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Mood instability and risk of gastrointestinal diseases - a univariable and multivariable mendelian randomization study

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Abstract

Background Mood instability, characterized by sudden and unpredictable mood shifts, is prevalent in psychiatric disorders and as a personality trait. Its association with gastrointestinal diseases has been recognized but remains poorly understood in terms of causality.

Methods This study aims to investigate the causal relationship between mood instability and a spectrum of gastrointestinal diseases by univariable and multivariable mendelian randomization analysis. The exposure and outcome data were retrieved from the IEU open GWAS database, the UK biobank and the FinnGen study. Instrumental variables were selected to meet relevance, independence, and exclusion restriction criteria. GWAS datasets for mood instability and 28 gastrointestinal diseases were utilized, incorporating diverse populations and genders. Univariable and multivariable Mendelian randomization analyses were conducted using R software. MR statistics from different datasets for the same disease were meta-analyzed to maximize the study population.

Results In univariable MR analysis, genetic predisposition to mood instability showed significant associations with increased risk for several gastrointestinal diseases, including: gastroesophageal reflux disease, gastric ulcer, acute gastritis, irritable bowel syndrome, internal hemorrhoids, cirrhosis, cholecystitis, cholelithiasis, acute pancreatitis, chronic pancreatitis. In multivariable MR analysis, after adjusting for major depression, bipolar disorder, anxiety disorder, and schizophrenia, associations with the following gastrointestinal diseases remained statistically significant: internal hemorrhoids, cirrhosis, acute pancreatitis, chronic pancreatitis.

Conclusion This study provides compelling evidence for a potential causal relationship between mood instability and certain gastrointestinal diseases underscoring the importance of considering mood instability as a potential risk factor for gastrointestinal diseases as well as the positive role of maintaining mood stability in the prevention of gastrointestinal disorders.

Keywords Mood instability, Gastrointestinal disease, Mendelian randomization

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Background

Mood instability is a subjective emotional state characterized by sudden, irregular, and unpredictable alterations in mood [1]. As an important aspect of the psychopathological phenotype, mood instability is a symptom that occurs in 40–60% of those with various psychiatric disorders, including depression, bipolar disorder, anxiety disorder, and post-traumatic stress disorder [2]. Moreover, mood instability is not confined to psychiatric populations; it is also a common personality trait observed in healthy individuals, with a prevalence of 13.9% reported in a survey conducted in private households in England [3]. The detrimental effects of mood instability extend beyond psychiatric symptoms, affecting physical health and overall well-being. Research has linked mood instability to adverse health outcomes, including autoimmune diseases [4] ,cardiovascular diseases [5], and cerebral hemorrhage [6]. However, the full extent of its impact on health remains incompletely understood.

Gastrointestinal diseases have emerged as a pervasive global health concern, significantly impacting the health status and quality of life of affected individuals [7]. These diseases not only cause physical discomfort and pain but also lead to psychological distress and impaired social functioning. Recent studies have increasingly highlighted the close association between mood disorders and gastrointestinal diseases. This relationship is evident in both functional gastrointestinal disorders, such as irritable bowel syndrome, and organic gastrointestinal diseases, such as ulcerative colitis [8]. Systematic reviews indicate that up to a third of irritable bowel syndrome patients experience anxiety, and a quarter experience depression, particularly during active disease phases [9]. Patients with ulcerative colitis have a high prevalence of mental disorders. Gut microbiota imbalance and disturbed metabolism have been suggested to play an important role in either ulcerative colitis or mental disorders [10, 11]. However, few studies have delved into the potential causal relationship between mood instability and gastrointestinal diseases. Understanding the potential causality between mood instability and gastrointestinal diseases not only sheds light on the complex interplay between mental health and gastrointestinal conditions but also offers valuable insights into healthcare management strategies, thereby improving patient outcomes and overall well-being.

Mendelian randomization (MR) stands as a powerful analytical method for investigating causal relationships. By leveraging single-nucleotide polymorphisms (SNPs) as instrumental variables, MR allows for the estimation of the effect of exposure on outcomes. Importantly, genetic variants used in MR are randomly assorted at conception and independent of environmental factors, akin to randomized controlled trials. Furthermore, MR can help mitigate the influence of reverse causality, as genetic variants remain fixed and unaffected by disease status [12]. Building upon existing knowledge and hypotheses, we posit that mood instability may play a role in increasing the risk of gastrointestinal diseases. Hence, we embarked on this MR analysis to investigate the potential causal relationship between mood instability and a spectrum of gastrointestinal diseases. Through our study, we aim to contribute to a deeper understanding of the complex interplay between mood instability and gastrointestinal health, ultimately paving the way for more targeted interventions and improved patient outcomes.

Methods

Study design

Figure 1 shows the overview of the present study design. All GWAS datasets involved in this study are from the Finnish database [13] and the IEU open GWAS database [14], both of which are public available. The detailed information on utilized datasets was displayed in Supplementary Table 1. After the MR Estimates for each gastrointestinal endpoint were calculated separately, for gastrointestinal diseases corresponding to multiple GWAS datasets, the OR values of MR results for all GWAS datasets were meta-analyzed as the final results. Multivariable mendelian randomization was also performed to determine whether the observed associations between mood instability and gastrointestinal diseases are independent of potential confounding psychological factors, including major depression, bipolar disorder, anxiety disorder, and schizophrenia. All GWASs received corresponding ethical approval and participant consent; no additional ethical approval was required.

