Observational Study

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Post-traumatic stress disorder, attention deficit and hyperactivity disorder, and 24 gastrointestinal diseases

Evidence from Mendelian randomization analysis

Liang Ma, MD[a], Xiaofeng Li, MD[a], Yang Zhang, MD[b,*]

Abstract

Post-traumatic stress disorder (PTSD) and Attention deficit and hyperactivity disorder (ADHD) are common mental illnesses. Observational studies have indicated that these conditions often co-occur with gastrointestinal diseases. However, the causal relationship between PTSD and ADHD with gastrointestinal diseases remain unclear. We conducted Mendelian randomization (MR) analysis to investigate these associations. We selected genetic instrument data with genome-wide significance levels for PTSD and ADHD from the psychiatric genomics consortium open genome-wide association study platform. Summary statistics for the 24 gastrointestinal diseases were obtained from the FinnGen study. We used the "TwoSampleMR" package in R to perform a 2-sample MR analysis and conducted sensitivity analysis of the results. We found that genetic susceptibility to PTSD was associated with 1 gastrointestinal disease, specifically pancreatic cancer ($P = .003$; odds ratios [OR] = 1.295; 95% CI, 1.094–1.531). Genetic susceptibility to ADHD was associated with 4 gastrointestinal diseases: gastroesophageal reflux ($P = .014$; OR = 1.100; 95% CI, 1.020–1.186), gastric ulcer ($P = .004$; OR = 1.208; 95% CI, 1.061–1.376), duodenal ulcer ($P = .020$; OR = 1.206; 95% CI, 1.029–1.413), and chronic gastritis ($P = .021$; OR = 1.122; 95% CI, 1.018–1.237). This study provides MR evidence supporting causal relationship between PTSD and ADHD with specific gastrointestinal diseases.

Abbreviations: ADHD = attention deficit and hyperactivity disorder, ASD = autism spectrum disorder, CL = confidence limits, GWAS = genome-wide association studies, HPA = hypothalamic-pituitary-adrenal, IBD = inflammatory bowel disease, ICD = International Classification of Diseases, IVs = instrumental variables, IVW = inverse-variance weighted, MR = Mendelian randomization, OR = odds ratio, PGC = psychiatric genomics consortium, PTSD = post-traumatic stress disorder, SD = standard deviation, SNPs = single nucleotide polymorphisms, TSMR = two-sample Mendelian randomization.

Keywords: attention deficit and hyperactive disorder, causal relationship, gastrointestinal diseases, Mendelian randomization, post-traumatic stress disorder

1. Introduction

Post-traumatic stress disorder (PTSD) is a debilitating mental disorder that occurs after traumatic events or severe accidents. Its prevalence in the general population is 6% to 8%, but it is higher in special groups (including veterans and refugees).[1] The World Health Organization's mental health survey across 24 countries showed a cross-national lifetime prevalence of PTSD at 3.9%.[2] Clinically, PTSD is characterized by intrusive memories, avoidance of triggers, negative emotions, irritability, hypervigilance, and symptoms persisting for over a month after trauma.[3] Additionally, PTSD is often comorbid with other mental disorders such as depression,[4] anxiety,[5] and substance use disorders.[6] Attention deficit and hyperactivity disorder (ADHD) is also a common neurobehavioral disorder, mainly characterized by inattention, impulsivity, and hyperactivity. It is most common in children, but 30% to 70% of patients continue to experience symptoms into adulthood.[7,8] The primary manifestations of ADHD are inattention, hyperactivity, and impulsivity, which are inappropriate for an individual's age, leading to problems in life, learning, and mental health.[9] Compared to healthy individuals, patients with ADHD are more prone to smoking, alcohol abuse, and antisocial behaviors.[10] These behaviors affect learning and life, resulting in costly consequences for both individuals and society.[9]

There is a close relationship between mental and physical health. Previous studies have shown that mental health

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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problems can cause functional or organic gastrointestinal diseases.[11] The brain and gut interact through various mechanisms. In contrast, mental activity can affect the gastrointestinal tract by altering autonomic nervous system activity and regulating hormone secretion. On the other hand, imbalances in gut cells and microbiota can cause changes in central nervous system bioactivity. Therefore, mental and gastrointestinal diseases often co-occur, as demonstrated in numerous clinical studies. For example, a clinical study of 184 veterans with PTSD showed that the incidence of irritable bowel syndrome and abdominal pain was significantly higher than that in the general population.[12] Similar situations occur among civilians who have experienced war trauma and postwar impacts.[13]

A cohort study indicated that children with inflammatory bowel disease (IBD) often concurrently had ADHD.[14] Additionally, evidence shows that adolescents with ADHD commonly suffer from severe gastrointestinal diseases and enuresis.[15] A cross-sectional study reported a close association between ADHD and Crohn disease and ulcerative colitis, with comorbidities more common in females than males.[16] Based on this connection between the mental and gastrointestinal systems, there are corresponding clinical treatments, such as psychological interventions to treat IBD.[17] However, no comprehensive study has explored the relationship between PTSD, ADHD, and other common gastrointestinal diseases. The causal relationship between PTSD and ADHD and the risk of gastrointestinal disease remains to be elucidated.

Mendelian randomization (MR) uses single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to infer the causal relationship between exposure and outcome.[18] This method can significantly reduce the risk of confounding and reverse causation. Although some cross-sectional or cohort studies have investigated the association between mental illnesses and gastrointestinal diseases, observational studies are susceptible to various confounding factors. Therefore, we used MR analysis to demonstrate the causal relationship between PTSD, ADHD, and the 24 types of gastrointestinal diseases. This approach helps explore the complex mechanistic relationship between mental illnesses and gastrointestinal diseases, providing a basis for risk prediction and treatment.

2. Materials and methods

2.1. Study design

In this study, we used a 2-sample MR analysis to explore the potential causal relationships between PTSD, ADHD, and 24 types of gastrointestinal diseases. A flowchart depicting the entire procedure is shown in Figure 1. This study adheres to the basic assumptions of the MR method: The IVs are highly associated with exposure. The IVs had no direct effect on potential confounders other than exposure and outcome. All IVs affected the outcome only through the exposure. In this study, PTSD and ADHD were the exposures, and 24 types of gastrointestinal diseases were the outcomes. It should be noted that all datasets used in this study were publicly available. Therefore, this study did not require additional ethical approval or consent.

2.2. Data sources

We obtained genetic data related to PTSD and ADHD from the Psychiatric Genomics Consortium open GWAS platform (https://pgc.unc.edu/). The PTSD data were obtained from a meta-GWAS involving 30,000 cases and 170,000 controls of European ancestry.[19] ADHD data were obtained from a meta-GWAS involving 38,691 cases and 186,843 controls of European ancestry.[20] The detailed data are presented in Table 1 and Table S1, Supplemental Digital Content, https://links.lww.com/MD/O863.

