Causal relationships between psychological disorders and functional gastrointestinal disorders: a bidirectional two-sample Mendelian randomization study

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Abstract

**Background and Aims:** Observational studies have shown bidirectional associations between phycological disorders (e.g., depression and anxiety) and functional gastrointestinal disorders. However, whether the relationships are causal is uncertain. Here we used a bidirectional two-sample Mendelian randomization (MR) method to investigate the association between phycological disorders and functional gastrointestinal disorders (FGIDs).

**Methods:** We obtained genome-wide association study (GWAS) summary statistics for two common phycological disorders (depression and anxiety) and three common FGIDs (functional dyspepsia (FD), constipation and irritable bowel syndrome (IBS)) from several publicly available GWAS databases. The inverse variance weighted (IVW) method was used as the main MR method.

**Results:** IVW MR analyses showed statistically significant associations between genetically predicted depression and risk of FD (OR 1.40, 95%CI 1.08-1.82), constipation (OR 1.28, 95%CI 1.13-1.44) and IBS (OR 1.51, 95%CI 1.37-1.67). Genetically predicted anxiety was associated with higher risk of IBS (OR 1.13, 95%CI 1.10-1.17) instead of FD and constipation. Additionally, genetically predicted IBS instead of FD and constipation was associated with higher risk of depression (OR 1.33, 95%CI 1.12-1.57) and anxiety (OR 2.05, 95%CI 1.05-4.03).

**Conclusions:** Depression is a causal risk factor for three common FGIDs. A bidirectional causal relationship between IBS and anxiety or depression was also identified.

Introduction

Functional gastrointestinal disorders (FGIDs) account for at least a third of referrals to gastroenterology clinics, and significantly impair quality of life. Irritable bowel syndrome (IBS), functional dyspepsia (FD) or constipation, although incompletely understood, and with complex and interactional risk factors, are the most prevalent FGIDs. Based on the biopsychosocial model, FGIDs have been redefined as complex bidirectional dysregulations of gut–brain interaction. It has been found that gastrointestinal symptoms and psychosocial states can influence each other. Several observational studies have suggested associations between FGIDs and anxiety or depression, in which individuals with FGIDs were more likely to develop anxiety or depression. Other studies showed that individuals with anxiety or depression at baseline were more likely to develop FGIDs. However, cause and effect cannot be disentangled from these studies.

According to the gut–brain bidirectional interaction model, psychosocial disorders, such as anxiety and depression, may induce or worsen gastrointestinal symptoms. Although there were several randomized controlled trials showed the beneficial roles of antidepressants on FGIDs, most of the studies were of relatively small sample size (less than 200) and some reported inconsistent results. To date, there is a lack of consensus as to whether anxiety or depression is an accompanying phenomenon or causal effect of FGIDs.

An efficient approach for assessing the potential causal effect of anxiety or depression on FGIDs is Mendelian randomization (MR). MR utilizes a genetic instrument, a significant association between genetic predisposition for exposure and outcome suggesting causality, which is minimally affected by reverse causation or confounding. Recently, a MR study had suggested a bidirectional relationship between depression and IBS. However, it remains unclear whether there are causal effects of anxiety and depression on different kinds of FGIDs. The causality for other common FGIDs, such as FD and constipation, deserves further investigation.
We hypothesized that there may be a directional causal effect between common phycological disorders (anxiety and depression) and common FGIDs (FD, constipation, and IBS). In this study, we performed a bidirectional two-sample MR analysis between common phycological disorders and FGIDs based on several large population cohorts.

**Methods**

**Overview of the study**

We conducted 2 sample MR analysis with publicly available summary-level data (unrestricted re-use is permitted via an open license). Declaration of Helsinki statement and informed consent procedure have been described in the original publications of these cohorts. We did not use individual-level data and therefore did not seek ethical approval for this study. The analysis process and data sources of MR were shown in Fig. 1.