Instrumental variable selection

As an instrumental variable, it must satisfy the following three assumptions: (1) Relevance assumption, the IVs are significantly associated with mood instability. (2) Independence assumption, the IVs are not associated with confounders (social status, racial diversity, mental disorders) of the risk factor-outcome association. (3) Exclusion restriction assumption, the IVs are only associated with the gastrointestinal endpoint through mood instability. A series of quality control techniques were performed: First, the SNPs associated with mood swings or experiencing mood swings with p-value less than 5×10^{-8} were selected. Secondly, independence hypothesis thresholds (clump r2=0.001, clump kb=10,000) were set to eliminate SNPs of linkage disequilibrium. Thirdly, SNPs with minor allele frequency (MAF) of less than 0.01 to avoid weak IVs. IF there's IVs with F less than 10, then two analyses are performed, one with IVs' F less than 10 and one without, and the results are considered reliable when they agree. Finally, exposure data and outcome data were

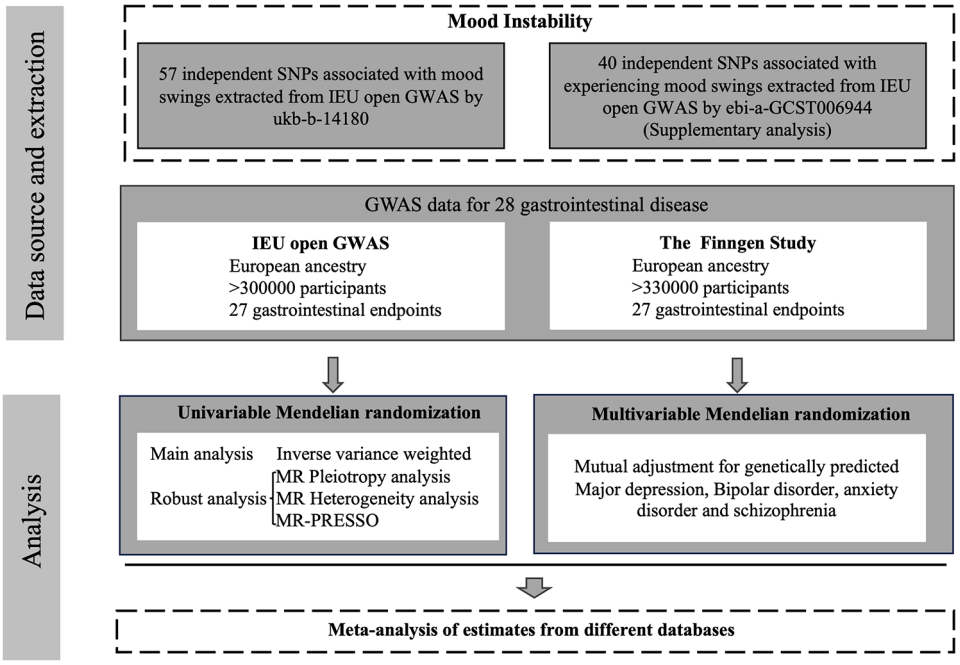

Fig. 1 Overview of the present study design. MR, Mendelian randomization; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; SNP, single nucleotide polymorphism

harmonized and then SNPs were excluded if unavailable in outcome datasets or defined as ambiguous (i.e., palindromic SNPs with minor allele frequencies > 0.42 and < 0.58). Additionally, we calculated the F statistics of each SNP using the formula:

$$F = (N - 2) \times \frac{R^2}{1 - R^2}$$

where N is the sample size and K is the number of instruments. And R^2 refers to the variation in exposure explained by each IV, calculated by: $R^2 = 2 \times \mathrm{EAF} \times (1 - \mathrm{EAF}) \times Beta^2$, where *Beta* represents the effect size of the genetic variant in the exposure GWAS, and EAF represents the effect allele frequency.

Data source

All participants in this study were of European descent and included both male and female. Two GWAS datasets for mood instability were obtained from the IEU open GWAS database, one was derived from the UK biobank (GWAS ID: ukb-b-14180) with 204,412 cases and 247,207 controls and the phenotype was determined by the question "Does your mood often go up and down", the other was derived from M. Nagel's GWAS study (GWAS ID: ebi-a-GCST006944) with 373,733 participants and the phenotype was determined by the item "experiencing mood swings" on personality inventories for neuroticism, which was served as a supplementary analysis [15].

The outcome data for 28 gastrointestinal diseases were retrieved from the IEU open GWAS database and the FinnGen study. The 28 diseases were then classified into three major groups based on their anatomical sites: (1) upper gastrointestinal diseases (gastroesophageal reflux disease, esophageal cancer, gastric ulcer, duodenal ulcer, acute gastritis, chronic gastritis, Barrett's esophagus); (2) lower gastrointestinal diseases (irritable bowel syndrome, celiac disease, diverticular disease, ulcerative colitis, Crohn's disease, colorectal cancer, colon cancer, internal hemorrhoids, ileus, acute appendicitis); (3) hepatobiliary and pancreatic diseases (nonalcoholic fatty liver disease, alcoholic liver disease, cirrhosis, hepatic cancer, cholangitis, cholecystitis, cholelithiasis, acute pancreatitis, chronic pancreatitis, pancreatic cancer). Gastrointestinal disease GWAS datasets from the IEU open GWAS, conducted by MRC-IEU or Neale Lab, were coded using ICD-9 and ICD-10. Additionally, GWAS datasets for gastrointestinal diseases from the FinnGen study's R10 data release were coded with ICD-8, ICD-9, and ICD-10. In addition, datasets that satisfy minimum requirements imported from the EBI database of complete GWAS summary data from the IEU open GWAS was also utilized [16–21]. Supplementary Table 1 provides details of sample size, ancestry, data categories and related links for 28 gastrointestinal disease data.

The GWAS datasets for four mental illness (major depression, bipolar disorder, anxiety disorder and schizophrenia) in multivariable mendelian were also obtained from the IEU open GWAS data, which were conducted

by Psychiatric Genomics Consortium (PGC, https://pgc.unc.edu/) and MRC IEU consortium. Supplementary Table 7 provides details of sample size, ancestry, data categories and related links for four mental illness data.

Statistical analysis

Inverse variance-weighted regression served as the primary model for inferring the causal association between mood instability and gastrointestinal diseases in univariable Mendelian randomization analysis. This model assumes that all SNPs are valid instruments, yielding the most precise estimates. The MR-Egger intercept and the Cochran Q test were employed to test for horizontal pleiotropy and assess heterogeneity [22]. The MR-PRESSO method was utilized to identify SNP outliers and provide results identical to that from IVW after removal of outliers [23]. Multivariable Mendelian Randomization method can be applied for multiple genetic instruments regardless of their association with the exposure [24]. We applied this method by considering all the instrumental variables for Mood instability, Major Depression, Bipolar Disorder, Anxiety Disorder, and Schizophrenia to determine their independent effects on gastrointestinal diseases. Meta-methods were utilized to integrate statistics from various data sources, and heterogeneity was assessed using I^2 and Cochran p-values. If I^2 exceeded 75% or the p-value was less than 0.05, we deemed heterogeneity to be present and employed a random-effects model for meta-analysis. Otherwise, in the absence of heterogeneity, we used a fixed-effect model for meta-analysis. We performed FDR correction (q-value) using the Benjamini-Hochberg method to adjust thep-value for the MR analyses. A q-value <0.05 was deemed statistically significant. A $P<0.05$ but FDR q-value ≥ 0.05 considered suggestive causal evidence.

