asian, including 6638 cases and 205,815 controls, with 8,885,805 SNPs analyzed.

TABLE 1. Baseline characteristics of urolithiasis in FinnGen and Biobank Japan.

	FinnGen	BioBank Japan
Total Participants	377,277	212,453
Number of cases	9713	6638
Sex		
Male	166,407	109,347
Female	210,870	103,106
Mean Age		
Case	-	54.8
Control	-	62.2
Ethnicity	European	East Asian
Number of Variants	20,175,454	8,712,794

2.4 Instrumental SNPs selection

The IVs involved were meticulously selected. To guarantee the robustness of causal inferences via MR analysis, a stringent quality control process for the selection of valid IVs was necessitated. Consequently, all the IVs used in subsequent analysis had to satisfy several critical criteria: First, the significance threshold was established when p-value $< 5 \times 10^{-8}$, so as to ensure a robust association between the genetic IVs and psychiatric traits. Secondly, to mitigate the risk of linkage disequilibrium (LD)—where genes at different loci are inherited together more frequently than expected by chance, a threshold of $r^2 = 0.1$, region size = 10,000 kb were adopted, thereby excluding SNPs within a 10,000 kb range exhibiting high LD. Additionally, palindromic SNPs which were unable to be accurately harmonized were also removed [22, 23]. Thirdly, to address potential confounders related to urinary calculus, each SNP was vetted using the Phenoscanner database in accordance with the guidelines of the European Association of Urology [24]. Finally, the strength of the IVs was quantitatively assessed using the F statistic, and was calculated as $F = R^2$ (n − k − 1)/k $(1 - R^2)$, where R means the proportion of the variance of the exposure explained by the IVs, n means the number of IVs, k means sample size. When F statistic >10 was it is indicated high strength of IVs [25].

2.5 Mendelian randomization analyses

The inverse variance-weighted (IVW) served as the primary statistical model, complemented by weighted median (WM) analysis and MR-Egger regression. In terms of the IVW method, all IVs are assumed to be valid with a negligible sum of horizontal pleiotropic effects, and the fixed-effects approach is utilized to meta-analyze the Wald ratio estimator of each IV initially. If a significant heterogeneity is observed in subsequent sensitivity analyses, a random-effects method will be introduced to counteract the effect of heterogeneity [26]. MR-Egger regression predicated on the assumption of universal IV invalidity and an unconstrained intercept enables reliable estimation even if all instruments contravene the third assumption [27]. The WM method acts as a robust auxiliary to MR-Egger regression, which will be consistent if more than 50% of the weight is contributed by valid IVs, regardless of the type of horizontal pleiotropy [28]. The significance threshold of $p < 0.00625$ (0.05/8) via Bonferroni correction, delineated causal relationships, with p-values ranging from 0.00625 to 0.05 considered indicative of a potential association.

Multiple sensitivity analyses including Cochran's Q test, MR-Egger intercept test, and leave-one-out analysis were conducted to evaluate the strength of the primary analysis results. The Cochran's Q-test was performed to assess the heterogeneity among IVs, with a p-value < 0.05 indicating significant heterogeneity [29]. The MR-Egger intercept test was conducted to gauged the potential for horizontal pleiotropy, with an intercept p-value < 0.05 suggesting substantial pleiotropy [27]. The leave-one-out technique was applied to assess result reliability by sequentially excluding each SNP. Additionally, the MR Steiger directionality test was also conducted to elucidate the direction of causality.

3. Result

3.1 MR and sensitivity analysis of FinnGen consortium

We conducted a comprehensive filtering process to identify valid the valid SNPs of the 8 neuropsychiatric disorders or psychiatric traits from different GWAS datasets. Selected SNPs were robustly associated with corresponding psychiatric disorders ($p < 5 \times 10^{-8}$), and LD independent ($r^2 = 0.1$, region size = 10,000 kb), excluding IVs significantly linked to confounders. Besides, ambiguous and palindromic SNPs were also excluded during the harmonization process. The characteristics of selected IVs is shown in Table 2, indicating that F statistics of each IV were higher than 10, affirming the absence of weak IVs in the analysis. **Supplementary Tables 1,2,3,4,5,6,7,8** provided the further details of the valid IVs. Then, the filtered IVs were used for subsequent causal estimates with FinnGen dataset, with a forest plot summarizing the effects of psychiatric traits on the risk of urolithiasis shown in Fig. 2. Notably, mood swing found to have a significant positive causal effect on urolithiasis risk, with an odds ratio of 2.272 (p = 0.023, 95% CI: 1.122–4.600), indicating that emotionally instable individuals are 2.2 times prone to develop urolithiasis. Furthermore, MDD was associated with a 1.26-fold increase in the urolithiasis risk (p = 0.014, OR: 1.259, 95% CI: 1.047–1.515). In addition, neuroticism also slightly contributes to increased risk of urolithiasis (p = 0.041, OR: 1.086, 95% CI: 1.007–1.171). Surprisingly, a significant protective effect of schizophrenia exhibited a potential protective effect against urolithiasis in the FinnGen dataset analysis (p = 0.026), corresponding to a 5.6% reduction in risk (OR: 0.944, 95% CI: 0.897–0.993). The outcomes of WM and MR-Egger regression analyses were detailed in **Supplementary Table 9**.

Sensitive analyses were performed to validate the precision and stability of the results, summarized in Table 2. The MR-Egger intercept test revealed no significant horizon pleiotropy within FinnGen consortium. However, the Cochran Q test indicated a significant heterogeneity in estimates for neuroticism (Q = 145.39, p = 0.001), and schizophrenia (Q = 246.72, p = 0.0002). To address this heterogeneity, we future applied the random-effect IVW in neuroticism and schizophrenia. The causal relationships between neuroticism and urolithiasis (p = 0.041, OR: 1.086, 95% CI: 1.007–1.171), and between schizophrenia and urolithiasis (p = 0.026, OR: 0.944, 95% CI: 0.897–0.993), remained significant in random-effect IVW model. Leave-one-out analyses and MR Steiger test for the 8 psychiatric traits were conducted (**Supplementary Figs. 1,2,3,4,5,6,7,8**), with the significant results depicted in Figs. 3,4. The main effects were consistent regardless of the exclusion of any SNPs, underscores the robustness of our results.