**Depression**

GWAS summary statistics were derived from a recently published largest GWAS meta-analysis by Howard DM et al for depression.\(^{19}\) Since 23andMe was not publicly available, we obtained a total of 500,199 individuals (170,756 depression cases and 329,443 controls) in Psychiatric Genomics Consortium (PGC) and UK Biobank (UKB). All participants were of European ancestry. Within PGC, depression cases were defined according to Structured Depression Inventory Assessment or International Classification of Diseases; Within UKB, depression cases were defined by self-reported help-seeking for depressive problems, self-reported depressive symptoms and associated impairment, or according to the International Classification of Diseases.\(^{20,21}\) The study reported 102 depression-associated independent single nucleotide polymorphisms (SNPs) reaching genome-wide significance \((p < 5 \times 10^{-8})\) by combined meta-analysis. Because of the lacking of 23andMe data, we only had 50 SNPs that reached the genome-wide association significance level.

**Anxiety**

GWAS summary statistics were derived from a recently published largest GWAS meta-analysis by Purves KL et al for anxiety.\(^ {22}\) The GWAS meta-analysis used summary statistics from UKB, the Integrative Psychiatric Research (iPSYCH) consortium and the Anxiety Neuro Genetics Study (ANGST) with a total of 114,019 individuals (31,977 anxiety cases and 82,114 controls). In UKB, anxiety cases were defined as self-reported anxiety disorder or lifetime diagnosis of DSM-IV generalized anxiety disorder. In iPSYCH, anxiety cases were diagnosed by psychiatrists.\(^ {23}\) In ANGST, anxiety cases were diagnosed according to DSM criteria.\(^ {24}\) All participants were of European ancestry. Summary statistics from this GWAS meta-analysis reported 2 anxiety-associated SNPs reaching genome-wide significance \((p < 5 \times 10^{-8})\).

**FGIDs**

Three most prevalent FGIDs, including irritable bowel syndrome (IBS), functional dyspepsia (FD), and constipation, were investigated in the current study.

GWAS summary statistics of FGIDs were mainly retrieved from FinnGen. This cohort including 7053 IBS cases and 253186 controls, 6,666 FD cases and 265,354 controls, and 26,919 constipation cases and 282,235 controls. All participants were of European ancestry. FGIDs cases were defined based on the International Classification of Diseases. This study reported 1 genome-wide significant independent SNP associated with constipation, 1 associated with IBS, and 0 associated with FD, respectively.
Besides, GWAS summary statistics of IBS was also retrieved from UKB, which provides the largest GWAS analysis results for IBS to date. This study including 53,400 IBS cases and 433,201 controls. IBS cases were selected based on the Rome III diagnostic criteria, which were widely used in clinical studies. A total of 6 IBS-associated independent SNPs were reported in this study. With a precise definition of IBS and the largest sample size, UKB-IBS sample was chosen as the primary MR analysis. However, due to the partial overlap in samples of depression, anxiety, and IBS in UKB, FinnGen-IBS sample was chosen as an additional analysis.

**Genetic instrumental variables selection**

We extracted significant variants associated with each trait (to the extent of $P < 5 \times 10^{-8}$) and adjusted the P value to $P < 1 \times 10^{-5}$ when insufficient SNPs were screened. Only SNPs with long physical distance ($\geq 1,0000$ kb) and low probability of linkage disequilibrium ($r^2 < 0.001$) were retained. We then evaluated the remaining SNPs’ power using the F statistics ($F = \beta^2/se^2$) and calculated a general F statistic for all SNPs. SNPs with a F-statistic < 10 indicates the presence of weak instrumental variables. $R^2$ is the proportion of the variability of the exposure explained by each SNP, the total $R^2$ represents the extent to which instrumental variables explain exposure. The formula used has been described by Papadimitriou N et al.

**Statistical analysis**

The mRnd was used to calculate the statistical power for MR (https://cnsgenomics.shinyapps.io/mRnd/). The random effects inverse variance weighted method was used as our main analysis because it performs best under a range of different scenarios that violate MR assumptions. Besides, the weighted median method was implemented as sensitivity MR analysis, which derives valid causal estimates even under conditions when invalid instruments are present. Since all $I^2_{ex}$ were less than 90% in this study, we did not use the results of MR Egger as a sensitivity analysis in our study. However, the intercept of MR Egger was used to determine whether there was horizontal pleiotropy.