All analyses were performed in R software (Version 4.2.3) using "TWOSampleMR" package (Version 0.5.7), "meta" package (Version 6.5.0), "Mendelian Randomization" package (Version 0.9.0). A significance threshold of a two-side p-value of less than 0.05 was used. All of the variable types used for mood swings, mental illness and gastrointestinal disease in this study were dichotomous, therefore the outcome statistics were expressed using OR values with 95% confidence intervals.

Results

Determination of instrumental variables

After performing a series of quality control techniques (removing those with P-values $>5\times10^{-8}$, LD R2 >0.001, MAF <0.01) to satisfy the three core assumptions, 59 SNPs and 40 SNPs were selected as instrumental variables for mood swings and for experiencing mood swings respectively. Supplementary Table 2 provides detailed information on these SNPs, including their IDs, positions on the chromosomes, allele frequencies, and phenotype-related statistics. These IVs collectively accounted for approximately 0.21% of the variation in mood swings and 0.41% of the variation in experiencing mood swings. Importantly, all selected IVs exhibited F-statistics above 10, indicating sufficient strength for Mendelian randomization.

Mood swings and 28 gastrointestinal diseases

In univariable MR analysis of mood swings and gastrointestinal diseases, 12 out of 28 gastrointestinal diseases were associated with mood swings, including 4 upper gastrointestinal disorders, 2 lower gastrointestinal disorders associated with emotional instability, and 6 hepatobiliary and pancreatic diseases (Table 1; Fig. 2). In detail, genetic susceptibility to mood swings were positively associated with gastroesophageal reflux disease (OR, 6.7614; 95% incidence interval [CI], 1.7957–25.4595; $p=0.0047$; q=0.0159), gastric ulcer (OR, 1.1650; 95% CI, 1.1566–1.1736; $p=0.0007$; q=0.0047), acute gastritis(OR, 4.7700; 95% CI, 1.4900–15.2300; $p=0.0085$; q=0.0208), chronic gastritis(OR, 1.0101; 95% CI, 1.0027–1.0176; $p=0.0078$; q=0.0209), irritable bowel syndrome(OR, 3.8720; 95% CI, 2.6711–5.6128; $p<0.0001$; q<0.0001), internal hemorrhoids(OR, 1.0071; 95% CI, 1.0026–1.0117; $p=0.0022$; q=0.0085), nonalcoholic fatty liver disease(OR, 1.9739; 95% CI, 1.3268–2.9365; $p=0.0080$; q=0.0209), cirrhosis(OR, 3.5680; 95% CI, 1.6176–7.8697; $p=0.0016$; q=0.0072), cholecystitis(OR, 2.2947; 95% CI, 1.4051–3.7473; $p=0.0009$; q=0.0049), cholelithiasis(OR, 1.9720; 95% CI, 1.0922–3.5603; $p=0.0243$; q=0.0546), acute pancreatitis(OR, 1.9952; 95% CI, 1.4479–2.7495; $p<0.0001$; q<0.0001), chronic pancreatitis(OR, 4.1076; 95% CI, 1.8479–9.1304; $p=0.0005$; q=0.0045) (Supplementary Table 3 for original two sample MR results, Supplementary Table 4 for results after meta).

In the multivariable MR analysis, we determined the independent effect of mood swings on gastrointestinal diseases, there were only 6 gastrointestinal diseases that were still associated with mood swings, including 1 upper gastrointestinal disorder, 2 lower gastrointestinal disorders associated with emotional instability, and 3 hepatobiliary and pancreatic diseases (Table 1; Fig. 2). In detail, genetic susceptibility to mood swings after adjusting for genetically predicted major depression, bipolar disorder, anxiety disorder and schizophrenia were positively associated with chronic gastritis (OR, 1.0090; 95% CI, 1.0020–1.0160; $p=0.0114$; q=0.0260), diverticular disease(OR, 1.0204; 95% CI, 1.0005–1.0406; $p=0.0411$; q=0.0845), internal hemorrhoids(OR, 1.0228; 95% CI, 1.0016–1.0444; $p=0.0347$; q=0.0382), cirrhosis(OR, 3.4050; 95% CI, 1.1862–9.7736; $p=0.0228$; q=0.0391), acute pancreatitis (OR, 4.9171; 95% CI, 2.4004–10.0725; $p<0.0001$; q<0.0001), chronic pancreatitis(OR, 5.4072;

Table 1 Association between genetic susceptibility to mood swings and 28 gastrointestinal diseases in univariable and multivariable mendelian randomization