We extracted genetic data for 24 types of gastrointestinal diseases from the FinnGen database (https://finngen.gitbook.io/documentation).[21] The 24 types of gastrointestinal diseases include: gastroesophageal reflux, esophageal cancer, gastric ulcer, duodenal ulcer, acute gastritis, chronic gastritis, gastric cancer, irritable bowel syndrome, celiac disease, ulcerative colitis, Crohn disease, diverticular disease, colorectal cancer,

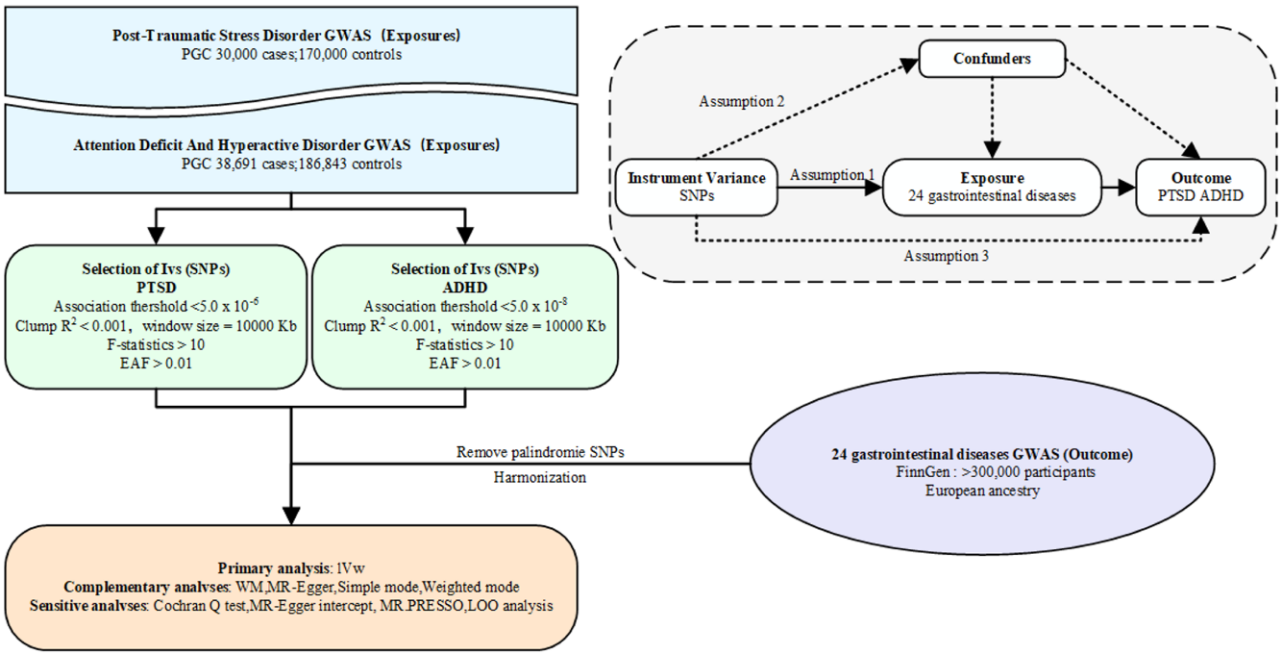

Figure 1. The analysis process of our research. Assumption 1: The IVs are significantly associated with PTSD and ADHD; Assumption 2: The IVs are not related to the confounders; Assumption 3: The IVs affect gastrointestinal diseases through PTSD and ADHD. ADHD = attention deficit and hyperactivity disorder, IVs = instrumental variables, PTSD = post-traumatic stress disorder.

Table 1

These GWAS datasets were chosen to illustrate the relationship between psychiatric.

Disease	PMID	Author	Cases/controls	Sample size
Psychiatric disorders				
Post-traumatic stress disorder	36,702,997	European	30,000/170,000	200,000
Attention deficit and hyperactive disorder	31,594,949	European	38,691/186,843	225,534
Gastrointestinal diseases				
Gastroesophageal reflux	NA	European	28,859/350,064	378,923
Esophageal cancer	NA	European	619/314,193	314,812
Gastric ulcer	NA	European	6459/350,064	356,523
Duodenal ulcer	NA	European	3795/350,064	353,859
Acute gastritis	NA	European	2558/350,064	352,622
Chronic gastritis	NA	European	10,317/350,064	360,381
Gastric cancer	NA	European	1432/314,193	319,384
Irritable bowel syndrome	NA	European	10,329/329,381	339,710
Celiac disease	NA	European	4115/394,391	398,506
Ulcerative colitis	NA	European	5931/405,386	411,317
Crohn disease	NA	European	2191/392,974	395,165
Diverticular disease	NA	European	33,619/329,381	363,000
Colorectal cancer	NA	European	6847/314,193	321,040
Nonalcoholic fatty liver disease	NA	European	2568/409,613	412,181
Alcoholic liver disease	NA	European	3047/400,247	403,294
Cirrhosis	NA	European	4380/407,801	412,181
Liver cancer	NA	European	500/314,193	314,693
Cholangitis	NA	European	545/387,771	388,316
Cholelithiasis	NA	European	40,191/361,641	401,832
Chlocystitis	NA	European	4697/361,641	366,338
Acute pancreatitis	NA	European	6787/361,641	368,428
Chronic pancreatitis	NA	European	3875/361,641	365,516
Pancreatic cancer	NA	European	1626/314,193	315,819
Acute appendicitis	NA	European	31,628/378,082	409,710

Abbreviation: GWAS = genome-wide association studies.

nonalcoholic fatty liver disease, alcoholic liver disease, cirrhosis, liver cancer, cholangitis, cholelithiasis, cholecystitis, acute pancreatitis, chronic pancreatitis, pancreatic cancer, acute appendicitis. Detailed data can be found in Table 1, and the number of participants and the International Classification of Diseases codes for the 24 gastrointestinal diseases are shown in Table S2, Supplemental Digital Content, http://links.lww.com/MD/O863.

2.3. Selection and validation of SNPs

The IVs used in our MR analysis were derived from 2 GWAS summary datasets. First, we used SNPs that reached the genome-wide significance threshold of $P < 5 \times 10^{-8}$.[22] Second, we processed these SNPs for linkage disequilibrium, retaining only independent IVs without any linkage disequilibrium (parameters set at $r^2 = 0.001$, kb = 10,000). Because the number of usable SNPs for PTSD was reduced after the above steps, to avoid statistical bias due to a small number of IVs, the threshold level for PTSD was adjusted to $P < 5 \times 10^{-6}$.[23] Additionally, SNPs related to the outcome were excluded, and palindromic SNP sequences characterized by intermediate allele frequencies were removed.[22] To ensure the strength of the IVs, we calculated the *F*-statistic,[24] using an *F*-statistic >10 as a robustness indicator, indicating no weak IVs bias. The *F*-statistic was calculated as $F = \beta^2/SE^2$. Before MR analysis, a data harmonization step is required to ensure that the effects of SNPs on exposure and outcome corresponded to the same allele. This step was performed to provide robust and reliable IVs for MR analysis (Tables S3 and S4, Supplemental Digital Content, http://links.lww.com/MD/O863).

2.4. Mendelian randomization analysis

In this study, the primary statistical method used was the inverse-variance weighted (IVW) method to calculate the main MR estimates, assessing the causal relationships between PTSD and ADHD with 24 types of gastrointestinal diseases. The basic assumption of the IVW method is that it satisfies all core MR assumptions and provides the most precise estimates, assuming that all IVs are valid.[25] Because IVs may have potential effects on the outcome through other pathways, indicating a certain level of pleiotropy, this can result in a range of causal estimate biases. Therefore, other statistical methods were also used for estimation, including MR-Egger,[26] weighted median,[27] Simple mode and weighted mode methods. Each method provides specific values to indicate causal relationships.