The MR pleiotropy residual sum and outlier (MR-PRESSO) was applied to detect SNPs outliers and provide the results of IVW analysis after removing the outliers. We performed a leave-one-out sensitivity test to visualize the effect of removing a single SNP on the causal estimates. Additionally, we checked each instrument SNP in the PhenoScanner database (http://phenoscanner.medschl.cam.ac.uk) to assess any associations ($P < 1\times10^{-5}$) with potential confounding or outcomes and duplicated MR analyses by manually removing these SNPs to see if the results change.

Given the genetic correlation between depression and anxiety, we performed additional multivariate mendelian randomization (MVMR) analyses if both variables were significant in univariate MR. We used MVMR-IVW as the primary outcome and MVMR-Egger, MVMR-Robust, MVMR-Median and MVMR-Lasso as pleiotropy robust analyses. In addition, we also calculated the conditional F-values in the MVMR setting.

All statistical analyses were performed using R software 4.2.1 with R package “TwoSampleMR”, “MR-PRESSO”, “MendelianRandomization” and “MVMR”.

**Results**

**Overview of instrumental variables**
The number of SNPs ranged from 4 to 47 (Table 1, Table 2), and the explained variances varied from 0.24–4.78% (Supplementary Table 1, Supplementary Table 2). The mean F-statistic were greater than the empirical threshold 10, suggesting that all instrumental variables had sufficient validity.
Table 1
Causal estimates (depression and FGIDs) from the summary-level databased mendelian randomization from the genome-wide association study summary statistics.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Cochran's Q statistics for heterogeneity</th>
<th>Pleiotropy test P value</th>
<th>Screening thresholds for SNPs</th>
<th>nSNP</th>
<th>Method</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>FD</td>
<td>0.047</td>
<td>0.341</td>
<td>5*E-8</td>
<td>36</td>
<td>IVW</td>
<td>1.40 (1.08 to 1.82)</td>
<td>0.012</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Weighted median</td>
<td>1.21 (0.87 to 1.68)</td>
<td>0.254</td>
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<tr>
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<td></td>
<td>MR PRESSO</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Depression</td>
<td>Constipation</td>
<td>0.302</td>
<td>0.404</td>
<td>5*E-8</td>
<td>36</td>
<td>IVW</td>
<td>1.28 (1.13 to 1.44)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Weighted median</td>
<td>1.28 (1.08 to 1.52)</td>
<td>0.005</td>
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<td></td>
<td>MR PRESSO</td>
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<td>NA</td>
</tr>
<tr>
<td>Depression</td>
<td>IBS</td>
<td>0.001</td>
<td>0.241</td>
<td>5*E-8</td>
<td>47</td>
<td>IVW</td>
<td>1.52 (1.37 to 1.67)</td>
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<td></td>
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<td></td>
<td>Weighted median</td>
<td>1.45 (1.30 to 1.63)</td>
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<td>MR PRESSO</td>
<td>1.49 (1.36 to 1.64)</td>
<td>0.000</td>
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<tr>
<td>FD</td>
<td>Depression</td>
<td>0.035</td>
<td>0.206</td>
<td>1*E-5</td>
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<td>IVW</td>
<td>1.02 (0.99 to 1.05)</td>
<td>0.232</td>
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<td></td>
<td>Weighted median</td>
<td>1.02 (0.99 to 1.06)</td>
<td>0.252</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval; OR, odds ratio; SNP, single nucleotide polymorphisms; IVW, inverse variance weighted method; FD, functional dyspepsia; IBS, irritable bowel syndrome; FGIDs, functional gastrointestinal disorders; MR-PRESSO, MR pleiotropy residual sum and outlier. NA indicates that MR PRESSO did not detect outliers and the analysis could not be performed by removing the outliers.
<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Cochran’s Q statistics for heterogeneity</th>
<th>Pleiotropy test P value</th>
<th>Screening thresholds for SNPs</th>
<th>nSNP</th>
<th>Method</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Depression</td>
<td>0.166</td>
<td>0.727</td>
<td>1*E-5</td>
<td>25</td>
<td>IVW</td>
<td>1.02 (0.99 to 1.06)</td>
<td>0.199</td>
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<td>Weighted median</td>
<td>1.03 (0.98 to 1.08)</td>
<td>0.192</td>
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<td>IBS</td>
<td>Depression</td>
<td>0.060</td>
<td>0.282</td>
<td>5*E-8</td>
<td>4</td>
<td>IVW</td>
<td>1.33 (1.12 to 1.57)</td>
<td>0.001</td>
</tr>
<tr>
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<td>Weighted median</td>
<td>1.28 (1.09 to 1.50)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

