Psychological Medicine

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Depression and risk of gastrointestinal disorders: a comprehensive two-sample Mendelian randomization study of European ancestry

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Original Article

Cite this article: Chen D, Zhang Y, Huang T, Jia J (2023). Depression and risk of gastrointestinal disorders: a comprehensive two-sample Mendelian randomization study of European ancestry. *Psychological Medicine* **53**, 7309–7321. https://doi.org/10.1017/S0033291723000867

Received: 5 October 2022
Revised: 16 March 2023
Accepted: 21 March 2023
First published online: 15 May 2023

Keywords:
Gastroesophageal reflux disease; irritable bowel syndrome; major depressive disorder; Mendelian randomization; non-alcoholic fatty liver disease; peptic ulcer disease

Abbreviations:
MDD: Major depressive disorder; GID: gastrointestinal disorders; GERD: Gastroesophageal reflux disease; PUD: Peptic ulcer disease; IBS: Irritable bowel syndrome; NAFLD: Non-alcoholic fatty liver disease; LDSC: Linkage disequilibrium score regression; MR: Mendelian randomization; GWAS: Genome-wide association study; SNP: Single nucleotide polymorphism; IVs: Instrumental variables; OR: Odds ratio; CI: Confidence interval.

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Abstract

Background. Major depressive disorder (MDD) is clinically documented to co-occur with multiple gastrointestinal disorders (GID), but the potential causal relationship between them remains unclear. We aimed to evaluate the potential causal relationship of MDD with 4 GID [gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), peptic ulcer disease (PUD), and non-alcoholic fatty liver disease (NAFLD)] using a two-sample Mendelian randomization (MR) design.

Methods. We obtained genome-wide association data for MDD from a meta-analysis ($N = 480\,359$), and for GID from the UK Biobank (N ranges: 332 601–486 601) and FinnGen (N ranges: 187 028–218 792) among individuals of European ancestry. Our primary method was inverse-variance weighted (IVW) MR, with a series of sensitivity analyses to test the hypothesis of MR. Individual study estimates were pooled using fixed-effect meta-analysis.

Results. Meta-analyses IVW MR found evidence that genetically predicted MDD may increase the risk of GERD, IBS, PUD and NAFLD. Additionally, reverse MR found evidence of genetically predicted GERD or IBS may increase the risk of MDD.

Conclusions. Genetically predicted MDD may increase the risk of GERD, IBS, PUD and NAFLD. Genetically predicted GERD or IBS may increase the risk of MDD. The findings may help elucidate the mechanisms underlying the co-morbidity of MDD and GID. Focusing on GID symptoms in patients with MDD and emotional problems in patients with GID is important for the clinical management.

Introduction

Major depressive disorder (MDD) was identified as one of the leading causes of nonfatal health loss in the 2019 Global Burden of Disease Study, affecting more than 400 million people globally ('Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019,', 2020). Given the potential pathophysiological mechanism behind the dysregulation of the brain-gut axis, the relationship between MDD and gastrointestinal disorders (GID) has attracted significant research during the past decade (Zhu, Tu, & Chen, 2022). Clinical observations have long identified the coexistence and interaction between MDD and numerous GID, with both illnesses frequently coexisting, responding to comparable therapies, aggravating each other, and sharing common molecular causes (Mayer, Craske, & Naliboff, 2001). Some studies have also suggested that MDD and GID share several risk factors, including but not limited to obesity (Emerenziani et al., 2019), diabetes (Verne & Sninsky, 1998) and insomnia (Ali, Choe, Awab, Wagener, & Orr, 2013). To comprehend the interplay between depression and GID and to propose clinical treatment strategies to improve the co-morbid population with MDD and GID, it is necessary to clarify the potential causal role between MDD and GID.

The findings of substantial observational studies support the concept that MDD may increase the risks of GID (Fang et al., 2019; Kim et al., 2019; Martín-Merino, Ruigómez, García Rodríguez, Wallander, & Johansson, 2010). Despite the plausible positive association between MDD and GID, there is also partial evidence to support the claim is non-existent (Kim et al., 2013; Lee, Otgonsuren, Younoszai, Mir, & Younossi, 2013; Shaheen, Kaplan, Sharkey, Lethebe, & Swain, 2021). Observational studies yield inconsistent results, and the

real direction of causal association cannot be ascertained owing to measurement error, confounding, and reverse causality bias (Fewell, Davey Smith, & Sterne, 2007).