Disease		*N* case	*N* total	UVMR			MVMR		
				OR [95% CI]	*p* value	q value	OR [95% CI]	*p* value	q value
Upper gastrointestinal diseases	Gastroesophageal reflux disease	157939	981527	6.7614 [1.7957; 25.4595]	**0.0047***	**0.0159***	3.2842 [0.8143; 13.2460]	0.0947	0.2841
	Esophageal cancer	1738	849062	1.0001 [0.9954; 1.0048]	0.9645	0.9872	1.0020 [0.9950; 1.0090]	0.572	0.6715
	Gastric ulcer	8239	717717	1.1650 [1.1566; 1.1736]	**0.0007***	**0.0047***	1.0100 [0.9989; 1.0212]	0.0775	0.2616
	Duodenal ulcer	5703	815852	1.4110 [0.5793; 3.4364]	0.4484	0.5264	1.0036 [0.9947; 1.0127]	0.426	0.5692
	Acute gastritis	2558	352622	4.7700 [1.4900; 15.230]	**0.0085***	**0.0208***	1.2910 [0.7910,2.1100]	0.3075	0.5692
	Chronic gastritis	11784	823391	1.0101 [1.0027; 1.0176]	**0.0078***	**0.0209***	1.0090 [1.0020; 1.0160]	**0.0114***	**0.0260***
	Barrett's esophagus	1630	870695	4.5969 [0.5416; 39.0206]	0.1621	0.2432	2.5808 [0.3291; 20.2411]	0.3669	0.5692
Lower gastrointestinal diseases	Irritable bowel syndrome	63829	826311	3.8720 [2.6711; 5.6128]	**<0.0001***	**<0.0001***	1.2436 [0.7330; 2.1097]	0.4189	0.5692
	Celiac disease	16345	38932	0.4856 [0.1262; 1.8679]	0.2933	0.3771	0.6099 [0.0726; 5.1241]	0.6489	0.7300
	Diverticular disease	42048	817581	1.3360 [0.7016; 2.5438]	0.3781	0.4640	1.0204 [1.0005; 1.0406]	**0.0441***	0.0845
	Ulcerative colitis	7918	874327	0.9997 [0.9937; 1.0057]	0.9191	0.9872	1.0030 [0.9945; 1.0115]	0.4893	0.6005
	Crohn's disease	3132	857638	1.0040 [0.9990; 1.0090]	0.1161	0.1959	1.0010 [0.9935; 1.0085]	0.7922	0.8393
	Colorectal cancer	11267	697476	0.9999 [0.9882; 1.0117]	0.9872	0.9872	1.0119 [0.9936; 1.0306	0.204	0.4590
	Colon cancer	5348	678599	1.0030 [0.9980; 1.0080]	0.24	0.3240	1.0060 [0.9941; 1.0181]	0.327	0.5692
	Internal hemorrhoids	9739	800209	1.0071 [1.0026; 1.0117]	**0.0022***	**0.0085**	1.0228 [1.0016; 1.0444]	**0.0347***	**0.0382***
	Acute appendicitis	33196	872720	1.1919 [0.7862; 1.8070]	0.0767	0.1381	0.9991 [0.9916; 1.0066]	0.8082	0.8393
	Ileus	2911	398631	1.9500 [0.8000; 4.7300]	0.1534	0.2432	2.5400 [0.6700,9.6300]	0.1691	0.4151
Hepatobiliary and pancreatic diseases	Nonalcoholic fatty liver disease	11002	1190795	1.9739 [1.3268; 2.9365]	**0.0080***	**0.0209***	1.6333 [0.5282; 5.0508]	0.3943	0.5692
	Alcoholic liver disease	1416	218792	5.7900 [0.9800,34.010]	0.0592	0.1230	2.6000 [0.2800,23.8100]	0.3976	0.5692
	Cirrhosis	43914	759587	3.5680 [1.6176; 7.8697]	**0.0016***	**0.0072***	3.4050 [1.1862; 9.7736]	**0.0228***	**0.0391***
	Hepatic cancer	1639	759587	1.0004 [0.9959; 1.0049]	0.8156	0.9176	1.0030 [0.9965; 1.0095]	0.3636	0.5692
	Cholangitis	2315	470123	1.0030 [0.9980; 1.0080]	0.238	0.3240	0.9998 [0.9928; 1.0068]	0.9549	0.9549
	Cholecystitis	14517	837589	2.2947 [1.4051; 3.7473]	**0.0009***	**0.0049***	1.8352 [0.8386; 4.0162]	0.1287	0.3475
	Cholelithiasis	66313	889385	1.9720 [1.0922; 3.5603]	**0.0243***	**0.0546***	1.2168 [0.7373; 2.0081]	0.4427	0.5692
	Acute pancreatitis	10585	848330	1.9952 [1.4479; 2.7495]	**<0.0001***	**<0.0001***	4.9171 [2.4004; 10.0725]	**<0.0001***	**<0.0001***
	Chronic pancreatitis	5299	843044	4.1076 [1.8479; 9.1304]	**0.0005***	**0.0045***	5.4072 [3.6882; 7.9274]	**<0.0001***	**<0.0001***
	Pancreatic cancer	2092	480080	1.3722 [0.3992; 4.7161]	0.0767	0.1381	6.4126 [0.9666; 42.5441]	0.0543	0.2094

UVMR, univariable Mendelian randomization. MVMR, multivariable Mendelian randomization. OR, odds ratio. CI, confidence interval. ***Significant association**

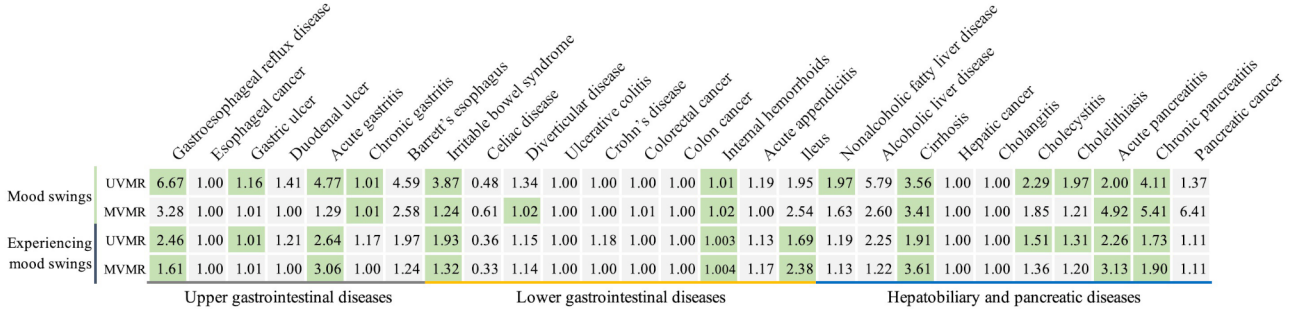

Fig. 2 Summary of associations of genetically predicted mood swings and experiencing mood swings with 28 gastrointestinal diseases after meta. UVMR, univariable Mendelian randomization; MVMR, multivariable Mendelian randomization. The number in the box are odds ratios for associations of mood instability to 28 gastrointestinal diseases, and the green means *p* values are less than 0.05 and statistically significant

95% CI, 3.6882–7.9274; $p<0.0001$; q<0.0001). (Supplementary Table 8 for original two sample MR results, Supplementary Table 9 for results after meta).