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Table 2
Causal estimates (Anxiety and FGIDs) from the summary-level databased mendelian randomization from the genome-wide association study summary statistics.

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Cochran's Q statistics for heterogeneity</th>
<th>Pleiotropy test P value</th>
<th>Screening thresholds for SNPs</th>
<th>nSNP</th>
<th>Method</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>FD</td>
<td>0.150</td>
<td>0.299</td>
<td>1*E-5</td>
<td>35</td>
<td>IVW</td>
<td>1.05 (0.96 to 1.16)</td>
<td>0.275</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Weighted median</td>
<td>1.10 (0.97 to 1.24)</td>
<td>0.132</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>MR PRESSO</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Constipation</td>
<td>0.236</td>
<td>0.892</td>
<td>1*E-5</td>
<td>35</td>
<td>IVW</td>
<td>1.04 (1.00 to 1.10)</td>
<td>0.074</td>
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<td>Weighted median</td>
<td>1.02 (0.95 to 1.09)</td>
<td>0.570</td>
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<tr>
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<td>MR PRESSO</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Anxiety</td>
<td>IBS</td>
<td>0.246</td>
<td>0.549</td>
<td>1*E-5</td>
<td>38</td>
<td>IVW</td>
<td>1.13 (1.10 to 1.17)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Weighted median</td>
<td>1.10 (1.05 to 1.15)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>MR PRESSO</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>FD</td>
<td>Anxiety</td>
<td>0.869</td>
<td>0.578</td>
<td>1*E-5</td>
<td>4</td>
<td>IVW</td>
<td>1.17 (1.00 to 1.37)</td>
<td>0.055</td>
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<td>Weighted median</td>
<td>1.19 (0.99 to 1.44)</td>
<td>0.070</td>
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<td></td>
<td>MR PRESSO</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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<th>nSNP</th>
<th>Method</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Anxiety</td>
<td>0.095</td>
<td>0.754</td>
<td>1*E-5</td>
<td>14</td>
<td>IVW</td>
<td>0.92 (0.76 to 1.12)</td>
<td>0.426</td>
</tr>
<tr>
<td>IBS</td>
<td>Anxiety</td>
<td>0.032</td>
<td>0.367</td>
<td>5*E-8</td>
<td>4</td>
<td>IVW</td>
<td>2.05 (1.05 to 4.03)</td>
<td>0.037</td>
</tr>
<tr>
<td>IBS</td>
<td>Anxiety</td>
<td>0.032</td>
<td>0.367</td>
<td>5*E-8</td>
<td>4</td>
<td>IVW</td>
<td>2.05 (1.05 to 4.03)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

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### Association between genetically predicted depression and FGIDs

Of the 50 SNPs for depression in the GWAS summary statistics, 36 SNPs remained as the genetic instruments for depression in the summary-level MR after excluding 11 palindromic SNPs and 3 missing SNPs. IVW MR analysis with a random-effects model showed a statistically significant association between genetically predicted depression and risk of FD (OR 1.40, 95%CI 1.08–1.82, p = 0.012; Table 1) with mild heterogeneity (p = 0.047). No horizontal pleiotropy was found in MR-Egger (p = 0.341). The direction of effect from weighted median method was consistent with IVW. MR-PRESSO method did not identify significant outliers.