Mendelian randomization (MR), a method for inferring causality between a modifiable exposure and an outcome that utilizes genetic variants as instrumental variables, is less likely to be affected by residual confounding and reverse causation than traditional observational approaches (Smith & Ebrahim, 2003). In the absence of randomized controlled trials (RCTs), MR is an effective way to strengthen causal inferences. A recent genome-wide association study (GWAS) meta-analysis has revealed 44 genetic loci associated with MDD that may be used within an MR framework (Wray et al., 2018). Yeda et al. had used the MR framework to explore the genetically predicted effects of MDD on gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS) and peptic ulcer disease (PUD) (Wu et al., 2021b). Here, we extend this analysis to include non-alcoholic fatty liver disease (NAFLD) and use additional methods and datasets to verify the robustness of our findings.

The aim of this two-sample MR study was to test the genetically predicted effects of MDD on multiple GID (i.e. GERD, IBS, PUD and NAFLD) using summary genetic association data from (1) Wray et al. (N cases = 135 458; N controls = 344 901) (Wray et al., 2018), (2) the UK Biobank and several international genetic consortia (N cases = 4761–71 522; N controls = 261 079–439 661) (An et al., 2019; Eijsbouts et al., 2021; Fairfield et al., 2022; Wu et al., 2021b) and (3) FinnGen (N cases = 894– 13 141; N controls = 182 423– 217 898).

Methods

Reporting guidelines and study design

This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) guideline (STROBE-MR Checklist) (Skrivankova et al., 2021). The overall study design is illustrated in Fig. 1. Three assumptions are deemed necessary for the MR study to guarantee the validity of results (described in Fig. 1) (Didelez & Sheehan, 2007).

Data source and sample overlap

Two-sample MR was performed using published summary-level data from GWAS of the traits of interest in European individuals. Details of the GWAS data sets utilized in this investigation are listed in Table 1. The ethical approval, participant informed consent, and participant eligibility criteria for each of the original GWAS can be found in their respective publications (An et al., 2019; Eijsbouts et al., 2021; Fairfield et al., 2022; Wray et al., 2018; Wu et al., 2021b).

Given the MDD GWAS includes a minor UK Biobank (UKB) sample (cases: 14 260, controls: 15 480), the dataset utilized for this investigation contains a partial sample overlap between MDD and GID. Sample overlap between exposure and outcome populations may skew two-sample MR estimates toward confounding relationships in the case of weak instruments (Burgess, Davies, & Thompson, 2016). To formally assess the risk of bias resulting from sample overlap, we performed a calculation of bias and type I error rate using the method proposed by Burgess et al. (https://sb452.shinyapps.io/overlap) (Burgess et al., 2016).

Genetic instruments for major depressive disorder

Selection of instrumental variants

We obtained summary genetic association estimates for MDD from Wray et al.'s GWAS meta-analysis, which included 480 359 participants of European ancestry (Wray et al., 2018). For MDD, we initially extracted independent genome-wide significant ($p < 5 \times 10^{-8}$) SNPs reported in the corresponding source literature as instrumental variants (IVs). This resulted in 43 IVs for MDD. The complete list of instruments is summarized in online Supplementary Tables S1.

Assessing instrumental strength

We identified 43 independent SNPs for MDD (online Supplementary Table S1). The proportions of trait variance explained by genetic instruments (R^2) and instrument strength (F statistic) were calculated using the following formulae: $R^2 = 2\beta^2 \times \text{MAF} \times (1\text{-MAF})$ and $F = [R^2 \times (N\text{-}2))/(1\text{-}R^2]$ (where MAF = minor allele frequency, β = effect estimate of the SNP in the exposure GWAS, N = sample size) (Burgess et al., 2016). The genetic instruments for MDD explained 1.84% of the trait variance. All the selected SNPs had F statistics greater than 10 (F statistics median 186 and range 167–436).

Genetic association data sources for gastrointestinal disorders outcomes

We obtained summary-level genetic association data for GID outcomes from the UK Biobank and FinnGen and several international genetic consortia: the QSkin health study, the Bellygenes cohorts and the Psychiatric Genomics Consortium (PGC) (Table 1). Further details of the studies and the data obtained are described in original publications (An et al., 2019; Eijsbouts et al., 2021; Fairfield et al., 2022; Wray et al., 2018; Wu et al., 2021b).