Experiencing mood swings and 28 gastrointestinal diseases

The association between experiencing mood swings and 28 gastrointestinal diseases was also analyzed by MR to serve a supplementary analysis, the results were largely consistent. In univariable MR analysis, 11 out of 28 gastrointestinal diseases were associated with mood swings, including 3 upper gastrointestinal disorders, 3 lower gastrointestinal disorders associated with emotional instability, and 5 hepatobiliary and pancreatic diseases (Table 2; Fig. 2). In detail, genetic susceptibility to experiencing mood swings were positively associated with gastroesophageal reflux disease (OR, 2.4673; 95% CI, 1.6938–3.5940; $p<0.0001$; q<0.0001), gastric ulcer (OR, 1.0070; 95% CI, 1.0030–1.0110; $p=0.0005$; q=0.0034), acute gastritis (OR, 2.6400; 95% CI, 1.3900–5.0200; $p=0.0030$; q=0.0135), irritable bowel syndrome (OR, 1.9305; 95% CI, 1.5924–2.34005; $p<0.0001$; q<0.0001), internal hemorrhoids (OR, 1.0029; 95% CI, 1.0002–3.5940; $p<0.0001$; q=0.0521), Ileus (OR, 1.6900; 95% CI, 1.0190–2.8030; $p=0.0420$; q=0.0909), cirrhosis (OR, 1.9100; 95% CI, 1.2137–3.0057; $p=0.0052$; q=0.0176), cholecystitis(OR, 1.5069; 95% CI, 1.1363–1.9984; $p=0.0044$; q=0.0170), cholelithiasis (OR, 1.3136; 95% CI, 1.1212–1.5390; $p=0.0007$; q=0.0038), acute pancreatitis (OR, 2.2647; 95% CI, 1.5994–3.2066; $p<0.0001$; q=0.0001), chronic pancreatitis(OR, 1.7286; 95% CI, 1.1020–2.7311; $p=0.0172$; q=0.0416). (Supplementary Table 5 for original two sample MR results, Supplementary Table 6 for results after meta).

In the multivariable MR analysis, we determined the independent effect of experiencing mood swings on gastrointestinal diseases, there were 8 out of the above 11 gastrointestinal diseases that were still associated with experiencing mood swings, including 2 upper gastrointestinal diseases, 3 lower gastrointestinal disease and 3 hepatobiliary and pancreatic diseases (Table 2; Fig. 2). Genetic susceptibility to experiencing mood swings after adjusting for genetically predicted major depression, bipolar disorder, anxiety disorder and schizophrenia were positively associated with gastroesophageal reflux disease (OR, 1.6052; 95% CI, 1.2968–1.9870; $p<0.0001$; q<0.0001), acute gastritis (OR, 3.0600; 95% CI, 1.1700–8.0200; $p=0.0229$; q=0.0335), irritable bowel syndrome (OR, 1.3160; 95% CI, 1.0144–81.7074; $p=0.0387$; q=0.0496), internal hemorrhoids (OR, 1.0041; 95% CI, 1.0002–1.0079; $p=0.0368$; q=0.0427), Ileus (OR, 2.3800; 95% CI, 1.2500–4.5400; $p=0.0083$; q=0.0393), cirrhosis (OR, 3.6071; 95% CI, 1.9291–6.74460; $p<0.0001$; q<0.0001), acute pancreatitis (OR, 3.1264; 95% CI, 1.9240–5.0800; $p<0.0001$; q<0.0001), chronic pancreatitis (OR, 1.8954; 95% CI, 1.0041–3.5777; $p=0.0485$; q=0.0758). (Supplementary Table 10 for original two sample MR results, Supplementary Table 11 for results after meta).

Taken together, 10 out of 28 gastrointestinal diseases were consistently associated with genetic susceptibility to both mood swing and experiencing mood swings during univariable MR, including gastroesophageal reflux disease, gastric ulcer, acute gastritis, irritable bowel syndrome, internal hemorrhoids, cirrhosis, cholecystitis, cholelithiasis, acute pancreatitis, chronic pancreatitis (Fig. 3). In multivariable MR, four gastrointestinal diseases were consistently associated with genetic susceptibility to both mood swing and experiencing mood swings, including cirrhosis, internal hemorrhoids, acute pancreatitis and chronic pancreatitis (Fig. 4).

Discussion

In this study, we conducted a comprehensive investigation to explore the potential causal relationship between mood instability and 28 common gastrointestinal diseases using Mendelian randomization (MR) analysis. This MR study first found that genetic predisposition to mood instability was associated with the increased risk of 10 gastrointestinal diseases. Notably, after adjusting for

Table 2 Association between genetic susceptibility to experiencing mood swings and 28 gastrointestinal diseases in univariable and multivariable mendelian randomization