With 36 SNPs, IVW MR analysis showed a statistically significant association between genetically predicted depression and risk of constipation (OR 1.28, 95%CI 1.13–1.44, p < 0.001; Fig. 2) without heterogeneity (p = 0.302) and horizontal pleiotropy (p = 0.404). Similar associations were observed with weighted median method. MR-PRESSO method did not identify significant outliers.

With 47 SNPs, IVW MR analysis showed that genetically predicted depression was significantly associated with an increased risk of IBS (OR 1.52, 95%CI 1.37–1.67, p < 0.001) with high heterogeneity (p < 0.001). No horizontal pleiotropy was found (p = 0.242). The causal estimates remained significant with weighted median method. The MR-PRESSO method identified 1 outlier, however exclusion of the outlier did not substantially affect the results (OR 1.49, 95%CI 1.36–1.64, p < 0.001). Furthermore, in the FinnGen dataset, we successfully replicated the statistically significant MR results of association between genetically predicted depression and risk of IBS (OR 1.53, 95%CI 1.22–1.91, p < 0.001, Supplementary Table 3).
We didn't found confounder- or outcome-associated SNPs (Supplementary Table 4).

**Association between genetically predicted FGIDs and depression**

Since there were extremely few FD- or constipation-associated SNPs (at a threshold of $p < 5 \times 10^{-8}$) were identified in the GWAS data set, SNPs at a threshold of $p < 1 \times 10^{-5}$ were used as genetic instruments. However, the MR did not show any significant causal estimates from FD or constipation to depression by all implemented MR methods (all $p > 0.05$). No confounder- or outcome-associated SNPs were found (Supplementary Tables 5 and 6).

The GWAS identified 6 IBS-associated SNPs, of which 2 SNPs were missed in the outcome data set. With the remaining 4 SNPs, IVW MR analysis showed statistically significant association between genetically predicted IBS and risk of depression (OR $1.33$, 95%CI $1.12$–$1.57$; $p < 0.001$) without heterogeneity ($p = 0.060$) and pleiotropy ($p = 0.282$). MR-PRESSO method did not identify significant outliers. Furthermore, when we removed 2 confounder-associated SNPs (rs10156602, rs7106434; Supplementary Table 7), the results remained significant (OR $1.17$, 95%CI $1.01$–$1.36$; $p = 0.04$; Supplementary Table 8). However, in the FinnGen dataset, we did not replicate the statistically significant finding (OR $1.01$, 95%CI $0.97$–$1.05$; $p = 0.603$, Supplementary Table 9).

The scatter plot of MR analysis was shown in Supplementary Fig. 1. The leave-one-out sensitivity analyses for all analyses suggested that these associations were unlikely to be driven by a certain extreme SNP (Supplementary Fig. 2–7).

**Association between genetically predicted anxiety and FGIDs**

Since there were only 2 anxiety-associated SNPs (a threshold of $p < 5 \times 10^{-8}$) were identified in the GWAS summary statistics, SNPs at a threshold of $p < 1 \times 10^{-5}$ were used as genetic instruments. After excluding 6 palindromic SNPs and 3 missing SNPs, 35 SNPs remained as the genetic instruments for anxiety. MR did not show any significant causal estimates from anxiety to FD or constipation (Fig. 3, Table 2). The null finding was again identified by removal of confounder- or outcome-associated SNPs. (Supplementary Tables 10 and 11).