We extracted genetic association data for the selected SNPs from each GID GWAS (for GERD, IBS, PUD and NAFLD). LD proxies ($r^2 > 0.8$) were used when the SNPs of interest were missing from the GID GWAS dataset. The 'LDlinkR' R package (version 1.2.0) was used to find proxies for GID data. Finally, we used the TwoSampleMR R package (Hemani et al., 2018) (version 0.5.6) to undertake a harmonization procedure for integrating IVs information between exposure and outcome (Hemani, Tilling, & Davey Smith, 2017). We also removed SNPs that were palindromic with intermediate allele frequencies. Then we applied Steiger filtering to ensure whether each IV explains more phenotypic variance in the exposure than the outcome and removes those genetic variants that do not satisfy this criterion (Hemani et al., 2017). The IVs with a 'False' Steiger direction will be excluded. online Supplementary Table S2–S3 contains further information on the harmonized datasets utilized in the current MR analysis.

Power calculation

We calculated the statistical power of this study based on the Burgess et al., method (https://sb452.shinyapps.io/power/) (Burgess, 2014). Calculations were performed separately for each MDD-GID combination. They were based on a type I error rate of 0.05, the proportion of phenotypic variance explained by genetic variants (R^2) for MDD, and the total sample size included in the meta-analysis for each GID. Across

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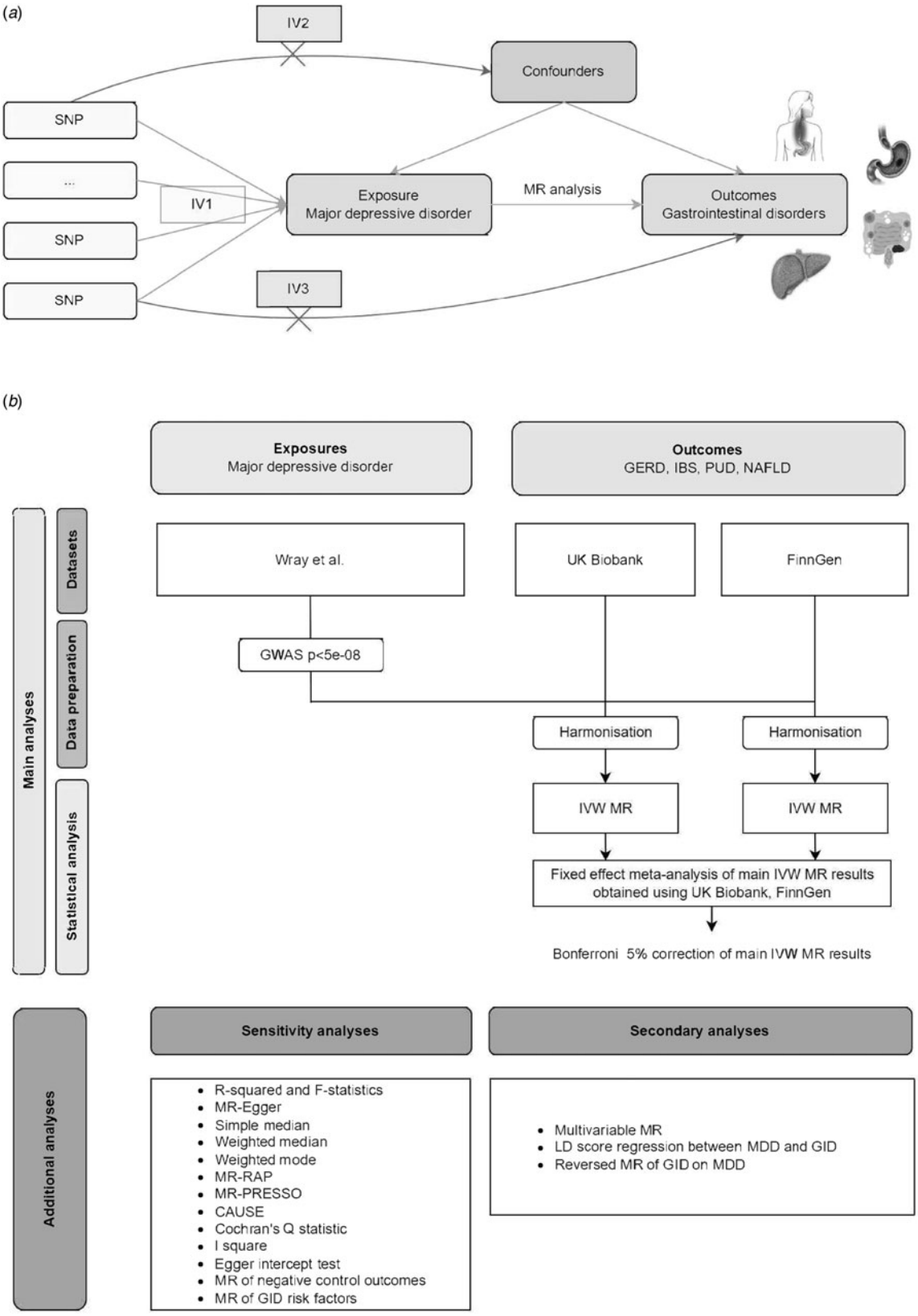