3.2 MR and sensitivity analysis of BioBank Japan consortium

To further explore the causal association between the 8 psychiatric traits and urolithiasis within Asian population, we utilized BioBank Japan dataset for MR analysis. The findings were presented in Fig. 5. Despite the presence of heterogeneity between neuroticism and urinary stones (Q = 135.82, p = 0.005), the significant positive causal link for neuroticism was confirmed using random-effect IVW (p = 0.041, OR: 1.111, 95% CI: 1.004–1.228). Furthermore, a significant positive relationship between mood swing and urolithiasis were also identified (p = 0.015), indicating a 3.4-fold increased risk for urinary stones (OR: 3.397, 95% CI: 1.273–9.062). In addition, MDD significantly increases urolithiasis risk by 1.44 times (p = 0.006, OR: 1.435, 95% CI: 1.107–1.861), aligning closely with the results of MDD in FinnGen dataset. However, no significant associations were observed for other psychiatric traits on urolithiasis, including ADHD, BDP, insomnia, anxiety and schizophrenia. The results of the complementary statistical models were summarized in **Supplementary Table 10**.

Sensitive analysis conducted using BioBank Japan are summarized in Table 3. The MR-Egger test revealed no substantial horizon pleiotropy, as all p-values exceeded 0.05. Heterogeneity tested by Cochran Q test in neuroticism (Q = 135.82, p = 0.005) was also addressed through random-effect IVW. Figs. 6,7 demonstrated that all the significant estimates maintained the correct inference direction from exposure to outcome as verified by MR Steiger filtering test. The robustness of these findings was further confirmed through leave-one-out analyses.

3.3 Results of the meta-analysis

Furthermore, a meta-analysis combining results from FinnGen and BioBank Japan was conduct, to enhance the statistical power, with findings detailed in Fig. 8. Notably, mood instability could significantly increase the risk of urolithiasis (p = 0.001), exhibiting a substantial effect size of 2.606 (95% CI: 1.470–4.620). The meta-analysis revealed that individuals with MDD are 31.6% higher likelihood of developing (p = 0.0003, OR: 1.316, 95% CI: 1.132–1.530). Additionally, a positive association between neuroticism and urolithiasis was also identified (p = 0.003, OR: 1.095, 95% CI: 1.031–1.163). Additionally, meta-analysis indicated a significant negative effect of schizophrenia on urolithiasis, with an odds ratio of 0.959 (95% CI: 0.922–0.997).

4. Discussion

In this study two-sample MR analysis was conducted based on two large-scale GWAS summary datasets to assess the causal effects of psychiatric factors on urolithiasis. Besides, these results were further verified by a comprehensive meta-analysis, which enhanced their robustness. The results demonstrated that individuals with mood instability (p = 0.001, OR: 2.606, 95% CI: 1.470–4.620), neuroticism (p = 0.003, OR: 1.095, 95% CI: 1.031–1.163) and MDD (p = 0.0003, OR: 1.316, 95% CI: 1.132–1.530) are more susceptible to urolithiasis. Conversely, a potential protective effect of schizophrenia on urolithiasis was observed (p = 0.04, OR: 0.959, 95% CI: 0.922–0.997). This may be the first to scientific attempt estimate the effect of psychiatric traits on urolithiasis, and these findings offer novel insights into the determinants urological health, emphasizing the critical role of mental health [9, 30]. Meanwhile, these findings underscore the importance

TABLE 2. Information of IVs selected for 8 psychiatric traits.

Exposure	Dataset	Valid IVs	Samples	*F* statistic
ADHD	PCG	12	55,374	34.161
BPD	PCG	14	51,710	34.591
Insomnia	IEU	30	336,965	39.122
Mood swing	IEU	54	451,619	41.025
MDD	PCG	30	480,359	37.698
Anxiety	IEU	44	459,560	45.311
Neuroticism	IEU	111	374,323	41.223
Schizophrenia	PCG	214	320,404	47.845

IVs: instrumental variables; ADHD: attention deficit hyperactivity disorder; BPD: bipolar disorder; MDD: major depressive disorder; PCG: Psychiatric Genomics Consortium; IEU: Integrative Epidemiology Unit.