After excluding 6 palindromic SNPs, 38 SNPs remained as the genetic instruments for anxiety. IVW MR analysis showed statistically significant association between genetically predicted anxiety and risk of IBS (OR $1.13$, 95%CI $1.10$, $1.17$; $p < 0.001$; Fig. 3, Table 2) without heterogeneity ($p = 0.246$) and pleiotropy ($p = 0.549$). MR-PRESSO method did not identify significant outliers. The results remained statistically significant (OR $1.14$, 95%CI $1.09$–$1.18$; $p < 0.001$, Supplementary Table 12) after removing 7 confounder or outcome-associated SNPs (rs10138360, rs11599236, rs2734837, rs30266, rs4131791, rs74338595, rs811901; Supplementary Table 13). Furthermore, in the FinnGen dataset, we replicated the statistically significant finding (OR $1.12$, 95%CI $1.03$–$1.22$; $p < 0.01$, Supplementary Table 14).

**Association between genetically predicted FGIDs and anxiety**

MR did not show any significant causal estimates from FD or constipation to anxiety (Fig. 3, Table 2). We didn't found confounder- or outcome-associated SNPs.

After excluding 2 palindromic SNPs, 4 SNPs remained as the genetic instruments for IBS. IVW MR analysis showed statistically significant association between genetically predicted IBS and risk of anxiety (OR $2.05$, 95%CI $1.05$–$4.03$; $p = 0.037$; Fig. 3, Table 2) with mild heterogeneity ($p = 0.032$) and without pleiotropy ($p = 0.367$). The direction of effect from weighted median method was consistent with IVW. MR-PRESSO method did not identify significant outliers.
The results remained statistically significant (OR 1.35, 95%CI 1.14–1.61; p < 0.001, Supplementary Table 15) after removing 7 confounder or outcome-associated SNPs (rs10044618, rs10156602, rs12549729, rs1280622, rs20551, rs6696068, rs7106434, rs940468; Supplementary Table 16). Furthermore, in the FinnGen dataset (threshold of p < 1x10^{-5}), we replicated the statistically significant finding (OR 1.22, 95%CI 1.08–1.38; p < 0.001, Supplementary Table 17).

The scatter plot of MR analysis was shown in Supplementary Fig. 8. The leave-one-out sensitivity analyses was shown in Supplementary Fig. 9–14.

**Direct Effect of Genetically Predicted Depression and Anxiety on FGIDs**

Since conditional F-values of MVMR for depression and anxiety were less than 10 (Supplementary Table 18), the direct effect of depression and anxiety on IBS using MVMR analysis we assessed was with low reliability (Supplementary Fig. 15–16).

**Discussion**

Although complex bidirectional dysregulations of gut–brain axis is considered the key mechanism of developing FGIDs, the causal relationship between the two remains unclear. In this MR analysis, by using the largest GWAS results to date, we demonstrated a causal relationship from depression instead of anxiety to three common FGIDs, including FD, constipation, and IBS. A bidirectional causal relationship between anxiety, depression and IBS was also identified. However, there was no evidence of a causal relationship between constipation or FD to anxiety or depression.

FGIDs comprise a large group of functional gastrointestinal disorders, with constipation, FD, and IBS accounting for more than 50% of all FGIDs.\(^{36}\) For the first time, we identified depression as the etiology of the three most common FGIDs. This is consistent with previous observational studies suggesting that depression was associated with an increased risks of FD, constipation an IBS.\(^{9–11}\) Additionally, there were also several studies found that depression was associated with development of other FGIDs, including functional diarrhea and functional abdominal pain and functional heartburn.\(^{37–39}\) These results indicate that depression may be a common etiology of FGIDs. However, because of the lack of GWAS data related to other FGIDs, we are currently unable to determine the causal relationships, which deserves further exploration in the future.

A recent MR study by Eijsbouts et al. have also suggested a bidirectional causal relationship between depression and IBS. However, this study reported inconsistent result on the causal relationship from IBS to anxiety. One of the reasons may be the effects from multiethnicity, which may have decreased their statistical power with potential false negative results.\(^{18}\) Whereas, our study minimized such potential biases by restricting sample to European populations, which revealed a causal relationship between constipation or FD to anxiety.