Figure 1. Diagrammatic overview of univariable and multivariable MR study design. (a) Three assumptions are deemed necessary for MR study to guarantee the validity of results, including (1) IVs are strongly related to the risk factor of interest (i.e. the relevance assumption); (2) IVs are independent of confounding factors (i.e. the independence assumption); (3) IVs affect outcomes only through exposure (i.e. the exclusion restriction assumption). (b) Flowchart summarizing study methods. Abbreviations: IVW, inverse variance weighted; MR, Mendelian randomization; GWAS, genome-wide association study; LD, Linkage disequilibrium; CAUSE, Causal Analysis Using Summary Effect estimates, SNP, single-nucleotide polymorphism; GID, gastrointestinal disorders; GERD, gastroesophageal reflux disease; PUD, Peptic ulcer disease; IBS, Irritable bowel syndrome; NAFLD, Non-alcoholic fatty liver disease.

https://doi.org/10.1017/S0033291723000867 Published online by Cambridge University Press

Table 1. Detailed information of GWAS summary statistics for main exposure and outcome phenotypes

Traits	Diagnostic	Unit	Sources	Participants (European descent)	Adjustments	Identified SNP	PubMed ID
GERD	ICD-10, ICD-9, self-reported, OPCS	One-unit in log-transformed odds ratio	UKB, QSkin health study	332 601 (71 522 cases, 261 079 controls)	Age, sex, and the first 10 principal components	25	31 527 586
	ICD-10, ICD-9	logOR	FinnGen	202 836 (13 141 cases, 189 695 controls)	Age, sex, genotyping batch and the first 10 genetically derived principal components	2	–
IBS	ICD-10, self-reported, Rome III	logOR	UKB, Bellygenes	486 601 (53 400 cases, 433 201 controls)	Age, sex, response status, the first 20 principal components	6	34 741 163
	ICD-10, ICD-9	logOR	FinnGen	187 028 (4605 cases, 182 423 cpntrols)	Age, sex, genotyping batch and the first 10 genetically derived principal components	1	–
PUD	ICD-9, self-reported,	logOR	UKB	456 327 (16 666 cases, 439 661 controls)	Sex, age and the first 20 ancestry principal components	8	33 608 531
	ICD-10, ICD-9	logOR	FinnGen	194 205 (4510 cases, 189 695 controls)	Age, sex, genotyping batch and the first 10 genetically derived principal components	2	–
NAFLD	ICD-10, ICD-9, self-reported	logOR	UKB	377 988 (4761 cases, 373 227 controls)	Age, sex, the first 20 genetic principal components,	6	34 535 985
	ICD-10, ICD-9	logOR	FinnGen	218 792 (894 cases, 217 898 controls)	Age, sex, genotyping batch and the first 10 genetically derived principal components	2	–
MDD	DSM-IV, ICD-9, or ICD-10	logOR	PGC, iPSYCH, deCODE, GenScot, GERA, 23andMe, UKB	480 359 (135 458 cases, 344 901 controls)	Sex, age and principal components	43	29 700 475

Abbreviations: GERD, gastroesophageal reflux disease; PUD, Peptic ulcer disease; IBS, Irritable bowel syndrome; NAFLD, Non-alcoholic fatty liver disease; MDD, major depressive disorder; ICD, International Classification of Diseases; OPCS, The OPCS Classification of Interventions and Procedures; DSM, The Diagnostic and Statistical Manual of Mental Disorders; UKB, UK biobank; PGC, Psychiatric Genomics Consortium; iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research; GenScot, Generation Scotland; GERA, Genetic Epidemiology Research on Adult Health and Aging.

combinations of the MDD and four GID measures, we had 80% power to detect ORs as small as 1.09–2 (online Supplementary Table S4).