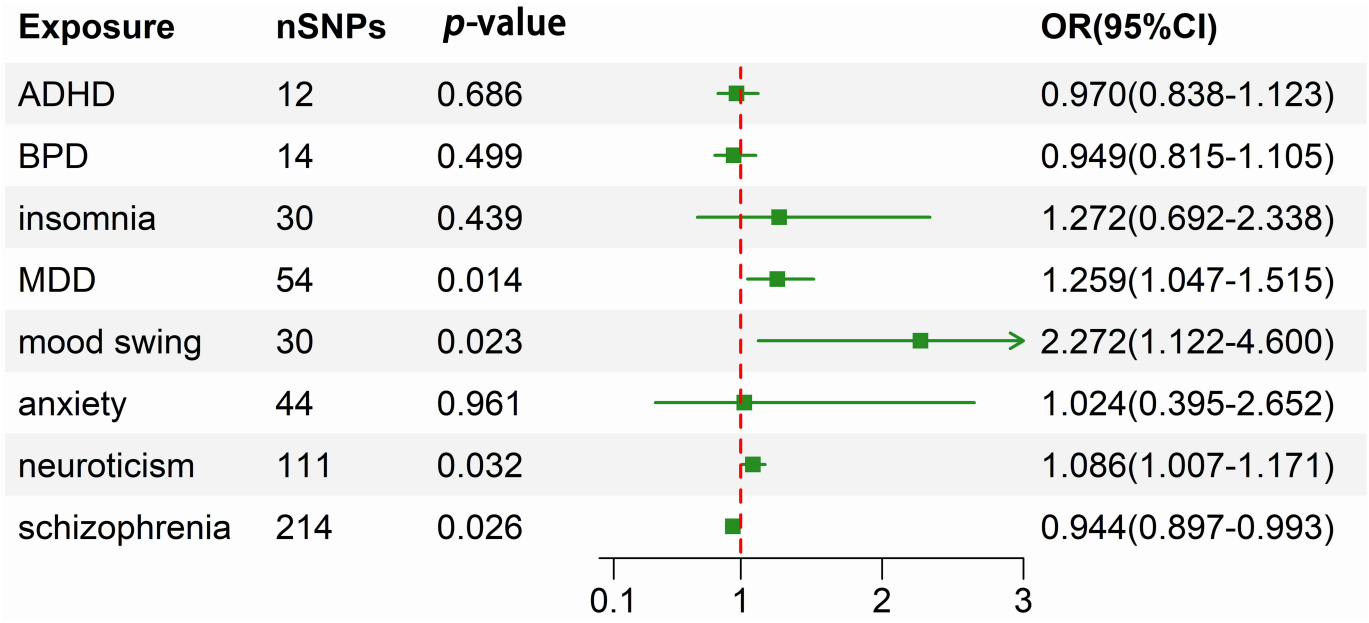

FIGURE 2. MR estimates the causality of 8 psychiatric traits and urolithiasis in FinnGen. ADHD: attention deficit hyperactivity disorder; BPD: bipolar disorder; MDD: major depressive disorder; OR: odds ratio; CI: confidence interval.

of resolving urolithiasis in patients with psychiatric traits in clinical practice. Moreover, the mechanisms of psychiatric traits influencing stone formation were further investigated, which may provide valuable preventative strategies.

The heightened risk of urolithiasis in individuals with depressive symptoms and high neuroticism has attracts increasing attention. Previous studies have revealed an elevated incidence of urological diseases, including urinary infections and urinary retention [31–33]. Moreover, a retrospective study, enrolling 24,892 individuals reported that those with moderate (OR: 1.38, 95% CI: 1.05–1.83) and severe (OR: 1.56, 95% CI: 1.02–2.40) depression had a higher risk of urolithiasis, which was consistent with our findings regarding the association between MDD and urolithiasis [9].

This study to some extent fills the gap in exploring the association between psychological traits and urolithiasis in the East Asian population. The incidence of urolithiasis varies significantly between different regions, thus highlighting the importance of statistical analyses on specific populations for identifying the regional differences in urolithiasis. Demographic factors such as median age, race, gender, level of education, and dietary habits contribute to the regional differences in the incidence of stone formation. In the Asian population, the incidence of stone formation ranges from 1% to 19.1% [34]. Due to such factors as population aging, urbanization, and high meat and sugar diets, the incidence of urolithiasis is higher in East Asia than in West Asia. Zeng *et al.* [35] conducted a survey involving 12,570 individuals in China. They concluded that the incidence of urolithiasis in China is 15.5%. In contrast, recent statistical studies from some West Asian regions have shown a lower incidence of urolithiasis. An epidemiological study in Iran revealed that the lifetime risk of urolithiasis in the Iranian population is about 6.6% [34]. Similarly, a cross-sectional study in the Saudi Arabia reported an incidence of approximately 6.2% for urolithiasis [36].

Psychiatric factors such as MDD, neuroticism, and mood swings, exert significantly impacts on urolithiasis, encompassing both bladder stones and kidney stones. A primary mechanism linking these psychiatric factors to cystolithiasis involves lower urinary tract symptoms (LUTs) precipitated