To enhance the robustness and reliability of our MR analysis, we employed additional statistical methods, each tailored to address potential biases in different scenarios. MR-PRESSO was used to detect and correct horizontal pleiotropy by identifying and removing outlier SNPs, recalculating estimates to minimize bias. MR-Egger regression assessed directional pleiotropy, with its intercept term providing evidence of systematic bias; this method also offered pleiotropy-adjusted causal estimates, albeit with lower precision. The weighted median method was applied to ensure reliable causal estimates even when up to 50% of the IVs were invalid. Furthermore, the simple mode and weighted mode methods identified consistent causal signals by clustering SNPs with similar effects, particularly suitable for complex datasets. The IVW method remained our primary approach, offering the most precise causal estimates under the assumption that all IVs are valid. To further validate the stability of our results, we performed sensitivity analyses, including Cochran *Q* test to assess heterogeneity and Leave-one-out analysis to examine the influence of individual SNPs on the overall findings.

As part of the sensitivity analyses, we rigorously tested the core assumptions of MR using multiple methods to ensure the reliability of our findings. MR-Egger regression was employed to evaluate directional pleiotropy.[28] The MR-PRESSO global test identified Y outlier SNPs, which were excluded, and subsequent reanalysis confirmed consistent causal estimates.[29]

Heterogeneity was assessed using Cochran *Q* statistic, revealing no significant heterogeneity ($P > .05$). Additionally, funnel plots were used to visualize the heterogeneity of SNP effects.[30] To further verify the stability of our results, a leave-one-out analysis demonstrated that no single SNP had a disproportionate influence on the overall causal estimates.[31] Additionally, density plots were used to visualize the normality of SNP effect estimates, supporting the robustness of the core MR assumptions.

For the results, we quantified the strength of causal relationships using odds ratios (OR) and their corresponding 95% confidence limits. The final results reported the causal estimates, *P*-values, β coefficients, and standard deviations (SDs). All estimated values of the aforementioned results are expressed as OR and their 95% confidence intervals (95% CI) per 1 SD increase in risk exposure. A *P*-value < .05 was considered statistically significant evidence of potential causal relationships. All analyses were performed using the TwoSampleMR[32] and MR-PRESSO[33] R packages in R software version 4.3.2.

3. Results

3.1. Causal effects of gastrointestinal disease on PTSD

Among the 24 gastrointestinal diseases examined, genetic susceptibility to PTSD was significantly associated with pancreatic cancer ($P = .003$; OR = 1.295; 95% CI, 1.094–1.531) (Table S4, Supplemental Digital Content, http://links.lww.com/MD/O863). Sensitivity analysis confirmed the robustness of this finding. Cochran *Q* test showed no significant heterogeneity, and MR-Egger regression intercept indicated no directional pleiotropy (*P*-intercept < .05). Heterogeneity was observed only in SNPs associated with diverticular disease and cholelithiasis. For diverticular disease, MR-PRESSO identified 2 outliers. After removal, no significant association remained, suggesting the initial result was likely influenced by outliers. Visualizations, including forest plots, scatter plots, density plots, leave-one-out analysis plots, and funnel plots, were used to illustrate causal relationships. These plots are available in Tables S5 to S7, Supplemental Digital Content (http://links.lww.com/MD/O863); Figures 2 to 5; Figure S1, Supplemental Digital Content, http://links.lww.com/MD/O864.

3.2. Causal effects of gastrointestinal disease on ADHD

Among the 24 gastrointestinal diseases examined, genetic susceptibility to ADHD was significantly associated with 4 gastrointestinal diseases: Gastroesophageal reflux ($P = .014$; OR = 1.100; 95% CI = 1.020–1.186), Gastric ulcer ($P = .004$; OR = 1.208; 95% CI = 1.061–1.376), duodenal ulcer ($P = .020$; OR = 1.206; 95% CI = 1.029–1.413), and chronic gastritis ($P = .021$; OR = 1.122; 95% CI = 1.018–1.237) (Table S5, Supplemental Digital Content, http://links.lww.com/MD/O863). Seven diseases exhibited SNP heterogeneity: gastroesophageal reflux, gastric ulcer, ulcerative colitis, diverticular disease, colorectal cancer, cholelithiasis, and acute appendicitis. However, since the random-effects IVW method was employed, this heterogeneity did not significantly affect the final results. Sensitivity analyses showed that most associations remained consistent in direction and significance. The MR-Egger intercept test detected significant horizontal pleiotropy in alcoholic liver disease and cholecystitis (*P*-intercept < .05), suggesting potential bias in these associations. Additionally, MR-PRESSO identified 1 to 3 outliers in gastric ulcer, ulcerative colitis, diverticular disease, and acute appendicitis. After removing the outliers, only gastric ulcer retained a significant causal association. Visualizations, including scatter plots, density plots, leave-one-out analysis plots, and funnel plots, were generated to illustrate causal relationships (Tables S5–S7, Supplemental Digital Content, https://links.lww.com/MD/O863; Figs. 6–9; Fig. S2, Supplemental Digital Content, https://links.lww.com/MD/O865).

4. Discussion

In this study, we conducted a comprehensive MR analysis to examine the relationship among PTSD, ADHD, and 24 gastrointestinal diseases. Our results indicated that PTSD is associated with an increased risk of 1 gastrointestinal disease, whereas ADHD is associated with an increased risk of 4 gastrointestinal