Conventional observational studies have confirmed that FD is longitudinally associated with increased risk of depression and anxiety.\(^{9,10}\) Besides, depression and anxiety are more prevalent in individuals with chronic constipation than in the general population.\(^{12}\) However, the current study has provided suggestive evidence that genetically predicted constipation or FD is unlikely to be causally associated with the risks of depression. The main reason may be due to the fact that there were few genetic variants (p < 5x10^{-8}) of constipation or FD in the datasets to date, which may have decreased their statistical power with potential false negative results. However, the null
finding was identified by utilizing more SNPs with a weaker \( (P < 1 \times 10^{-5}) \) association with constipation or FD as the genetic instruments throughout the MR IVW and sensitivity analyses. Another reason is the burden of chronic illness can lead to depression. Living with chronic illness, regardless of the diagnosis, is known to cause significant psychological disorders.\(^{40}\) Since many chronic conditions can lead to constipation or dyspepsia,\(^{41,42}\) the association between constipation or dyspepsia and depression reported in observational studies may reflect a reverse causality or residual confounding. Regardless, further investigations should be carried out to verify these findings.

Our study further support the concept of bidirectional brain-gut pathways in FGIDs by using MR analysis. It highlights the importance of integrated management of depression, anxiety and common FGIDs together. Firstly, as depression is a causal risk factor for FGIDs, appropriate management of depression may lead to alleviated FGIDs symptoms or improved health-related quality of life. The beneficial effects of anti-depression on IBS and constipation has been reported in previous studies.\(^{43–45}\) Thus, future clinical trials assessing the effectiveness of novel treatments related to depression on FGIDs may be valuable. Secondly, earlier or more widely screening for depression in FGIDs patients can be performed. In particular, those with common risk factors (e.g., female gender, life stress or insomnia) for depression may be the target group that warrants such a strategy, and such early screening may lead to a reduced risk of worsening of common FGIDs.\(^{46,47}\) Thirdly, clinicians may monitor gastrointestinal symptoms in depression patients because they bear a burden of increased risk of FGIDs due to the presence of depression.

There are several limitations in this study. Firstly, the diagnosis of three common FGIDs were not standardized. ROME IV criteria,\(^2\) as the widely used diagnostic criteria of FGIDs, are not strictly followed in the three large cohorts included in our study, which will bias our results. For example, the overall prevalence of FD was only 2.45%, much lower than that reported in the epidemiological studies,\(^{49}\) which may lead to a dilution of the causal effect of FD to depression or anxiety. Secondly, the statistical power of some findings is insufficient, which is related to the limited sample size and instrumental variables. A larger sample size of GWAS data is needed in the future. Thirdly, there was partial samples overlap for the two summary statistics implemented in our study, which is indeed a known bias factor in the presence of weak instrumental variables when conducting two-sample MR.\(^{49}\) However, there are no weak instrumental variables in our univariate MR. In addition, our analysis decrease the possibility of false-positive findings by replicating the results in two non-overlapping sample (IBS from FinnGen). Finally, the current study relied on genetic data conducted in a population of European ancestry, which limits the generalizability of the present findings in other ancestry.

In conclusion, this study suggests that depression is a causal risk factor for common FGIDs. A bidirectional causal relationship between anxiety, depression and IBS was also identified. Clinicians may need to pay attention to depression in FGIDs patients and monitor gastrointestinal symptoms in those with depression or anxiety.

**Abbreviations**

FGIDs, Functional gastrointestinal disorders; IBS, Irritable bowel syndrome; FD, functional dyspepsia; CI, Confidence interval; UKB, UK Biobank; MR, Mendelian Randomization; IVW, inverse variance weighted; MVMR, multivariable Mendelian Randomization.

**Declarations**

**Author Contributions**

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Role of the funding source

The study’s funder had no role in study design, data collection, analysis, interpretation, or report writing.

Conflict of interest disclosure

The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

Data availability

GWAS summary statistics for depression was downloaded from the PGC database (https://pgc.unc.edu/for-researchers/download-results/). GWAS summary statistics for anxiety was obtained by contacting the authors. GWAS summary statistics for constipation, irritable bowel syndrome, and functional dyspepsia from FinnGen was downloaded from this website https://www.finngen.fi/en/access_results. GWAS summary statistics for irritable bowel syndrome from UKB was downloaded from this website (https://www.ebi.ac.uk/gwas/studies/GCST90016564).