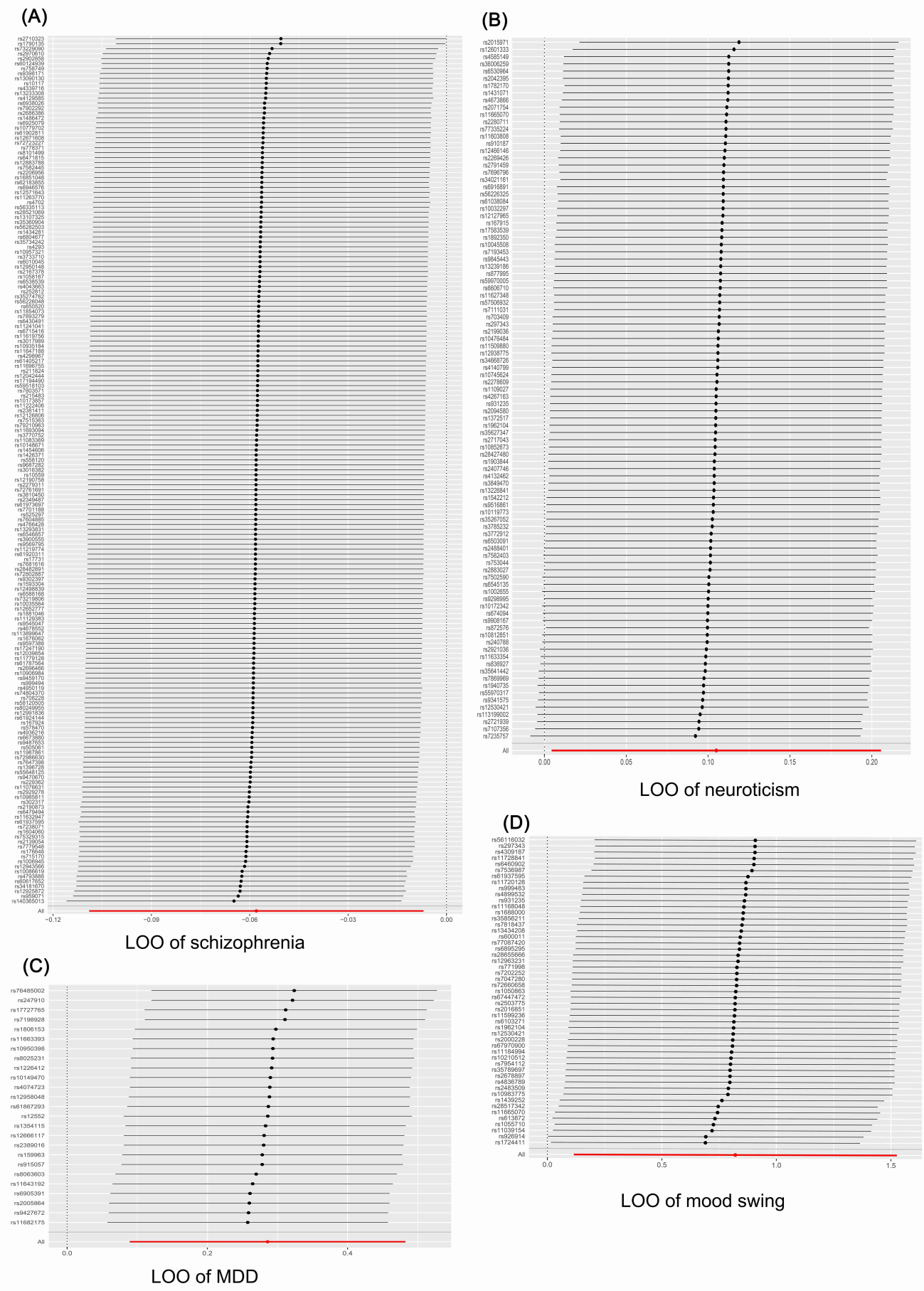

FIGURE 3. Leave-one-out analyses of (A) schizophrenia, (B) neuroticism, (C) MDD, (D) mood swing indicate high stability of the results from FinnGen. LOO: leave-one-out; MDD: major depressive disorder.

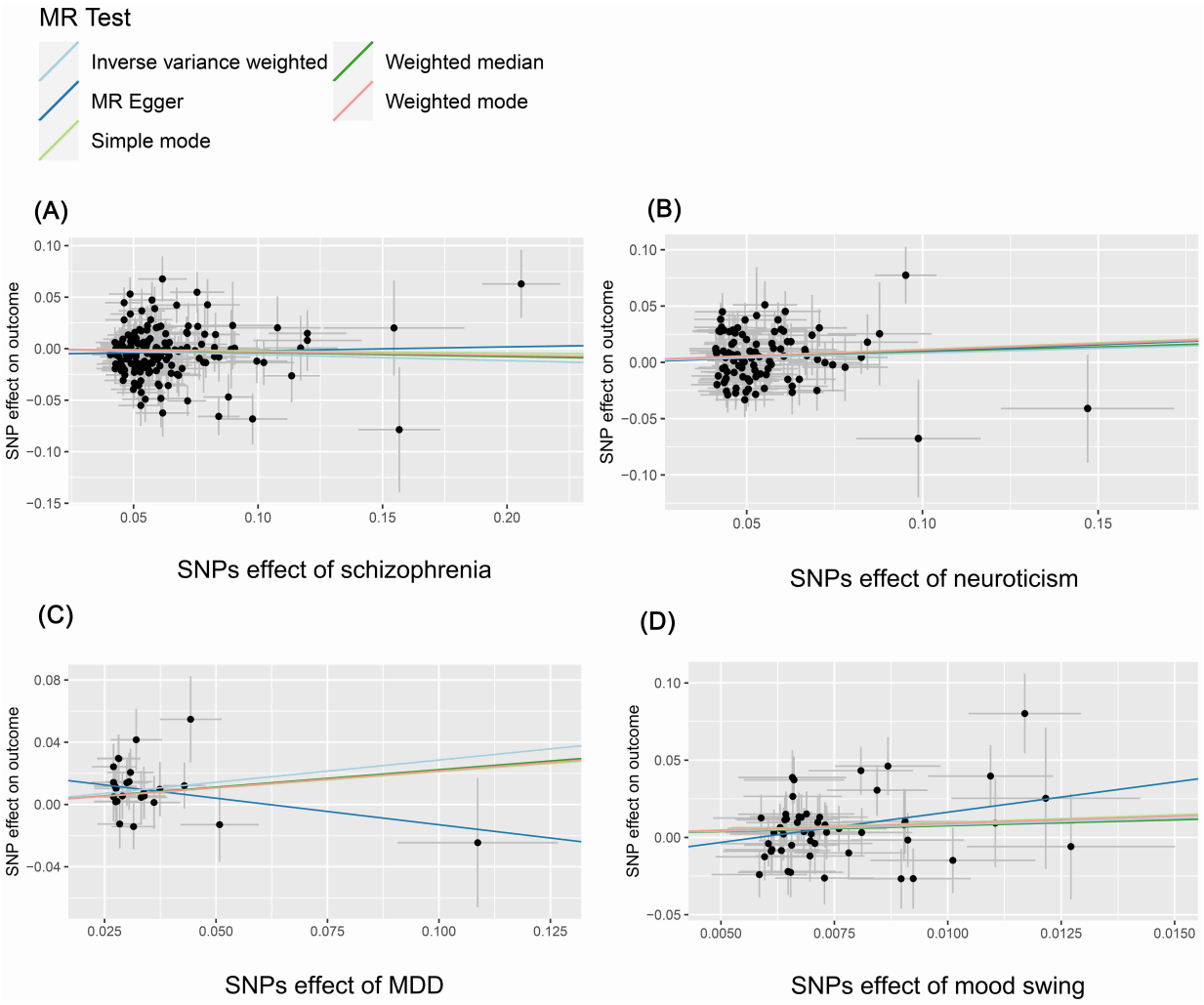

FIGURE 4. Scatter plots for (A) schizophrenia, (B) neuroticism, (C) MDD, (D) mood swing from FinnGen. The x-axis represents effect of selected IVs on psychiatric traits, and the y-axis represents effect of selected IVs on urolithiasis. MR: Mendelian randomization; SNP: single-nucleotide polymorphism; MDD: major depressive disorder.