Main.outcome	Method	nSNP	P.value	OR(95%CI)	Heterogeneity.Test.P	MR.Egger.Intercept.P	MR.PRESSO.Global.Test.P
REFLUX_Finn	Inverse variance weighted	20	0.50106419	1.02(0.97 to 1.07)	0.10660927	0.3258592	0.107(raw, 0 outliers)
OESOPHAGUS_Finn	Inverse variance weighted	20	0.08486342	1.27(0.97 to 1.67)	0.60497543	0.3569007	0.654(raw, 0 outliers)
GULC_Finn	Inverse variance weighted	20	0.85896637	1.01(0.93 to 1.10)	0.96627425	0.8416802	0.965(raw, 0 outliers)
DULC_Finn	Inverse variance weighted	20	0.13404572	1.10(0.97 to 1.24)	0.22211582	0.5628042	0.263(raw, 0 outliers)
ACUTGASTR_Finn	Inverse variance weighted	20	0.99876536	1.00(0.87 to 1.14)	0.74690470	0.9711733	0.738(raw, 0 outliers)
CHRONGASTR_Finn	Inverse variance weighted	20	0.80632729	1.01(0.94 to 1.08)	0.46842272	0.0584463	0.942(raw, 0 outliers)
STOMACH_Finn	Inverse variance weighted	20	0.82268211	1.02(0.85 to 1.22)	0.72317112	0.3911796	0.699(raw, 0 outliers)
IBS_Finn	Inverse variance weighted	20	0.28535555	1.04(0.97 to 1.12)	0.33027541	0.9657341	0.33(raw, 0 outliers)
COELIAC_Finn	Inverse variance weighted	20	0.82837719	0.99(0.89 to 1.10)	0.95976576	0.1767931	0.928(raw, 0 outliers)
UC_STRICT2_Finn	Inverse variance weighted	20	0.49852357	1.03(0.94 to 1.13)	0.69534887	0.2550672	0.69(raw, 0 outliers)
CHRONNAS_Finn	Inverse variance weighted	20	0.48024340	0.94(0.80 to 1.11)	0.15141187	0.8462639	0.171(raw, 0 outliers)
DIVERTIC_Finn	Inverse variance weighted	18	0.76191919	0.99(0.95 to 1.04)	0.90322487	0.7829936	0.877(outlier corrected, 2 outlier)
COLORECTAL_Finn	Inverse variance weighted	20	0.25264164	1.05(0.96 to 1.15)	0.37188464	0.8724617	0.306(raw, 0 outliers)
NAFLD_Finn	Inverse variance weighted	20	0.79336613	1.02(0.89 to 1.17)	0.35132369	0.8838344	0.399(raw, 0 outliers)
ALCOLIV_Finn	Inverse variance weighted	20	0.99734384	1.00(0.88 to 1.13)	0.44472557	0.6965858	0.469(raw, 0 outliers)
CIRRHOSIS_BROAD_Finn	Inverse variance weighted	20	0.46621189	1.04(0.94 to 1.15)	0.70457125	0.7757236	0.721(raw, 0 outliers)
HEPATOCELLU_Finn	Inverse variance weighted	20	0.05417069	1.37(0.99 to 1.88)	0.32664964	0.4200960	0.325(raw, 0 outliers)
CHOLANGI_Finn	Inverse variance weighted	20	0.58576982	0.96(0.82 to 1.12)	0.73161092	0.4317315	0.745(raw, 0 outliers)
CHOLELITH_Finn	Inverse variance weighted	20	0.29914985	0.98(0.93 to 1.02)	0.03574177	0.8509986	0.039(raw, 0 outliers)
CHOLECYST_Finn	Inverse variance weighted	20	0.56874057	0.97(0.88 to 1.07)	0.83110846	0.6928875	0.786(raw, 0 outliers)
ACUTPANC_Finn	Inverse variance weighted	20	0.19362199	0.94(0.85 to 1.03)	0.10467019	0.6294667	0.13(raw, 0 outliers)
CHRONPANCS_Finn	Inverse variance weighted	20	0.42652081	1.05(0.94 to 1.17)	0.46387686	0.3010842	0.509(raw, 0 outliers)
PANCREAS_Finn	Inverse variance weighted	20	0.00258672	1.29(1.09 to 1.53)	0.50926183	0.6833673	0.514(raw, 0 outliers)
APPENDACUT_Finn	Inverse variance weighted	20	0.23029791	1.02(0.98 to 1.07)	0.82606888	0.6684805	0.837(raw, 0 outliers)

P<0.05 was considered statistically significant

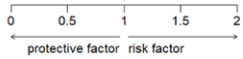

Figure 2. Forest plots of Mendelian randomization analyses of the causal effects of gastrointestinal diseases on PTSD. This is the forest plot from the FinnGen database, visually presenting the MR estimates and corresponding 95% confidence intervals for each SNP. Main outcome: 24 gastrointestinal diseases; Method: IVW method; nSNP: Number of usable SNPs after screening; *P*. value: *P*-value; OR (95% CI): OR value and 95% confidence interval; heterogeneity test *P*: *P*-value for heterogeneity; MR. Egger intercept *P*: *P*-value for the intercept; MR. PRESSO. Global test *P*: *P*-value after removing and adjusting for outliers using MR-PRESSO. IVW = inverse-variance weighted, MR = Mendelian randomization, OR = odds ratio, PTSD = post-traumatic stress disorder, SNP = single nucleotide polymorphism.

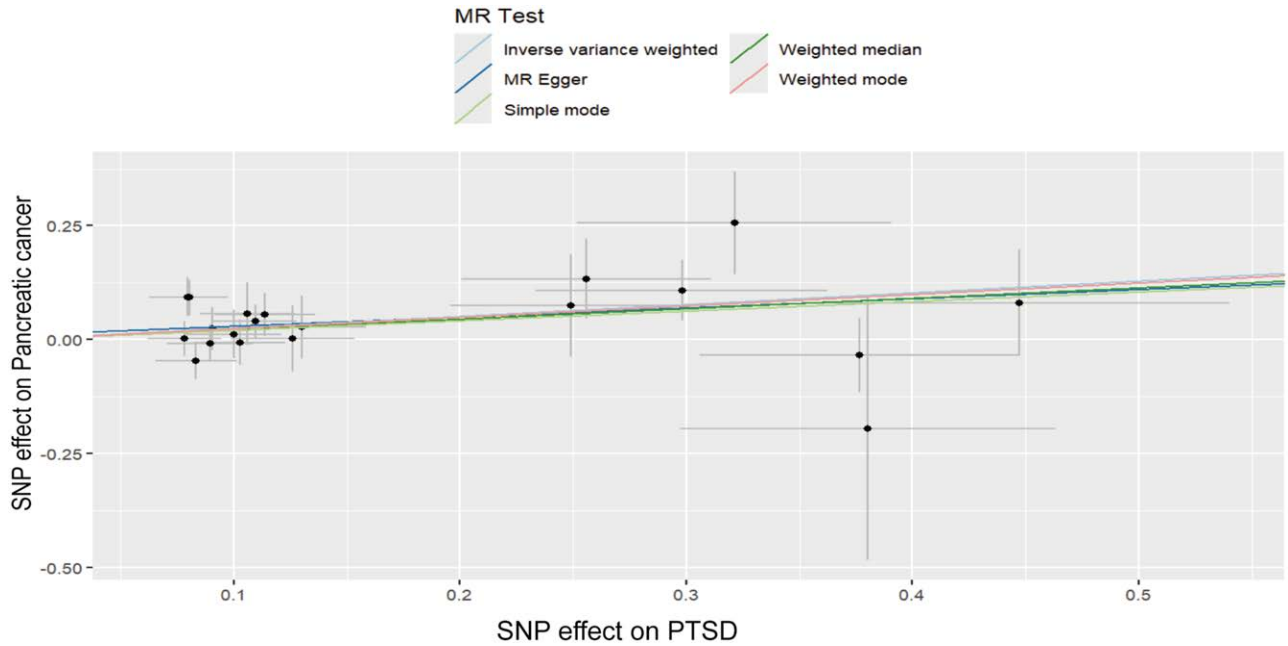

Figure 3. Scatter plots of Mendelian randomization analyses of the causal effects of gastrointestinal diseases on PTSD. This scatter plot illustrates the relationship between PTSD and pancreatic cancer in the FinnGen database. The plot describes the 5 methods used in this study, with light blue, dark blue, light green, dark green, and red lines representing the IVW, MR-Egger, simple model, weighted median, and weighted mode methods, respectively. IVW = inverse-variance weighted, MR = Mendelian randomization, PTSD = post-traumatic stress disorder.