Statistical analyses

We estimated the genetically predicted effects of MDD on multiple GID using a two-sample MR framework (Fig. 1).

Main analyses

Main analyses were performed using multiplicative random effects inverse-variance weighted (IVW)-MR, a method that combines the genetically predicted effect of MDD on GID across genetic variants (Burgess, Butterworth, & Thompson, 2013). We used fixed-effect meta-analysis to pool results across studies (i.e. UK Biobank and FinnGen). I^2 statistics and their corresponding confidence intervals (CI) were used to estimate heterogeneity across study estimates (von Hippel, 2015). A Bonferroni corrected p value < 0.0125 (0.05/4 for 4 GID) was used to correct the pooled main IVW results for multiple testing. The methods for ***Sensitivity analyses*** and ***Secondary analyses*** are detailed in the online Supplementary methods section.

All MR analyses were performed using R software (version 3.6.1). Two sample MR analyses were conducted using the 'TwoSampleMR' (version 0.5.6), 'MendelianRandomization' (version 0.6.0), 'mr.raps' (version 0.3.1), 'MRPRESSO' (version 1.0) packages. Meta-analyses of IVW results were performed using the 'meta' package (version 4.14). CAUSE analyses were conducted using the 'cause' package (version 1.2.0). MVMR was performed using the 'MVMR' package (version 0.3). Forest plots were created using the 'forestplot' package (version 1.10). LD Scores were computed using the 'ldsc' command line tool (version 1.0.1). The code used in this study is available at: https://github.com/Rick-Chen-PKU/Depression_GI.

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Results

Gastroesophageal reflux disease

Meta-analyses IVW MR findings suggested that genetically predicted MDD increased the risk of GERD [odds ratio (OR) = 1.293 per logOR change in MDD, 95% CI 1.204–1.389, $p < 0.001$] (Fig. 2, online Supplementary Table S8). These results survived multiple testing correction (Bonferroni $p < 0.001$) and there was little evidence of heterogeneity across UKB and FinnGen estimates ($I^2 = 0\%$, 95% CI 'NA', $p = 0.37$). Additionally, the direction of the genetically predicted effect was consistent across other sensitivity MR analyses (i.e. MR-Egger, simple median, weighted median, weighted mode, MR-RAPS, MR-PRESSO) (Fig. 2, online Supplementary Tables S6–S8) and results were consistent in the main discovery cohort (IVW OR 1.318, 95% CI 1.214–1.431, $p < 0.001$) (Fig. 2, online Supplementary Table S6). This causal association did not change substantially in the sensitivity analysis after excluding the SNPs associated with potential confounders (IVW OR 1.321, 95% CI 1.196–1.459, $p < 0.001$; online Supplementary Table S9).

In multivariable IVW MR analysis adjusting for BMI, the causal association between MDD and GERD was attenuated (OR 1.274; 95% CI 1.101–1.431). With adjustment for insomnia, the causal association was expanded (OR 1.469; 95% CI 1.353–1.595). There was little change in causal estimate after adjustment for T2D (Fig. 3).

We did not find evidence of residual population stratification in MR analyses using negative control outcomes (online Supplementary Table S10), nor did we find evidence of horizontal pleiotropy via potential GID risk factors (online Supplementary Table S11). Reversed MR analysis revealed that genetically predicted GERD increased the risk of MDD (IVW OR 1.398, 95% CI 1.114–1.754, $p = 0.0038$; online Supplementary Table S12). Additionally, LDSC coefficients for MDD and GERD were also in the expected direction (rg = 0.53, $p < 0.001$; Table 2). MR-CAUSE sensitivity analysis revealed that the causal models of genetically predicted MDD on GERD outperformed the shared model and null model, indicating no bias due to correlated pleiotropy (Table 3). Formal assessment revealed a minimal risk of bias from sample overlap (<0.002, regardless of overlap proportion) (online Supplementary Table S13), with a minimum F statistic of 167.