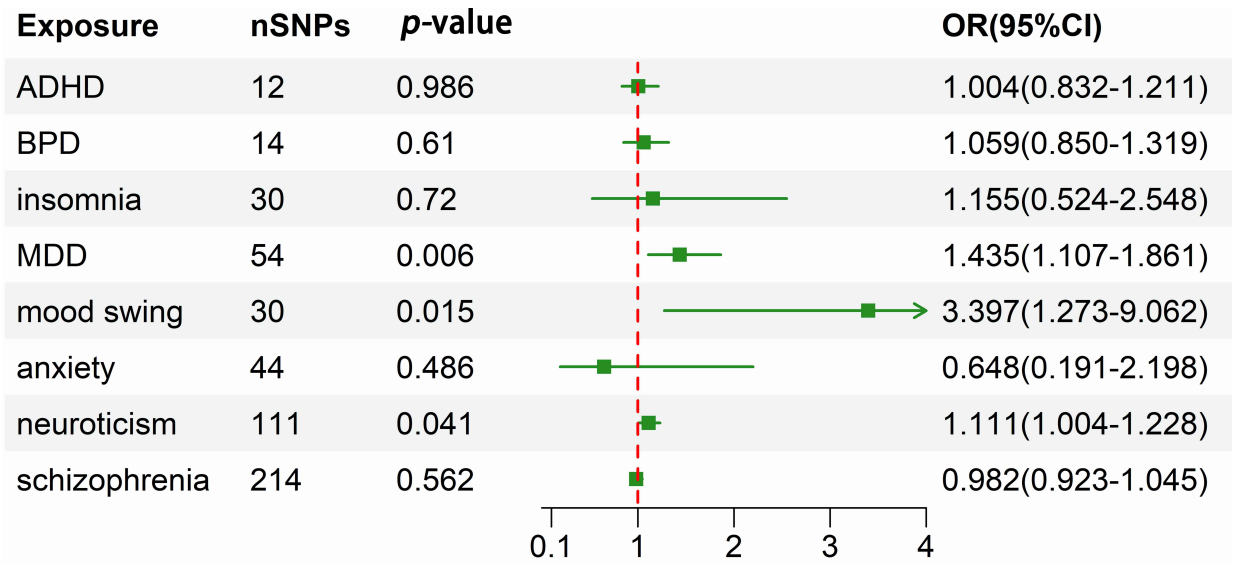

FIGURE 5. MR estimates the causality of 8 psychiatric traits and urolithiasis in BioBank Japan. SNP: single-nucleotide polymorphism; ADHD: attention deficit hyperactivity disorder; BPD: bipolar disorder; MDD: major depressive disorder; OR: odds ratio; CI: confidence interval.

TABLE 3. Sensitivity analysis of the causality of 8 psychiatric traits and urolithiasis.

Consortium	Exposure	Cochran Q		MR-Egger	
		Q value	*p*	intercept	*p*
FinnGen					
	ADHD	11.28	0.186	0.011	0.721
	BPD	15.41	0.080	−0.026	0.579
	Insomnia	34.26	0.080	0.010	0.095
	MDD	19.50	0.725	0.021	0.131
	Mood swing	62.63	0.108	0.015	0.138
	Anxiety	38.95	0.185	−0.004	0.830
	Neuroticism	145.39	0.001	0.010	0.868
	Schizophrenia	246.72	0.0002	−0.006	0.346
BioBank Japan					
	ADHD	12.52	0.130	−0.047	0.409
	BPD	27.54	0.010	−0.092	0.185
	Insomnia	31.18	0.183	−0.029	0.430
	MDD	21.58	0.711	0.020	0.547
	Mood swing	41.06	0.424	−0.007	0.747
	Anxiety	25.25	0.713	0.018	0.542
	Neuroticism	135.82	0.005	0.004	0.781
	Schizophrenia	198.08	0.133	0.008	0.327

ADHD: attention deficit hyperactivity disorder; BPD: bipolar disorder; MDD: major depressive disorder; MR: Mendelian randomization.

by mental health issues. Mental conditions characterized by excessive worry and mood instability may induce developing bladder dysfunction, altering urodynamic properties and leading to LUTs [32]. It has been unraveled that the incidence of urodynamic abnormalities including urinary hesitancy, weak stream and intermittency is significantly higher in the depressive cohort [32], which may be elevated by urinary difficulty, detrusor underactivity, and common LUTs linked to mental disorders risk [37]. The MR research indicated that individuals with neurotic traits may experience urination difficulties more frequently ($p < 0.01$, 95% CI = 1.001–1.002). Emotional fluctuations and anxiety states can heighten the excitability of the central nervous system, which would adversely affect bladder muscle contraction and leading to urination difficulties and urinary retention, thereby heightening the risk of cystolithiasis risk [38]. In addition, chronic inflammation and infection of the lower urinary tract caused by psychogenic factors, also play a crucial role in bladder stone formation. As reported in an MR study, individuals with depression and neuroticism have an increased risk of cystitis, and depressed individuals facing a 14% higher risk of bladder infections compared with the normal population ($p < 0.01$, 95% CI = 1.013–1.285). This may be attributed to the fact that anxiety compromises the immune barrier thus contributing to chronic bladder inflammation and stone formation [39].