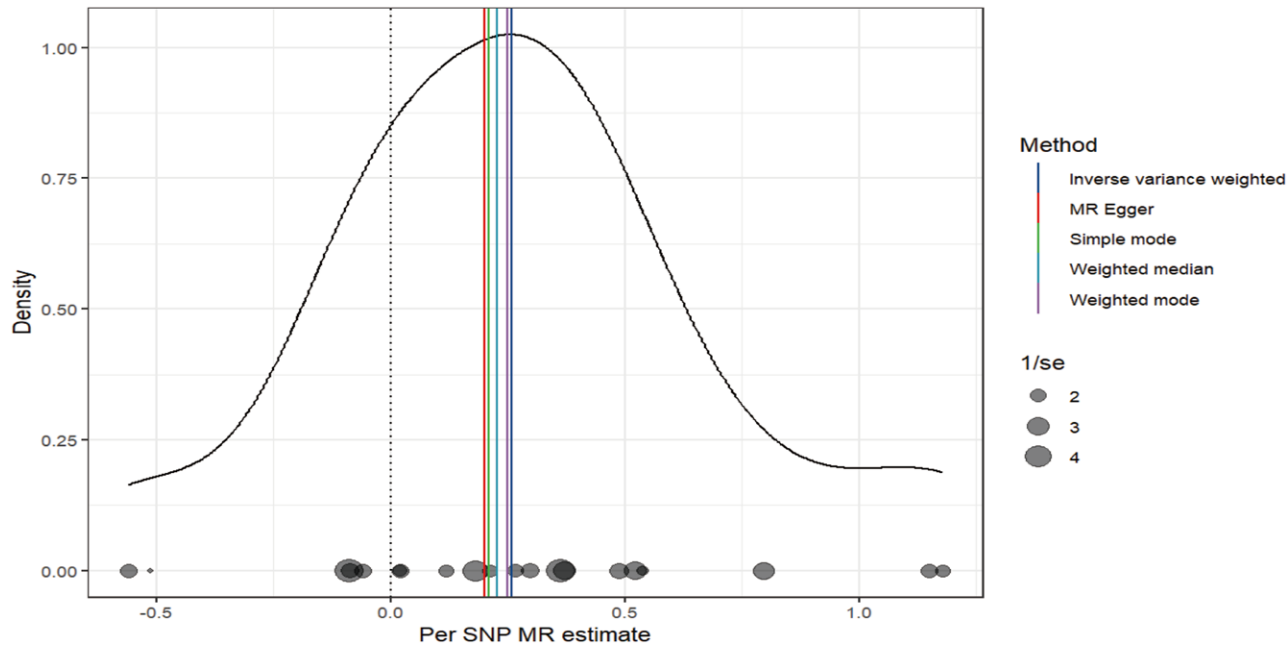

Figure 4. Density plots of Mendelian randomization analyses of the causal effects of Gastrointestinal Diseases on PTSD. This density plot illustrates the relationship between PTSD and pancreatic cancer in the FinnGen database. The plot describes the 5 methods used in this study, with dark blue, red, light green, light blue, and purple lines representing the IVW, MR-Egger, simple model, weighted median, and weighted mode methods, respectively. IVW = inverse-variance weighted, MR = Mendelian randomization, PTSD = post-traumatic stress disorder.

diseases. Notably, although the initial MR analysis did not demonstrate causality between ADHD and gastric ulcer, this association became significant after the removal of heterogeneous values. These findings provide new insights into the relationship between mental disorders and gastrointestinal diseases. This study is unique in its systematic evaluation of 24 gastrointestinal diseases, offering a comprehensive perspective that surpasses the narrower focus of previous studies. Unlike prior research, which often examines isolated conditions, our approach allows a broader understanding of the brain-gut axis and its role in mental and gastrointestinal health.

A meta-analysis has suggested that PTSD was not associated with risk factors for gastrointestinal cancer.[34] However, a cross-sectional study reported that PTSD significantly increases the incidence of any cancer, including gastrointestinal cancer.[35] The association between PTSD and gastrointestinal cancer remains controversial, potentially due to variations in sample size and confounding bias. In our MR analysis, no association

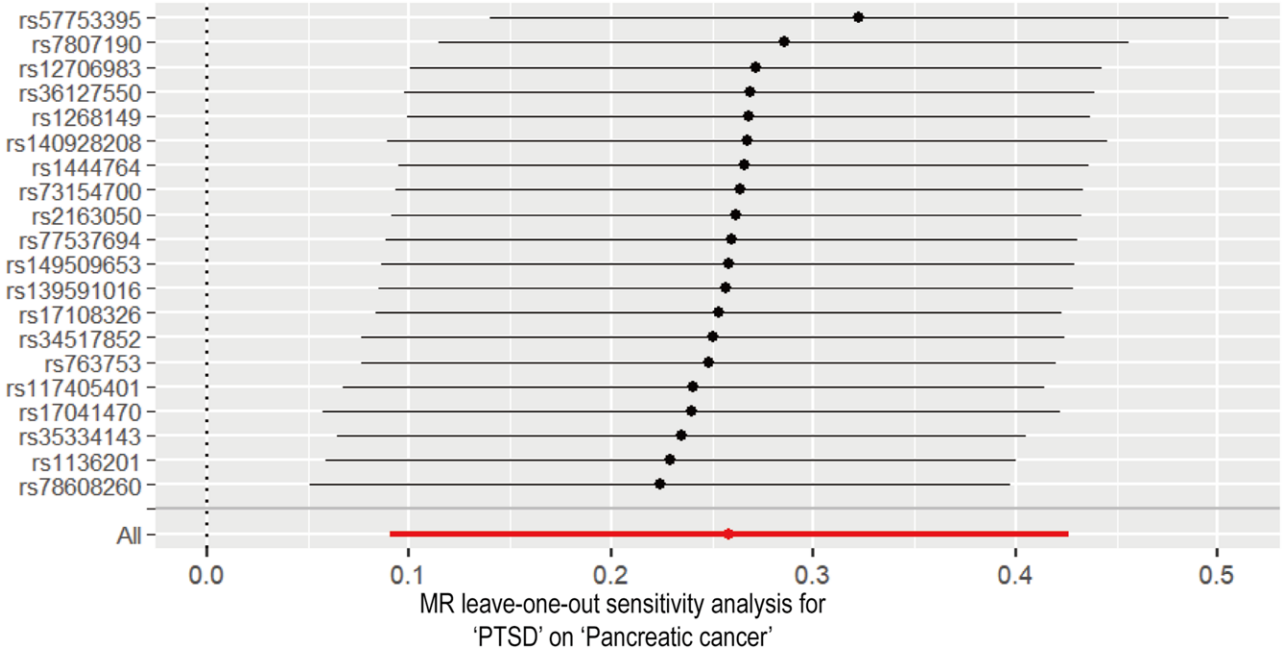

Figure 5. Leave-one-out plot of Mendelian randomization analyses of the causal effects of gastrointestinal diseases on PTSD. This leave-one-out analysis illustrates the relationship between PTSD and pancreatic cancer in the FinnGen database. The leave-one-out analysis is conducted to determine whether any individual instrumental variable has a disproportionate impact on the estimated causal effect. PTSD = post-traumatic stress disorder.