Irritable bowel syndrome

Meta-analyses IVW MR found evidence that genetically predicted MDD increased the risk of IBS (OR 1.484, 95% CI 1.358–1.621, $p < 0.001$) (Fig. 2, online Supplementary Table S8). These results survived multiple testing correction (Bonferroni $p < 0.001$) and there was little evidence of heterogeneity across UKB and FinnGen estimates ($I^2 = 0\%$, 95% CI 'NA', $p = 0.47$). Additionally, the direction of the genetically predicted effect was consistent across other sensitivity MR analyses (i.e. MR-Egger, simple median, weighted median, weighted mode, MR-RAPS, MR-PRESSO) (Fig. 2, online Supplementary Tables S6–S8) and results were consistent in the main discovery cohort (IVW OR 1.464, 95% CI 1.329–1.612, $p < 0.001$) (Fig. 2, online Supplementary Table S6). This causal association did not change substantially in the sensitivity analysis after excluding the SNPs associated with potential confounders (IVW OR 1.447, 95% CI 1.305–1.605, $p < 0.001$; online Supplementary Table S9).

In multivariable IVW MR analysis adjusting for BMI, T2D or insomnia, the causal association between MDD and IBS were attenuated (BMI OR 1.338; 95% CI 1.174–1.525; T2D OR 1.362; 95% CI 1.225–1.513; Insomnia OR 1.388; 95% CI 1.209–1.592) (Fig. 3). Reversed MR analysis found evidence that genetically predicted IBS increased the risk of MDD (IVW OR 1.301, 95% CI 1.003–1.688, $p = 0.047$; online Supplementary Table S12). Additionally, LDSC coefficients for MDD and IBS were also in the expected direction (rg = 0.56, $p < 0.001$; Table 2). MR-CAUSE sensitivity analysis revealed that the causal models of genetically predicted MDD on IBS outperformed the shared model and null model, indicating no bias due to correlated pleiotropy (Table 3).

Peptic ulcer disease

Meta-analyses IVW MR found evidence that genetically predicted MDD increased the risk of PUD (OR 1.218, 95% CI 1.092–1.358, $p < 0.001$) (Fig. 2, online Supplementary Table S8). These results survived multiple testing correction (Bonferroni $p = 0.0016$) and there was little evidence of heterogeneity across UKB and FinnGen estimates ($I^2 = 0\%$, 95% CI 'NA', $p = 0.59$). Additionally, the direction of the genetically predicted effect was consistent across other sensitivity MR analyses (i.e. MR-Egger, simple median, weighted median, weighted mode, MR-RAPS, MR-PRESSO) (Fig. 2, online Supplementary Tables S6–S8) and results were consistent in the main discovery cohort (IVW OR 1.237, 95% CI 1.093–1.401, $p < 0.001$) (Fig. 2, online Supplementary Table S6). This causal association did not change substantially in the sensitivity analysis after excluding the SNPs associated with potential confounders (IVW OR 1.217, 95% CI 1.055–1.405, $p = 0.0072$; online Supplementary Table S9).

In multivariable IVW MR analysis adjusting for BMI, T2D or insomnia, we found little evidence of the causal association between MDD and PUD (Fig. 3). Reversed MR analysis found no evidence that genetically predicted PUD had a potential causal association with MDD (online Supplementary Table S12). Additionally, LDSC coefficients for MDD and PUD were in the expected direction (rg = 0.50, $p < 0.001$; Table 2). MR-CAUSE sensitivity analysis revealed that the causal models of genetically predicted MDD on PUD outperformed the shared model and null model, indicating no bias due to correlated pleiotropy (Table 3).

Non-alcoholic fatty liver disease

Meta-analyses IVW MR found evidence that genetically predicted MDD increased the risk of NAFLD (OR 1.310, 95% CI 1.084–1.583, $p = 0.005$) (Fig. 2, online Supplementary Table S8). These results survived multiple testing correction (Bonferroni $p = 0.021$) and there was little evidence of heterogeneity across UKB and FinnGen estimates ($I^2 = 0\%$, 95% CI 'NA', $p = 0.61$). Additionally, the direction of the genetically predicted effect was consistent across other sensitivity MR analyses (i.e. MR-Egger, simple median, weighted median, weighted mode, MR-RAPS, MR-PRESSO) (Fig. 2, online Supplementary Tables S6–S8) and results were consistent in the main discovery cohort (IVW OR 1.284, 95% CI 1.047–1.576, $p = 0.017$) (Fig. 2, online Supplementary Table S6). This causal association did not change substantially in the sensitivity analysis after excluding the SNPs associated with potential confounders (IVW OR 1.378, 95% CI 1.084–1.751, $p = 0.0088$; online Supplementary Table S9).