In addition to cystolithiasis, psychiatric traits are linked to metabolic disorders such as hypercalciuria, hyperuricosuria and hypocitraturia, which may induce nephrolithiasis. It has been reported that patients suffering from depression and mood instability frequently present with urine composition alteration, which may account for kidney stone formation in psychiatric disorders. As suggested in an observational study, depression and stress events in life increase the uric acid and urine calcium levels, which may promote the development of nephrolithiasis [11]. Conversely, inhibitory factors of kidney stones formation in urine composition such as magnesium ion and citric acid are significantly lower in these patients [40, 41]. The abnormal activation of the hypothalamic-pituitary-adrenocortical axis in patients with depression and high neuroticism leads to metabolic abnormalities, including elevated plasma cortisol levels, which interfere with calcium absorption and promote hypercalciuria [40]. Another possible mechanism underlying increase in nephrolithiasis risk is that, patients with MDD are often in a state of high oxidative stress [42], which may aggravate renal injury. There is an elevated level of oxidative stress markers and decreased level of antioxidants in patients with depression [43] This results in the excessive production of reactive oxygen species (ROS), which may induce the apoptosis of renal tubular epithelial cell and ultimately contributes to urolithiasis [44]. In addition, hyper-inflammation response and change in gut microbiota in psychiatric disorders also stimulate kidney stone formation [9].

Unexpectedly, schizophrenia has the potential to be negatively associated with urolithiasis, accounting for a 4.1% decrease in the risk of urolithiasis. However, it is important to note that the causal relationship between schizophrenia and urolithiasis is not as robust as that with mood instability, neuroticism and MDD. Thus, caution is warranted when inferring

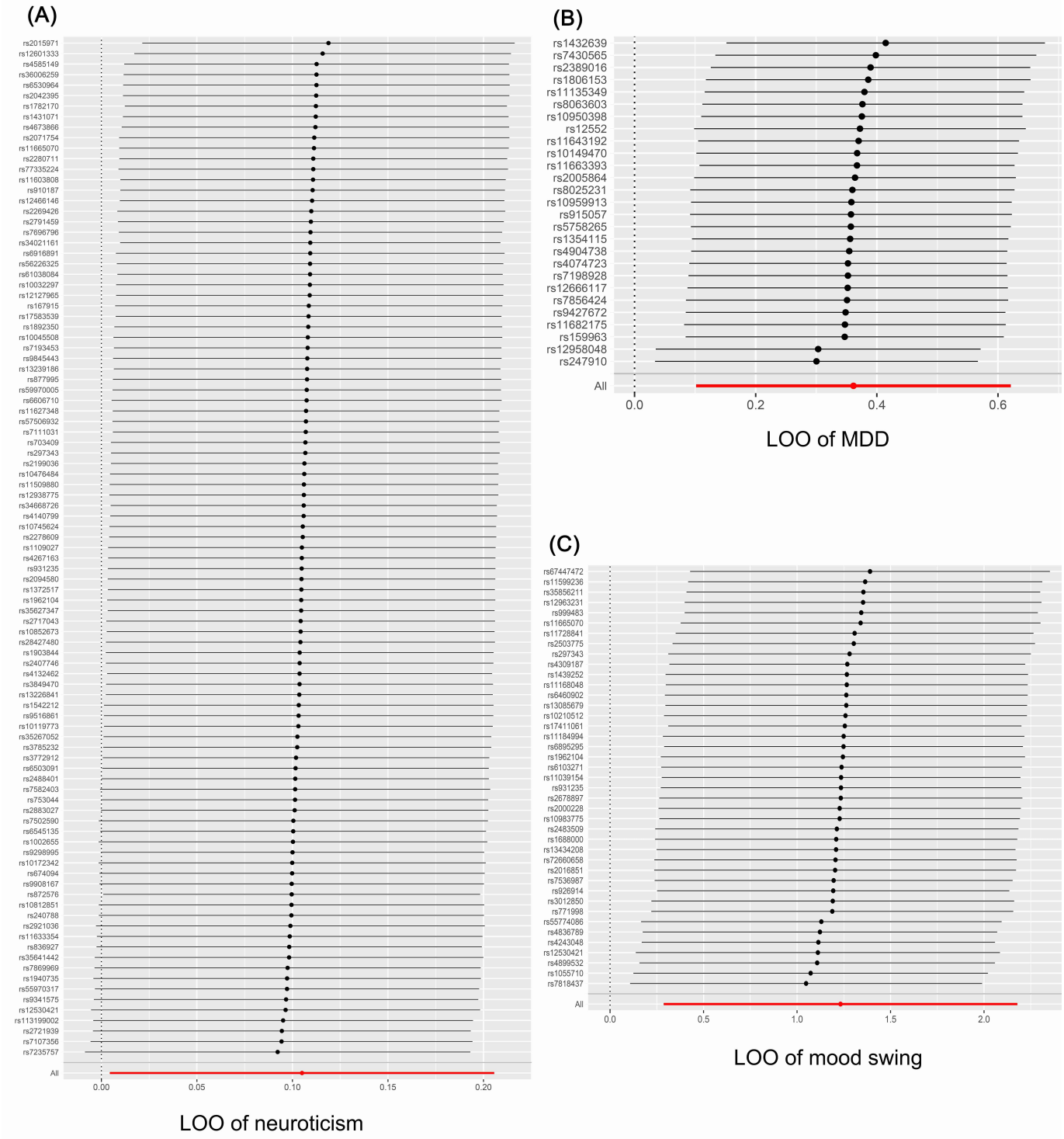

FIGURE 6. Leave-one-out analyses of (A) neuroticism, (B) MDD, (C) mood swing, indicate high stability of the results from BioBank Japan. LOO: leave-one-out; MDD: major depressive disorder.

causality. This finding is consistent with the result of sole observational study known to explore the causal relationship between schizophrenia and urolithiasis [45]. A case-control study including 53,965 urinary calculi patients and 269,825 controls, reveals a 31% decrease in urolithiasis occurrence ($p < 0.001$, 95% CI: 0.62–0.76) [45]. Of note, such observational studies may be subject to potential information biases and confounders. For instance, patients with severe schizophrenia might not accurately report their medical history, or severe schizophrenia could mask the symptoms of urolithiasis, leading to a lower reported incidence reported. Furthermore, certain lifestyle choices, genetic factors, and environmental exposures could act as potential confounders, affecting both schizophrenia and urolithiasis simultaneously. Compared with the observational study, our results had a smaller effect size (OR: 0.959, 95% CI: 0.922–0.997), due to the less significant influence from confounding bias and reverse causality in MR analyses.