Main.outcome	Method	nSNP	P.value	OR(95%CI)	Heterogeneity.Test.P	MR.Egger.Intercept.P	MR.PRESSO.Global.Test.P
REFLUX_Finn	Inverse variance weighted	25	0.013508619	1.10(1.02 to 1.19)	0.014011523	0.07023229	0.018(raw, 0 outliers)
OESOPHAGUS_Finn	Inverse variance weighted	25	0.123129310	1.34(0.92 to 1.95)	0.646621141	0.69624160	0.643(raw, 0 outliers)
GULC_Finn	Inverse variance weighted	24	0.004404613	1.21(1.06 to 1.38)	0.298478605	0.12857681	0.304(raw, 0 outliers)
DULC_Finn	Inverse variance weighted	25	0.020442601	1.21(1.03 to 1.41)	0.362665490	0.52868910	0.369(raw, 0 outliers)
ACUTGASTR_Finn	Inverse variance weighted	25	0.830471622	0.98(0.81 to 1.18)	0.391226949	0.38835133	0.402(raw, 0 outliers)
CHRONGASTR_Finn	Inverse variance weighted	25	0.020548071	1.12(1.02 to 1.24)	0.357009195	0.14123592	0.372(raw, 0 outliers)
STOMACH_Finn	Inverse variance weighted	25	0.547401826	1.08(0.84 to 1.38)	0.457361328	0.66261433	0.47(raw, 0 outliers)
IBS_Finn	Inverse variance weighted	25	0.073001696	1.09(0.99 to 1.20)	0.876677240	0.33699210	0.871(raw, 0 outliers)
COELIAC_Finn	Inverse variance weighted	25	0.822583961	0.98(0.83 to 1.16)	0.134061060	0.34054743	0.126(raw, 0 outliers)
UC_STRICT2_Finn	Inverse variance weighted	24	0.831339211	0.99(0.86 to 1.13)	0.204919531	0.87577449	0.231(outlier corrected, 1 outlier)
CHRONNAS_Finn	Inverse variance weighted	25	0.419401595	0.91(0.72 to 1.15)	0.081645254	0.33972251	0.077(raw, 0 outliers)
DIVERTIC_Finn	Inverse variance weighted	23	0.275194877	1.03(0.97 to 1.09)	0.507482474	0.22724712	0.494(outlier corrected, 2 outlier)
COLORECTAL_Finn	Inverse variance weighted	25	0.952145453	1.00(0.85 to 1.17)	0.003781979	0.98421655	0.003(raw, 0 outliers)
NAFLD_Finn	Inverse variance weighted	25	0.544663808	0.93(0.75 to 1.16)	0.088836325	0.22215558	0.081(raw, 0 outliers)
ALCOLIV_Finn	Inverse variance weighted	25	0.231460642	0.90(0.75 to 1.07)	0.294835479	0.02324656	0.264(raw, 0 outliers)
CIRRHOSIS_BROAD_Finn	Inverse variance weighted	25	0.089322990	0.88(0.76 to 1.02)	0.359720694	0.05574838	0.36(raw, 0 outliers)
HEPATOCELLU_Finn	Inverse variance weighted	25	0.187960945	0.75(0.49 to 1.15)	0.374506429	0.67580149	0.385(raw, 0 outliers)
CHOLANGI_Finn	Inverse variance weighted	25	0.396249535	0.91(0.73 to 1.13)	0.570859213	0.90708652	0.573(raw, 0 outliers)
CHOLELITH_Finn	Inverse variance weighted	25	0.169970204	1.05(0.98 to 1.11)	0.030691083	0.70416506	0.03(raw, 0 outliers)
CHOLECYST_Finn	Inverse variance weighted	25	0.060130294	1.15(0.99 to 1.33)	0.277927236	0.01894077	0.293(raw, 0 outliers)
ACUTPANC_Finn	Inverse variance weighted	25	0.620641911	1.03(0.90 to 1.18)	0.090882088	0.39884119	0.105(raw, 0 outliers)
CHRONPANCS_Finn	Inverse variance weighted	25	0.600031674	1.04(0.89 to 1.22)	0.384750962	0.93348134	0.376(raw, 0 outliers)
PANCREAS_Finn	Inverse variance weighted	25	0.417745134	1.10(0.87 to 1.39)	0.831187847	0.48490805	0.83(raw, 0 outliers)
APPENDACUT_Finn	Inverse variance weighted	23	0.050385294	1.07(1.00 to 1.15)	0.055031061	0.06242812	0.058(outlier corrected, 2 outlier)

P<0.05 was considered statistically significant

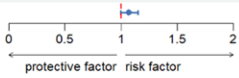

Figure 6. Forest plots of Mendelian randomization analyses of the causal effects of gastrointestinal diseases on ADHD. This is the forest plot from the FinnGen database, visually presenting the MR estimates and corresponding 95% confidence intervals for each SNP. Main outcome: 24 gastrointestinal diseases; method: IVW method; nSNP: number of usable SNPs after screening; *P* value: *P*-value; OR (95% CI): OR value and 95% confidence interval; heterogeneity test. *P*: *P*-value for heterogeneity; MR Egger intercept *P*: *P*-value for the intercept; MR PRESSO global test. *P*: *P*-value after removing and adjusting for outliers using MR-PRESSO. ADHD = attention deficit and hyperactivity disorder, IVW = inverse-variance weighted, MR = Mendelian randomization, OR = odds ratio, SNPs = single nucleotide polymorphisms.

was found between PTSD and gastrointestinal cancer. Further research is needed to clarify the relationship between PTSD and gastrointestinal cancer.

Research on pancreatic diseases has shown that genetic loci for severe painful pancreatitis overlap with risk loci for PTSD.[36] PTSD may be closely associated with pancreatitis, which can worsen to varying degrees due to exacerbation of PTSD symptoms. Pancreatitis can also aggravate PTSD symptoms, creating a stressor that induces psychopathology in genetically at-risk patients.[37–39] Our MR analysis demonstrated a positive association between PTSD and pancreatic cancer.

ADHD frequently co-occurs with gastroesophageal reflux, particularly in obese patients.[40,41] A genome-wide pleiotropic association study demonstrated that ADHD is associated with gastroesophageal reflux.[42] MR analyses have indicated a causal relationship between ADHD and Autism Spectrum Disorder (ASD), with ASD patients often experiencing gastrointestinal issues, notably gastroesophageal reflux.[43,44] Our MR study corroborated these findings, further reinforcing the causal relationship between ADHD and gastroesophageal reflux. By systematically examining multiple gastrointestinal diseases simultaneously, this study expands upon earlier studies that