In multivariable IVW MR analysis adjusting for BMI, T2D or insomnia, we found little evidence of the causal association

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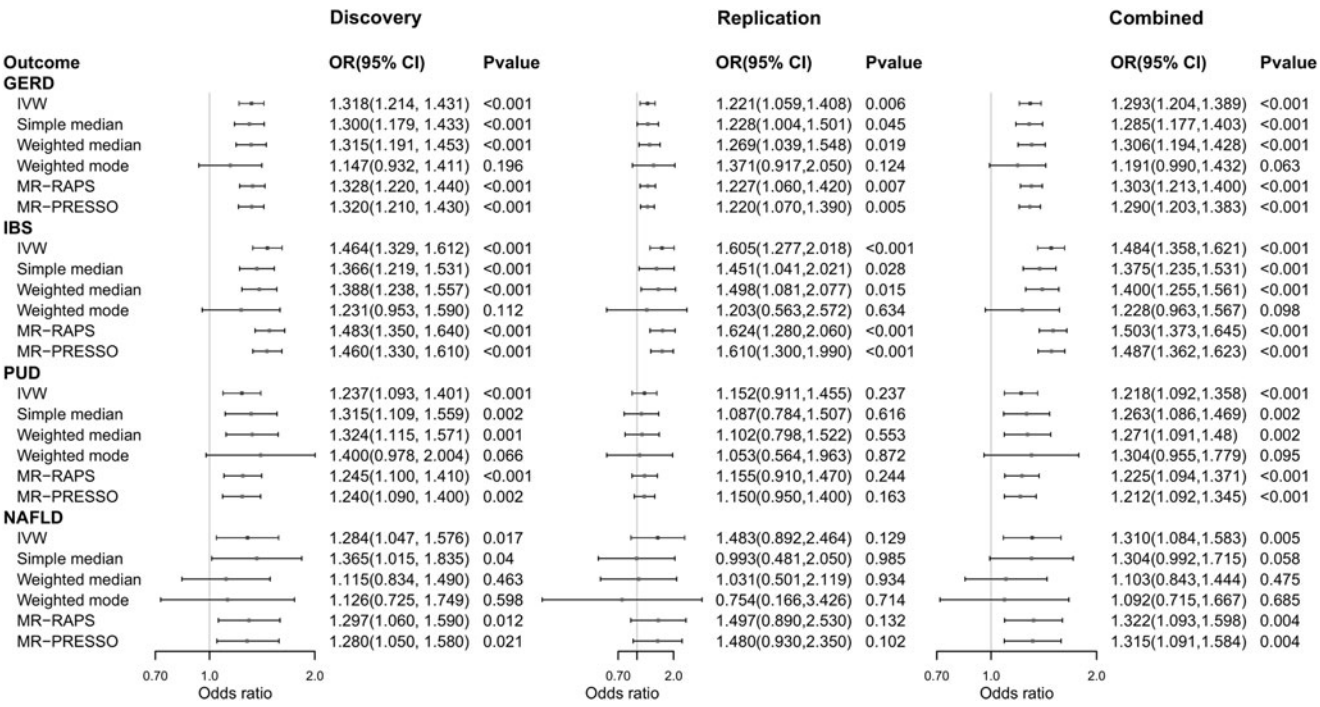

Figure 2. Associations of genetically predicted depression with risk of gastrointestinal disorders in discovery, replication, and combined datasets. OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted; GERD, Gastroesophageal reflux disease; PUD, Peptic ulcer disease; IBS, Irritable bowel syndrome; NAFLD, Non-alcoholic fatty liver disease.

between MDD and NAFLD (Fig. 3). Reversed MR analysis found no evidence that genetically predicted NAFLD had a potential causal association with MDD (online Supplementary Table S12). Additionally, LDSC coefficients for MDD and NAFLD were in the expected direction (rg = 0.40, $p < 0.001$; Table 2). MR-CAUSE sensitivity analysis revealed that the causal model of genetically predicted MDD on NAFLD was inferior to the shared model and null model (Table 3).