In addition to psychological factors, diabetes, obesity, hypertension, metabolic syndrome and other physical diseases

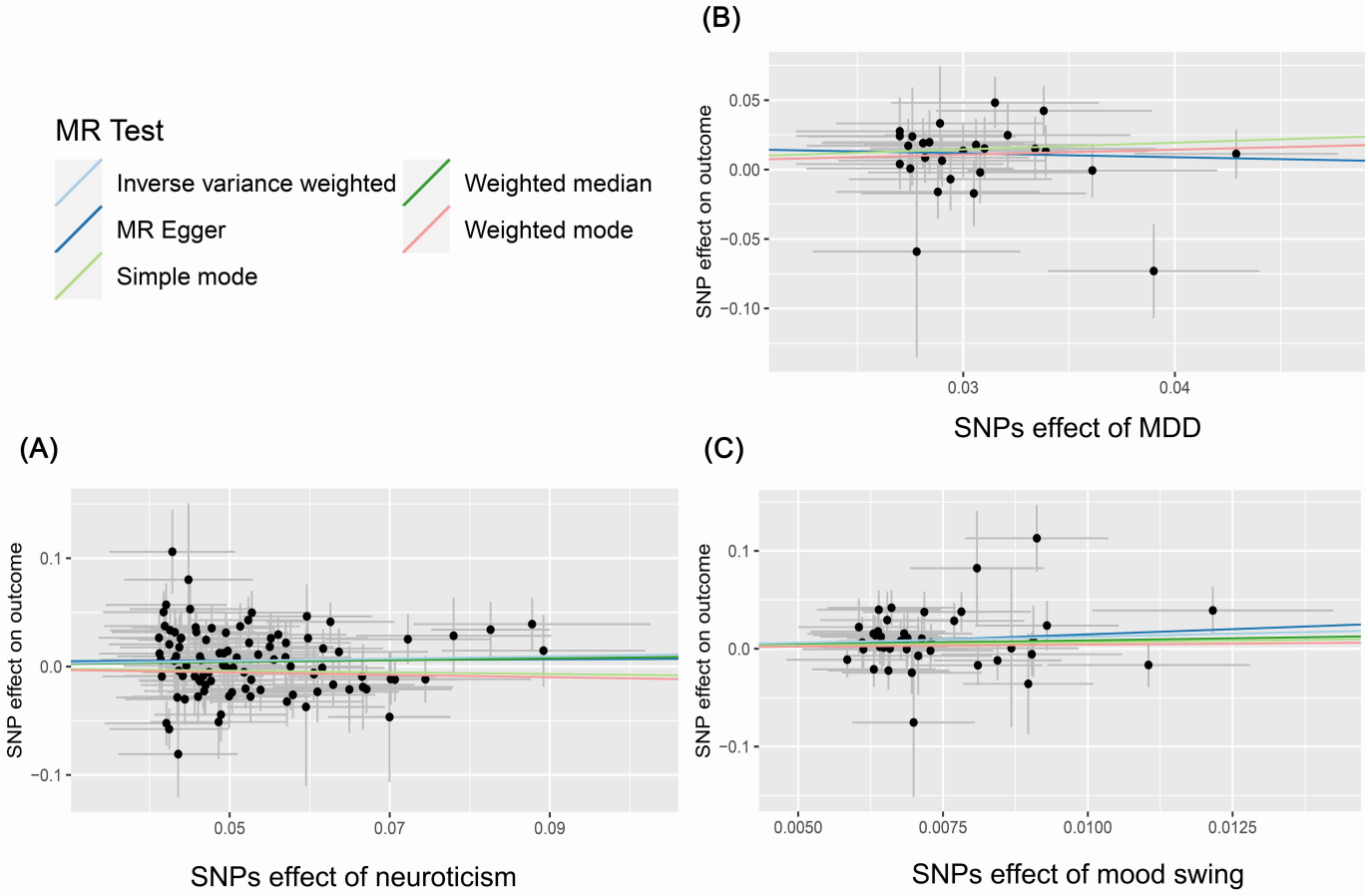

FIGURE 7. Scatter plots for (A) neuroticism, (B) MDD, (C) mood swing, from BioBank Japan. The x-axis represents effect of selected IVs on psychiatric traits, and the y-axis represents effect of selected IVs on urolithiasis. MR: Mendelian randomization; SNP: single-nucleotide polymorphism; MDD: major depressive disorder.

Exposure	nSNPs	*p*-value	OR(95%CI)
ADHD	12	0.77	0.983(0.876-1.103)
BPD	14	0.79	0.983(0.867-1.114)
insomnia	30	0.41	1.227(0.758-1.998)
MDD	54	0.0003	1.316(1.132-1.530)
mood swing	30	0.001	2.606(1.470-4.620)
anxiety	44	0.7	0.861(0.407-1.825)
neuroticism	111	0.003	1.095(1.031-1.163)
schizophrenia	214	0.04	0.959(0.922-0.997)

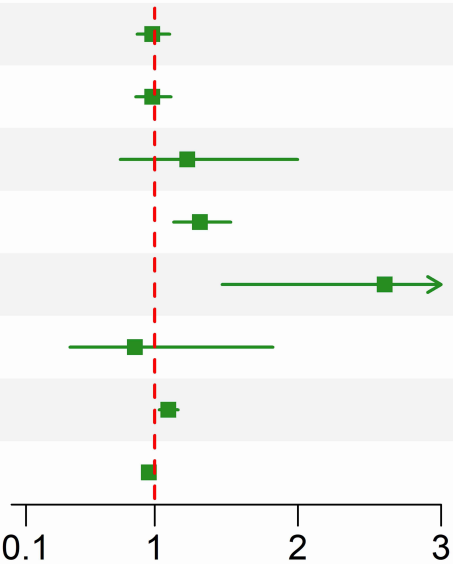

FIGURE 8. Meta-analysis estimates the causality of 8 psychiatric traits and urolithiasis combining results from FinnGen and BioBank Japan. SNP: single-nucleotide polymorphism; ADHD: attention deficit hyperactivity disorder; BPD: bipolar disorder; MDD: major depressive disorder; OR: odds ratio; CI: confidence interval.