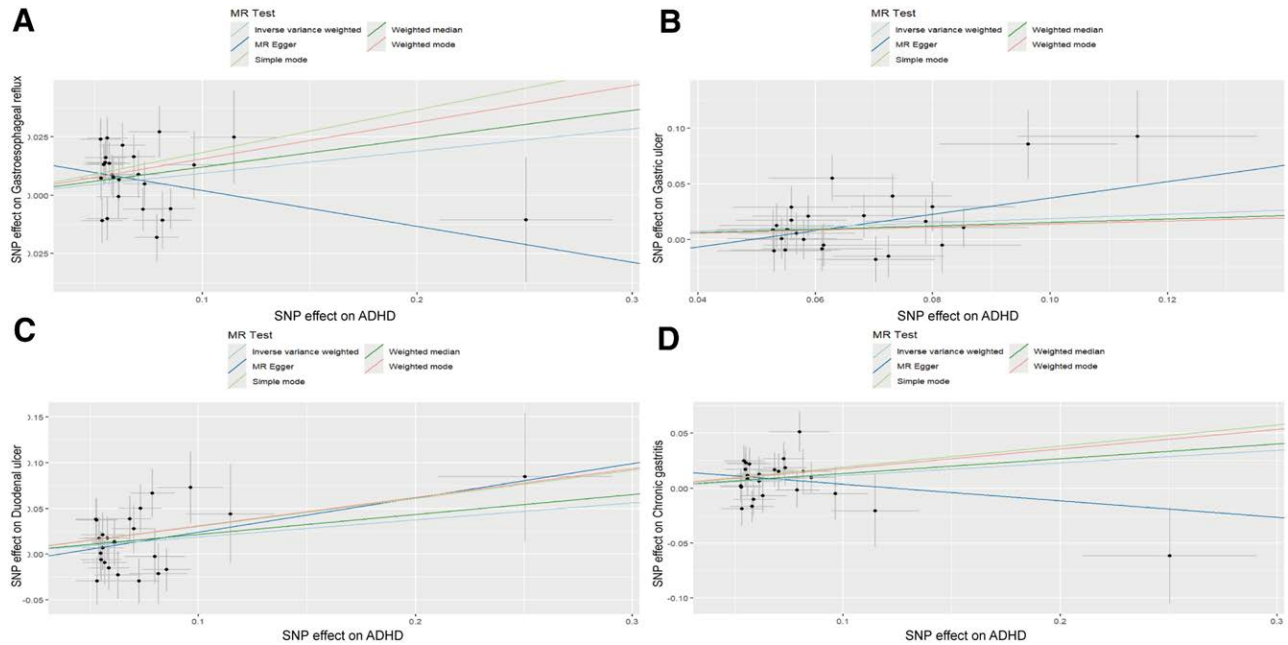

Figure 7. Scatter plots of Mendelian randomization analyses of the causal effects of Gastrointestinal Diseases on ADHD. This scatter plot illustrates the relationships between ADHD and gastroesophageal reflux, gastric ulcer, duodenal ulcer, and chronic gastritis in the FinnGen database. The plot describes the 5 methods used in this study, with light blue, dark blue, light green, dark green, and red lines representing the IVW, MR-Egger, simple model, weighted median, and weighted mode methods, respectively. (A) Scatter Plot between ADHD and Gastroesophageal reflux disease; (B) scatter Plot between ADHD and gastric ulcer; (C) scatter plot between ADHD and duodenal ulcer; (d) scatter plot between ADHD and chronic gastric disease. ADHD = attention deficit and hyperactivity disorder, IVW = inverse-variance weighted, MR = Mendelian randomization.

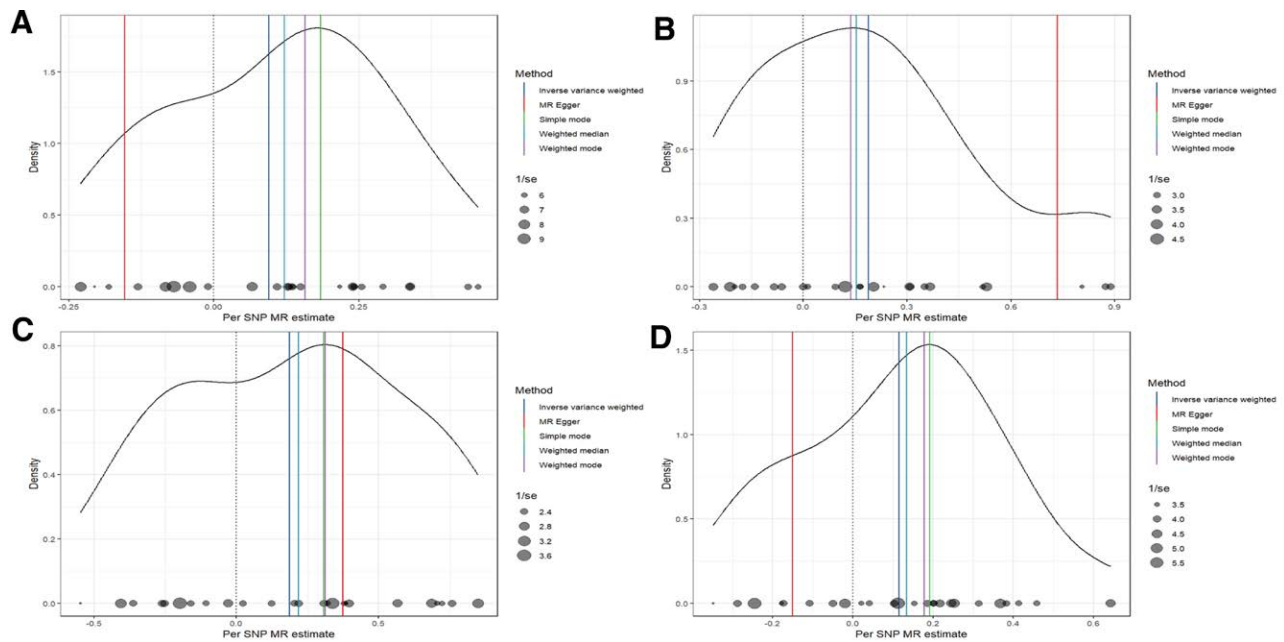

Figure 8. Density plots of Mendelian randomization analyses of the causal effects of gastrointestinal diseases on ADHD. This density plot illustrates the relationships between ADHD and gastroesophageal reflux, gastric ulcer, duodenal ulcer, and chronic gastritis in the FinnGen database. The plot describes the 5 methods used in this study, with dark blue, red, light green, light blue, and purple lines representing the IVW, MR-Egger, simple model, weighted median, and weighted mode methods, respectively. (A) Density plot between ADHD and gastroesophageal reflux disease; (B) Density plot between ADHD and gastric ulcer; (C) density plot between ADHD and duodenal ulcer; (D) density plot between ADHD and chronic gastric disease. ADHD = attention deficit and hyperactivity disorder, IVW = inverse-variance weighted, MR = Mendelian randomization.

focused on specific conditions, such as peptic ulcers or gastroesophageal reflux, providing a more holistic understanding of the gastrointestinal comorbidities associated with ADHD.