Disease		*N* case	*N* total	UVMR			MVMR		
				OR [95% CI]	*p* value	q value	OR [95% CI]	*p* value	q value
Upper gastrointestinal diseases	Gastroesophageal reflux disease	157,939	981,527	2.4673 [1.6938; 3.5940]	**< 0.0001***	**< 0.0001***	1.6052 [1.2968; 1.9870]	**< 0.0001***	**< 0.0001***
	Esophageal cancer	1738	849,062	1.0010 [0.9985; 1.0035]	0.4317	0.5254	1.0020 [0.9985; 1.0055]	0.2606	0.4691
	Gastric ulcer	8239	717,717	1.0070 [1.0030; 1.0110]	**0.0005***	**0.0034***	1.0050 [0.9990; 1.0110]	0.1036	0.2543
	Duodenal ulcer	5703	815,852	1.2040 [0.7457; 1.9441]	0.4476	0.5254	0.9980 [0.9930; 1.0030]	0.434	0.6167
	Acute gastritis	2558	352,622	2.6400 [1.3900;5.0200]	**0.0030***	**0.0135***	3.0600 [1.1700;8.0200]	**0.0229***	**0.0335***
	Chronic gastritis	11,784	823,391	1.1743 [0.8067; 1.7096]	0.4017	0.5254	1.0020 [0.9985; 1.0055]	0.2574	0.4691
	Barrett's esophagus	1630	870,695	1.9741 [0.7908; 4.9280]	0.1451	0.2798	1.2421 [0.6242; 2.4718]	0.5368	0.6902
Lower gastrointestinal diseases	Irritable bowel syndrome	63,829	826,311	1.9305 [1.5924; 2.3405]	**< 0.0001***	**< 0.0001***	1.3160 [1.0144; 1.7074]	**0.0387***	**0.0496***
	Celiac disease	16,345	38,932	0.3603 [0.1259; 1.0312]	0.0571	0.1285	0.3377 [0.1105; 1.0326]	0.0569	0.1707
	Diverticular disease	42,048	817,581	1.1496 [0.8405; 1.5724]	0.3828	0.5254	1.1428 [0.8579; 1.5223]	0.3617	0.5744
	Ulcerative colitis	7918	874,327	0.9980 [0.9945; 1.0015]	0.2632	0.4663	0.9960 [0.9914; 1.0007]	0.0934	0.2521
	Crohn's disease	3132	857,638	1.1808 [0.6958; 2.0038]	0.5381	0.6054	0.9990 [0.9950; 1.0030]	0.6264	07185
	Colorectal cancer	11,267	697,476	1.0030 [0.9955; 1.0106]	0.4296	0.5254	1.0010 [0.9925; 1.0095]	0.8229	0.8229
	Colon cancer	5348	678,599	0.9996 [0.9954; 1.0038]	0.8535	0.8535	0.9980 [0.9920; 1.0040]	0.5135	0.6902
	Internal hemorrhoids	9739	800,209	1.0029 [1.0002; 1.0056]	**0.0341***	0.0521	1.0041 [1.0002; 1.0079]	**0.0368***	**0.0427***
	Acute appendicitis	33,196	872,720	1.1271 [0.8512; 1.4926]	0.4036	0.5254	1.1700[0.7974;1.7168]	0.4221	0.6167
	Ileus	2911	398,631	1.6900 [1.0190;2.8030]	**0.0420***	0.0909*	2.3800 [1.2500;4.5400]	**0.0083***	**0.0393***
Hepatobiliary and pancreatic diseases	Nonalcoholic fatty liver disease	11,002	1,190,795	1.1894 [0.8704; 1.6252]	0.2763	0.4663	1.1376 [0.7338; 1.7637]	0.5643	0.6926
	Alcoholic liver disease	1416	218,792	2.2500 [0.8500;5.9400]	0.1024	0.2127	1.2200 [0.3200;4.6400]	0.7752	0.8050
	Cirrhosis	43,914	759,587	1.9100 [1.2137; 3.0057]	**0.0052***	**0.0176***	3.6071 [1.9291; 6.7446]	**< 0.0001***	**< 0.0001***
	Hepatic cancer	1639	759,587	1.0010 [0.9985; 1.0035]	0.4328	0.5254	1.0010 [0.9970; 1.0050]	0.6387	0.7185
	Cholangitis	2315	470,123	1.0009 [0.9978; 1.0041]	0.5722	0.6180	0.9980 [0.9940; 1.0020]	0.3273	0.5523
	Cholecystitis	14,517	837,589	1.5069 [1.1363; 1.9984]	**0.0044***	**0.0170***	1.3581 [0.8790; 2.0982]	0.1679	0.3778
	Cholelithiasis	66,313	889,385	1.3136 [1.1212; 1.5390]	**0.0007***	**0.0038***	1.1990 [0.8939; 1.6082]	0.2257	0.4688
	Acute pancreatitis	10,585	848,330	2.2647 [1.5994; 3.2066]	**< 0.0001***	**0.0001***	3.1264 [1.9240; 5.0800]	**< 0.0001***	**< 0.0001***
	Chronic pancreatitis	5299	843,044	1.7286 [1.1020; 2.7113]	**0.0172***	**0.0416***	1.8954 [1.0041; 3.5777]	**0.0485***	0.0758
	Pancreatic cancer	2092	480,080	1.1073 [0.5331; 2.3000]	0.7847	0.8149	1.1078 [0.6462; 1.8991]	0.7097	0.7665

UVMR, univariable Mendelian randomization. MVMR, multivariable Mendelian randomization. OR, odds ratio. CI, confidence interval. ***Significant association**