References


Figures

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**Psychological disorders**

- **Depression:** Howard DM et al (PGC+UKB), 170,756 depression cases and 329,443 controls
- **Anxiety:** Purves KL et al (UKB+iPSYCH+ANGST), 31,977 anxiety cases and 82,114 controls

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**FGIDs**

- **FD:** FinnGen, 6,666 FD cases and 265,354 controls
- **Constipation:** FinnGen, 26,919 FC cases and 282,235 controls
- **IBS:** UKB, 53,400 IBS cases and 433,201 controls

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**Figure 1**

Bidirectional Mendelian randomization of psychological disorders and FGIDs. FGIDs, Functional Gastrointestinal Disorders. IBS, Irritable Bowel Syndrome; FD, Functional Dyspepsia; PGC, Psychiatric Genomics Consortium; UKB, UK Biobank.
<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>SNPs</th>
<th>IVW</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>FD</td>
<td>36</td>
<td></td>
<td>1.40 (1.08 to 1.82)</td>
<td>0.012</td>
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<tr>
<td>Depression</td>
<td>Constipation</td>
<td>36</td>
<td></td>
<td>1.28 (1.13 to 1.44)</td>
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<tr>
<td>Depression</td>
<td>IBS</td>
<td>47</td>
<td></td>
<td>1.52 (1.37 to 1.67)</td>
<td>0.000</td>
</tr>
<tr>
<td>FD</td>
<td>Depression</td>
<td>15</td>
<td></td>
<td>1.02 (0.99 to 1.05)</td>
<td>0.232</td>
</tr>
<tr>
<td>Constipation</td>
<td>Depression</td>
<td>25</td>
<td></td>
<td>1.02 (0.99 to 1.06)</td>
<td>0.199</td>
</tr>
<tr>
<td>IBS</td>
<td>Depression</td>
<td>4</td>
<td></td>
<td>1.33 (1.12 to 1.57)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Bidirectional MR analysis of Depression and FGIDs

Figure 2

The bidirectional causality of depression and FGIDs was investigated using a random effects inverse variance weighted method. CI, confidence interval; OR, odds ratio; SNPs, single nucleotide polymorphisms; IVW, inverse variance weighted method; FD, functional dyspepsia; IBS, irritable bowel syndrome; FGIDs, functional gastrointestinal disorders.
<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>SNPs</th>
<th>IVW</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Anxiety</td>
<td>FD</td>
<td>35</td>
<td></td>
<td>1.05 (0.96 to 1.16)</td>
<td>0.275</td>
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<tr>
<td>Anxiety</td>
<td>Constipation</td>
<td>35</td>
<td></td>
<td>1.04 (1.00 to 1.10)</td>
<td>0.074</td>
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<tr>
<td>Anxiety</td>
<td>IBS</td>
<td>38</td>
<td></td>
<td>1.13 (1.10 to 1.17)</td>
<td>0.000</td>
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<tr>
<td>FD</td>
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<td>4</td>
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<tr>
<td>Constipation</td>
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<td>14</td>
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<td>0.92 (0.76 to 1.12)</td>
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<tr>
<td>IBS</td>
<td>Anxiety</td>
<td>4</td>
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<td>2.05 (1.05 to 4.03)</td>
<td>0.037</td>
</tr>
</tbody>
</table>

*Bidirectional MR analysis of Anxiety and FGIDs*

**Figure 3**

The bidirectional causality of Anxiety and FGIDs was investigated using a random effects inverse variance weighted method. CI, confidence interval; OR, odds ratio; SNPs, single nucleotide polymorphisms; IVW, inverse variance weighted method; FD, functional dyspepsia; IBS, irritable bowel syndrome; FGIDs, functional gastrointestinal disorders.

**Supplementary Files**

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