are also risk factors for urolithiasis. Patients with type 2 diabetes have a 94% higher risk of developing urolithiasis compared with the general population. Insulin resistance can lead to changes in the urine pH and the renal metabolism of ammonia and calcium, which may promote the formation of urolithiasis [5]. Similarly, metabolic syndrome can reduce the secretion of ammonia by the proximal renal tubules, thereby decreasing the urine pH. A lower urine pH provides a conducive environment for kidney stone formation. Moreover, obesity secondary to metabolic syndrome increases the renal excretion of oxalate, promoting the formation of calcium oxalate stones [6]. The large cohort studies have demonstrated a causal relationship between metabolic syndrome and urolithiasis. West *et al.* [6] found that the risk of developing urolithiasis in individuals with metabolic syndrome is twice as high as that in the normal population by an analysis of the National Health and Nutrition Examination Survey in the United States. Additionally, hypertension has a bidirectional causal relationship with urolithiasis. Hypertension may lead to an increased risk of urolithiasis through mechanisms involving hypercalciuria, insulin resistance, and chronic renal failure. In summary, apart from psychological traits, diabetes, hypertension, metabolic syndrome, and other conditions also affect the occurrence of urolithiasis [3].

To the best of our knowledge, this is the first study to systematically estimate the causal relationship between psychiatric traits and urolithiasis based on MR analyses. The strengths of this study include the use of two large-scale and independent GWAS datasets, incorporating data from East Asian populations to ensure a large sample size and substantial statistical power. Moreover, the subsequent meta-analysis combining the results of two groups further elucidated the potential risk factors and decreases the likelihood of false-positives. Moreover, the study minimizes confounding bias and reverse causality by employing randomly allocated IVs. Finally, our causal inference is performed based on three MR statistical models including IVW, WM analysis and MR-Egger regression, alongside comprehensive heterogeneity, pleiotropy, and leave-one-out sensitivity analyses, thus ensuring the credibility and robustness of our findings.

Nevertheless, there are also several limitations in this study. Firstly, although multiple sensitivity analyses were conducted to control heterogeneity and horizon pleiotropy as well as possible, the effect of them could not be eliminated. Secondly, the GWAS data from various sources and populations were utilized in this study. Even though the heterogeneity between studies has been minimized, the results might still be affected by variations in allele frequency, effect sizes and quality control standards. Thirdly, it is difficult to accurately assess the psychiatric traits, which leads to large standard errors in estimating the effect sizes of IVs on psychiatric factors [46]. Fourthly, although confounding factors have been minimized, the potential influence may still exist due to the incompleteness of the baseline characteristics of the cohort. Finally, the results of this study only suggest the causal effect of psychiatric factors on urolithiasis, and the relevant mechanisms requires further exploration.

5. Conclusions

In conclusion, our findings reveal the positive causal effect of mood instability, neuroticism and MDD on urolithiasis risk, and the potentially negative causality between schizophrenia and urolithiasis, based on a large scale two-sample MR analysis. Hence, it is necessary to pay more attention to urolithiasis in patients with psychiatric disorders. Overall, these findings may have important implications for the prevention of urolithiasis.

ABBREVIATIONS

GWAS, Genome-wide association study; MR, Mendelian randomization; IVs, Instruments; SNPs, Single-nucleotide polymorphisms; ADHD, Attention deficit hyperactivity disorder; BPD, Bipolar disorder; MDD, Major depressive disorder; PGC, Psychiatric Genomics Consortium; LD, Linkage disequilibrium; IVW, Inverse variance-weighted; WM, weighted median; ICD-10, International Classification of Diseases 10th revision; OR, Odds Ratio; CI, Confidence Interval; IEU, Integrative Epidemiology Unit; MRC, Medical Research Council; ROS, Reactive Oxygen Species.

AVAILABILITY OF DATA AND MATERIALS

The summary-level GWAS data for urolithiasis were downloaded from the FinnGen consortium, Freeze 9 (https://r9.finngen.fi/pheno/N14_CALCUKIDUR). Psychiatric Genomics Consortium provided the summary GWAS data for ADHD (https://figshare.com/articles/dataset/adhd2019/14671965), BPD (https://figshare.com/articles/dataset/bip2019/14671998), MDD (https://figshare.com/articles/dataset/mdd2018/14672085), and schizophrenia (https://figshare.com/articles/dataset/scz2022/19426775). The summary-level GWAS data correlated with mood swing (https://gwas.mrcieu.ac.uk/datasets/ukb-b-14180/), insomnia (https://gwas.mrcieu.ac.uk/datasets/ukb-a-13/), anxiety (https://gwas.mrcieu.ac.uk/datasets/ukb-b-6991/) and neuroticism (https://gwas.mrcieu.ac.uk/datasets/ukb-b-4630/) were obtained from IEU OpenGWAS.

AUTHOR CONTRIBUTIONS

QHJ, CTD—design of the study; contributed equally to this work and share the first authorship. QHJ, RJ, CW, CS—the acquisition, analysis, interpretation of data. QHJ, CTD, SXY, CS—wrote the manuscript and revised it. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

We want to acknowledge the participants and investigators of the FinnGen study.

FUNDING

This research was funded by the National Natural Science Foundation of China, grant number No. 82270797 and No. 82070723.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jomh.org/files/article/1829443816657960960/attachment/Supplementary%20material.zip.

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How to cite this article: Qinhong Jiang, Caitao Dong, Chuan Wang, Rong Jiang, Chao Song, Sixing Yang. Causal effects of psychiatric traits on the risk of urolithiasis in European and East Asian population: a Mendelian randomization analysis. Journal of Men's Health. 2024; 20(8): 35-47. doi: 10.22514/jomh.2024.127.