Both gastric ulcer and duodenal ulcer are components of peptic ulcer disease. Previous research has suggested an association between ADHD and peptic ulcers.[42] Our MR analysis predicted a causal relationship between ADHD and peptic ulcers at the genetic level. Additionally, a retrospective study indicated that boys with ADHD frequently experience long-term and chronic stomach pain.[45] Our study also demonstrated an association between ADHD and chronic gastritis. While previous observational studies reported associations between ADHD and IBD,

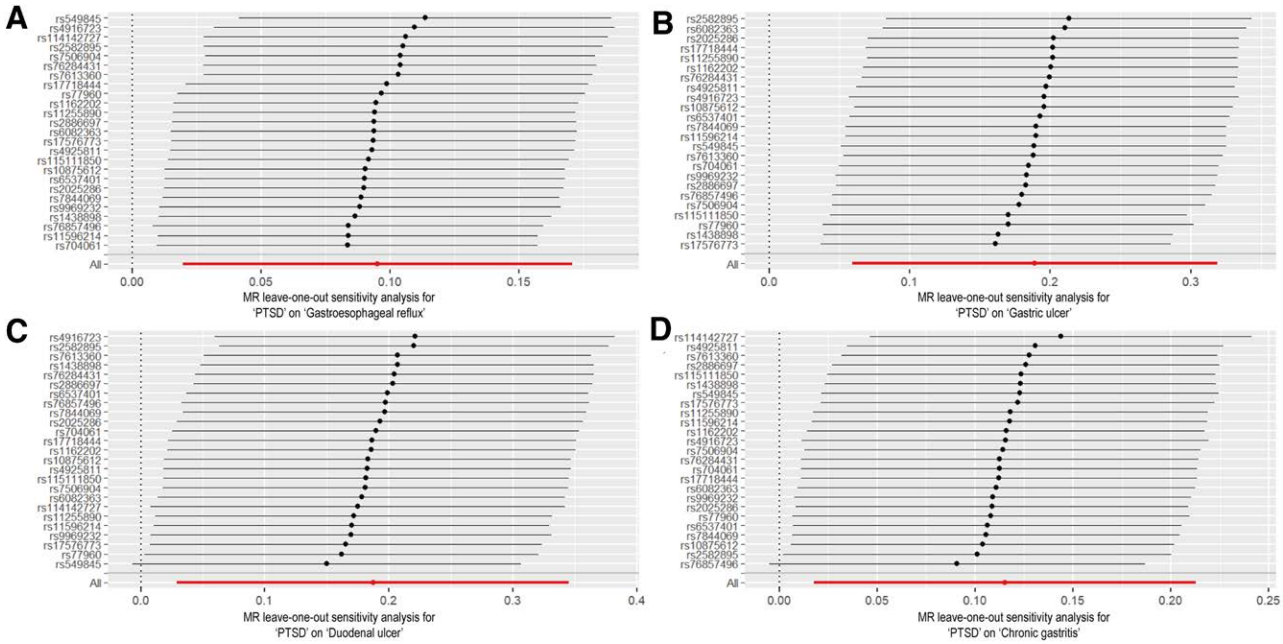

Figure 9. Leave-one-out plot of Mendelian randomization analyses of the causal effects of Gastrointestinal Diseases on ADHD. This leave-one-out analysis illustrates the relationships between ADHD and gastroesophageal reflux, gastric ulcer, duodenal ulcer, and chronic gastritis in the FinnGen database. The leave-one-out analysis is conducted to determine whether any individual instrumental variable has a disproportionate impact on the estimated causal effect. (A) Leave-one-out analysis between ADHD and gastroesophageal reflux disease; (B) leave-one-out analysis between ADHD and gastric ulcer; (C) leave-one-out analysis between ADHD and duodenal ulcer; (D) leave-one-out analysis between ADHD and chronic gastric disease. ADHD = attention deficit and hyperactivity disorder.

our MR analysis found no causal relationship.[14] This discrepancy may stem from methodological differences: MR reduces confounding inherent in observational designs, suggesting that earlier reported associations might reflect shared environmental factors or diagnostic bias rather than biological causation. Additionally, our study focused on genetic liability across the lifespan, whereas prior work examined pediatric populations where comorbidities may manifest differently.

We speculate that the connection between mental disorders and gastrointestinal diseases may be related to the brain-gut axis system. Studies have shown that the hypothalamic-pituitary-adrenal (HPA) axis may play a central coordinating role in the mental system response to stress, acting as a key player in the stress response.[46] The onset of mental disorders is often associated with changes in the HPA axis.[47] Dysfunction of the HPA axis may be a significant factor in mental disorders leading to gastrointestinal diseases. Stressful events excessively activate the HPA axis, inducing the secretion of glucocorticoids (such as cortisol), and altering levels of inflammatory factors and other mediators, thereby affecting gastrointestinal function and health. Mental disorders can also impact gastrointestinal function by regulating the gut microbiome. Gut microbiota secretions, such as acetylcholine, serotonin, and dopamine, influence the gut microbiome and also have systemic and peripheral effects on brain function.[48] Animal experiments have demonstrated that transplanting the fecal microbiota of patients with mental disorders into normal mice induces abnormal behaviors and physiological characteristics in the mice.[49] Moreover, the gut microbiota of individuals with mental disorders differs from that of healthy individuals.[50] This further illustrates the association between mental disorders and gastrointestinal diseases.

This study systematically evaluated the associations between PTSD and ADHD with gastrointestinal diseases using genome-wide association study (GWAS) data. To address the common criticisms of 2-sample MR (TSMR) studies, such as methodological simplicity and lack of robustness, we applied multiple sensitivity analyses, including MR-PRESSO, MR-Egger regression, Cochran Q test, and leave-one-out analysis. These methods minimized potential biases, such as horizontal pleiotropy and SNP heterogeneity, thereby enhancing the reliability and reproducibility of our findings.

Despite the advantages of our MR analysis, several limitations should be acknowledged. First, the complexity of the traits in this study cannot entirely rule out pleiotropy. Although we conducted a series of sensitivity analyses that did not indicate evidence of bias, our findings may have been influenced by unexplained confounding factors. Second, PTSD and ADHD are dynamic processes, with symptoms that may partially remit or worsen over time, even without therapeutic intervention. Consequently, the results of this MR analysis may differ from those of observational studies. Third, our study exclusively included individuals of European ancestry, which may have limited the generalizability of our findings to other populations. Therefore, future research should further explore these complex causal relationships, considering multifactorial and multimodal properties, to enhance our understanding of these diseases and develop effective prevention and management strategies. The connection between PTSD and ADHD with gastrointestinal diseases, and the related mechanisms of the brain-gut axis, warrants further investigation. For example, the significant association between PTSD and pancreatic cancer highlights the need for early mental health interventions to reduce gastrointestinal risk. Similarly, the relationship between ADHD and chronic gastritis or peptic ulcers underscores the importance of integrative care models that address mental and gastrointestinal health. These findings pave the way for future research to explore targeted prevention and treatment strategies to bridge the gap between psychiatric and gastrointestinal care.

5. Conclusion

In summary, our MR analysis systematically identified causal relationships among PTSD, ADHD, and multiple gastrointestinal diseases, highlighting the significant impact of mental disorders on gastrointestinal health. Notably, PTSD was associated

with pancreatic cancer, whereas ADHD was associated with gastroesophageal reflux and peptic ulcers. These findings underscore the intricate interplay between mental disorders and gastrointestinal diseases, offering new insights into the brain-gut axis. This study emphasizing the need for integrative health approaches addressing both mental and gastrointestinal health risks. Further research is warranted to clarify the mechanisms underlying these associations, particularly the roles of the HPA axis and gut microbiota, and to expand investigations into diverse populations for broader applicability.

Author contributions

Conceptualization: Liang Ma.
Data curation: Liang Ma.
Methodology: Liang Ma.
Resources: Liang Ma, Xiaofeng Li.
Software: Liang Ma, Xiaofeng Li.
Supervision: Yang Zhang.
Visualization: Xiaofeng Li.
Writing – original draft: Liang Ma.
Writing – review & editing: Xiaofeng Li, Yang Zhang.

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