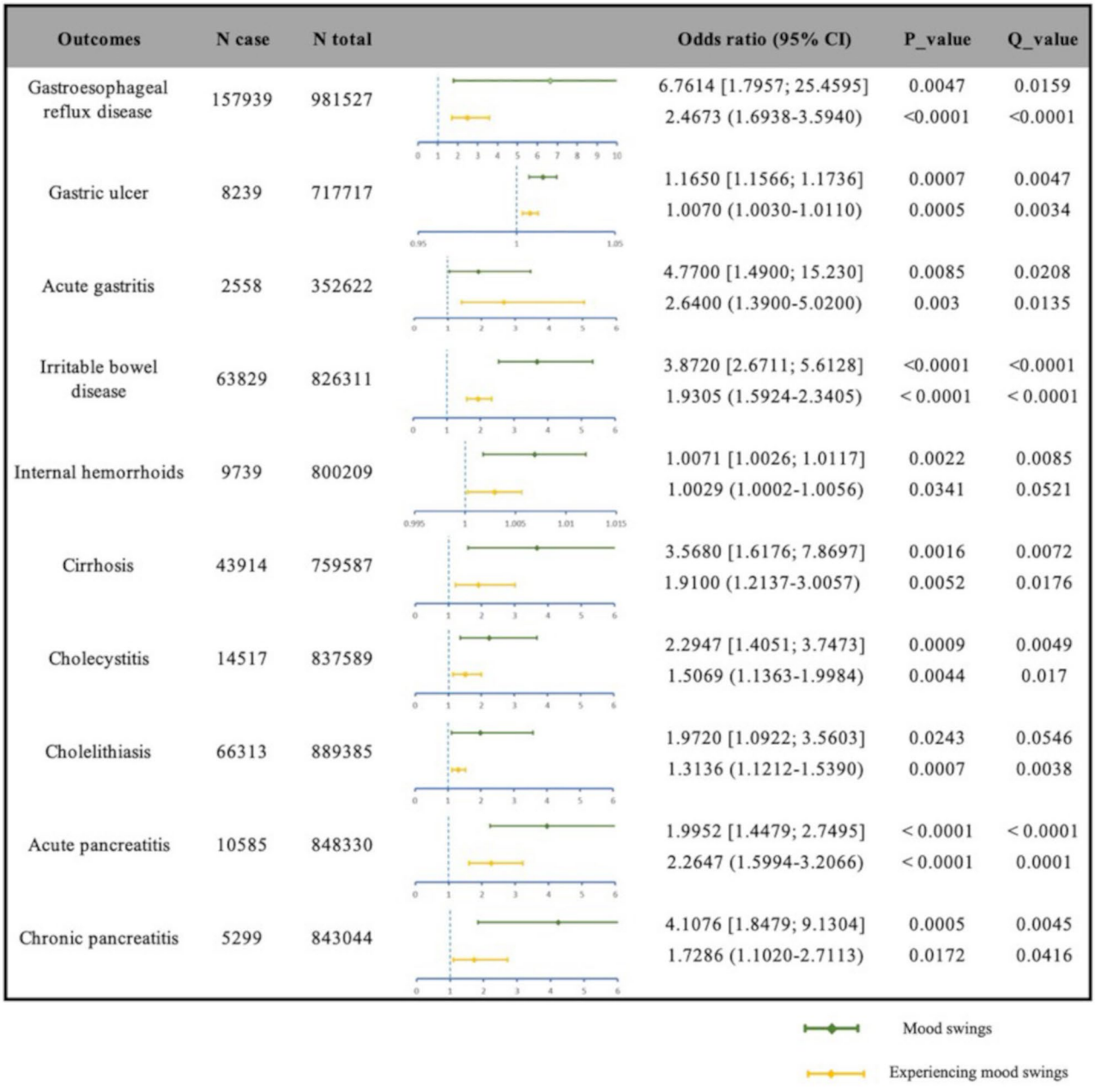

Fig. 3 Forest plot of genetically predicted mood instability with 10 gastrointestinal diseases in univariable Mendelian randomization analysis. The green bar means the diseases were associated with genetic susceptibility to mood swing, and yellow bar means the diseases were associated with genetic susceptibility to experiencing mood swings

the genetic predisposition for common psychiatric disorders such as major depression, bipolar disorder, anxiety disorder, and schizophrenia, associations with four gastrointestinal diseases remained statistically significant. Our findings provide novel insights into the association between mood instability and gastrointestinal diseases, shedding light on their potential interplay.

Mood instability is a common symptom observed in various mental disorders [25], including bipolar disorder [26] and major depression [27], and is also prevalent as a personality trait in healthy individuals [28]. Previous observational studies have suggested links between these psychiatric disorders and gastrointestinal diseases [29–33]. Moreover, Gastrointestinal symptoms was detected to be more significant when patients with bipolar were experiencing emotion instability and stress [29]. However, direct evidence linking mood instability specifically to gastrointestinal diseases has been lacking. Our study aimed to address this gap by employing MR analysis, a

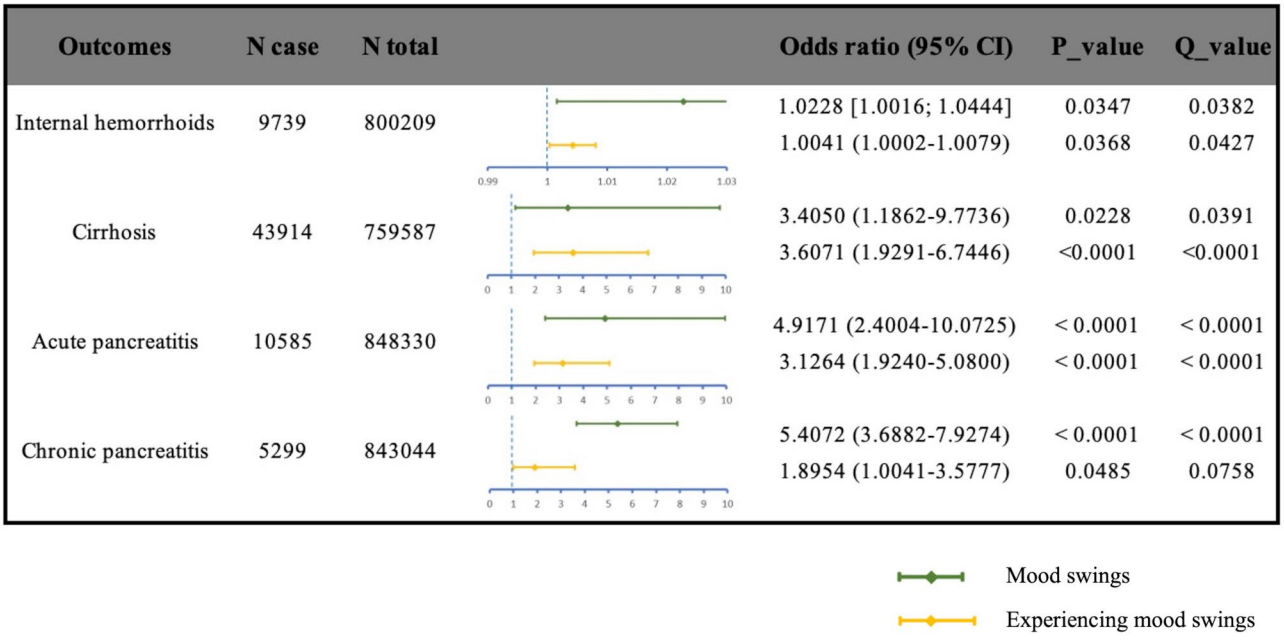

Fig. 4 Forest plot of genetically predicted mood instability with 4 gastrointestinal diseases in multivariable Mendelian randomization analysis. The green bar means the diseases were associated with genetic susceptibility to mood swing, and yellow bar means the diseases were associated with genetic susceptibility to experiencing mood swings

robust method that utilizes genetic variants as instrumental variables to assess causality.

In our analysis, 10 out of 28 gastrointestinal diseases were associated with genetic susceptibility to both mood swings and experiencing mood swings during univariable MR. Some results including gastroesophageal reflux disease, gastric ulcer, irritable bowel syndrome, internal hemorrhoids, cholecystitis, cholelithiasis, acute pancreatitis, chronic pancreatitis were consistent with the previous MR study examining the associations of genetic liability to psychiatric disorders with gastrointestinal diseases [34–36]. Moreover, our MR investigation provided novel findings for cirrhosis. However, despite previous research indicating the association between mental disorders and some other gastrointestinal diseases including duodenal ulcer, Crohn's disease, ulcerative colitis, nonalcoholic fatty liver disease, and alcoholic liver disease [34, 37], no causal relationship was found in our study.

Significant genetic correlations have been identified between mood instability and common psychiatric disorders including major depressive disorder, bipolar disorder, schizophrenia, and anxiety disorder [38]. Given the known impact of psychiatric disorders on gastrointestinal diseases, we postulated that the common psychiatric disorders could act as confounding factors in the association between mood instability and gastrointestinal diseases. After adjusting for depression, bipolar disorder, schizophrenia, and anxiety disorder, our analysis indicated that the associations between mood instability and internal hemorrhoids, cirrhosis, acute pancreatitis, and chronic pancreatitis remain statistically significant. These results suggested that mood instability might be an important risk factor for these gastrointestinal diseases, not only in healthy people but also in patients with psychiatric disorders.

To ensure the robustness of our findings, we utilized two different GWAS datasets for mood instability and observed consistent results between them. However, some discrepancies were noted in the associations between mood swings and experiencing mood swings with gastrointestinal diseases. Three gastrointestinal diseases in the univariable MR analysis and six gastrointestinal diseases in the multivariable MR analysis were associated with either mood swings or experiencing mood swings. These inconsistencies could be attributed to undetected horizontal pleiotropy or variations in the definitions of mood instability across different GWAS datasets. We selected gastrointestinal diseases that were reported to be consistent with results for two mood instability variables to ensure the accuracy of our results. However, in clinical practice, it is still necessary to pay attention to diseases that have a positive result for only one variable.

Several behavioral and biological mechanisms could explain the observed causal relationship between mood instability and gastrointestinal diseases. First, lifestyle factors influenced by mood instability - such as alcohol consumption, smoking, body mass index, and triglyceride levels - have been shown to contribute to the increased risk of cirrhosis, acute pancreatitis, chronic

pancreatitis and internal hemorrhoids [39–42]. Alcohol use is one of the top three risk factors of cirrhosis [39] and has been implicated in the development of pancreatitis in 60-90% of patients [41]. Smoking and elevated triglyceride levels are also independent risk factors for cirrhosis and pancreatitis [41, 42]. Secondly, it is well-known that areas processing visceral afferents are closely linked to regions involved in regulating of affective and sensory processes [43]. Frequent alterations in mood states might affect the function of the gastrointestinal tract. Mood instability may influence the function of the gastrointestinal tract through alterations in mood states, impacting endocrine and immune metabolic processes [44]. During periods of negative emotion, the release of catecholamines (adrenaline and noradrenaline) and adrenocorticotropic hormone (ACTH) can affect immune function, potentially leading to impaired gastrointestinal function [45]. Chronic stress, often associated with mood instability, could also affect gut microbiota composition and cause inflammation in the gastrointestinal tract [46]. Although similar mechanisms could explain a potential causal link between mood instability and other gastrointestinal diseases, our univariable MR analysis revealed associations between mood instability and 10 gastrointestinal diseases. However, when psychiatric disorders were included in a multivariable MR analysis, mood instability was independently linked to only four diseases. This shift may be due to the co-occurrence of psychiatric disorders and mood instability, suggesting that the six diseases losing significance in the multivariable analysis are more strongly associated with psychiatric conditions.

Strengths of our study include the utilization of the MR design, which minimizes biases due to reverse causality and residual confounding. We also bolstered the robustness of our results by extracting genetic associations from diverse GWAS datasets and conducting multivariable MR analysis to account for potential confounding factors. In addition, MR statistics from different datasets of the same disease were pooled through meta-feeding, making our study population the largest.

However, several limitations should be acknowledged. The potential for horizontal pleiotropy in MR studies remains a concern, although our analysis including MR-Egger intercept test and multivariable MR indicated limited evidence of its presence. Secondly, our study is limited by the use of a binary variable to represent mood instability, as our current GWAS data do not allow for its quantification. This limitation may lead to a violation of the assumption that the genetic variant can influence the outcome through the continuous risk factor, even if the binary exposure remains unchanged [47]. Future research with more granular data could provide deeper insights into the relationship between varying degrees of mood instability and gastrointestinal diseases. Furthermore, discrepancies in outcomes between mood swings and experiencing mood swings underscore the need for further exploration. Lastly, the generalizability of our findings to populations beyond those of European ancestry warrants future investigation.

Conclusion

Our study provides compelling evidence for a potential causal relationship between mood instability and certain gastrointestinal diseases. These findings underscore the importance of considering mood instability as a potential risk factor for gastrointestinal diseases and highlight the need for further research to elucidate the underlying mechanisms and validate our findings in diverse populations.

Abbreviations

MR	Mendelian randomization
SNPs	Single-nucleotide polymorphisms
MAF	Minor allele frequency
ACTH	Adrenocorticotropic hormone
GWAS	Genome-Wide Association Studies

Supplementary Information

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Supplementary Material 1

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Author contributions

Rui-lin Liu and Qing-chun Song conceived and designed the research. Rui-lin Liu and Qing-chun Song managed the data and performed the bioinformatics analyses. The manuscript was written and modified by Rui-lin Liu, Qing-chun Song, Li-ming Liu, Yi-feng Yang and Wei-hong Zhu. All authors reviewed the manuscript.

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Data availability

Our study used publicly available summary-level data of GWAS. The summary statistics for all data sources are available via the IEU Open GWAS project(https://gwas.mrcieu.ac.uk/) and FinnGen database. The codes used in this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

We used summary-level data from publicly available GWAS studies which have received ethical approval from their respective institutional review boards and informed consent from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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