Discussion

In this comprehensive two-sample MR study of MDD and GID, we found evidence that genetically predicted MDD may increase the risk of GERD, IBS, PUD and NAFLD. Reverse MR found evidence of GERD or IBS may increase the risk of MDD. We also investigated if any potential confounder/mediator plays a role in the causal pathway from MDD to GID. LDSC analyses revealed that MDD and GID may have shared genetic etiology. Our

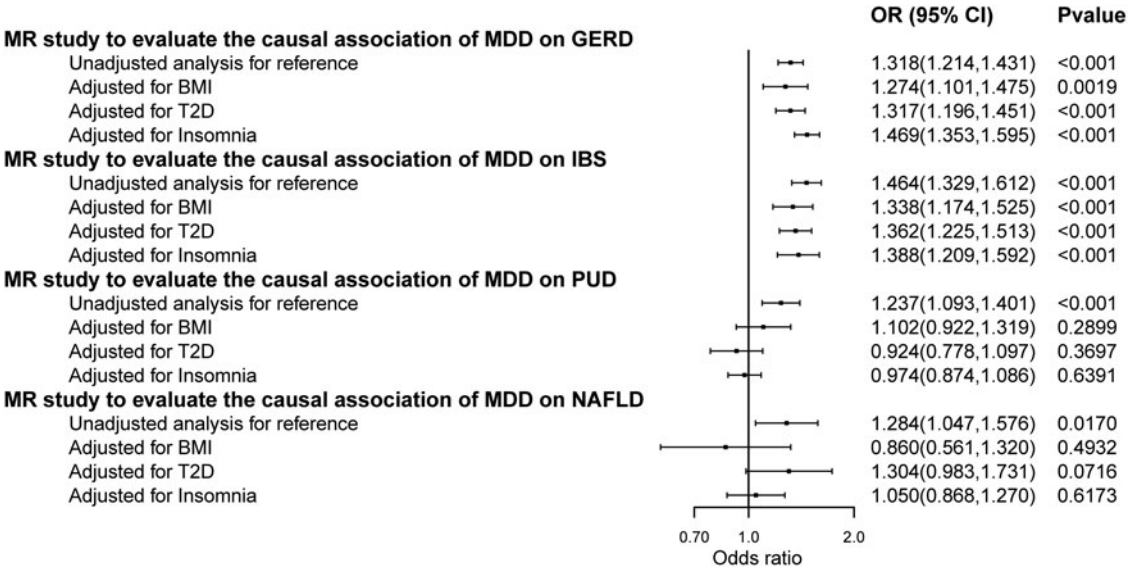

Figure 3. Result of multivariable Mendelian Randomization analysis in evaluating the casual association between depression and numerous GID (based on UK biobank sample). OR, odds ratio; CI, confidence interval; GERD, gastroesophageal reflux disease; PUD, Peptic ulcer disease; IBS, Irritable bowel syndrome; NAFLD, Non-alcoholic fatty liver disease; BMI, body mass index; T2D, type 2 diabetes.

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Table 2. Genetic correlation of major depressive disorder (MDD) with gastrointestinal disorders (GID, based on UK biobank sample), estimated by linkage disequilibrium score regression

Trait 1	Trait 2	rg	rg, SE	rg, 95% CI	*p* Value
MDD	**GERD**	0.53	0.035	0.46–0.6	2.42×10^{-50}
MDD	**IBS**	0.56	0.043	0.48–0.64	2.01×10^{-39}
MDD	**PUD**	0.50	0.063	0.38–0.62	1.48×10^{-15}
MDD	**NAFLD**	0.40	0.074	0.25–0.55	6.14×10^{-08}

Note: Summary statistics for each trait were merged with Hapmap3 SNPs excluding the HLA region to estimate rg; GERD, gastroesophageal reflux disease; PUD, Peptic ulcer disease; IBS, Irritable bowel syndrome; NAFLD, Non-alcoholic fatty liver disease

findings are timely to draw attention to the co-morbid risk of MDD and GID and to provide more robust scientific evidence to guide treatment.

The novelty of this study is mainly reflected in the following aspects. First, it is the first time that a quasi-experimental approach based on a large sample has been used to explore the potential causal relationship between MDD and GID. There are currently no relevant RCTs in the field and the results of this study would be a strong addition to the evidence for a potential causal relationship in this area, given the available evidence. Furthermore, previous studies have reported higher statistical power for two-sample MR methods compared to classical epidemiological study design methods (Bowden et al., 2019). Second, we pooled results from multiple sources using fixed effects meta-analysis to improve the precision of the estimates and adopted a thorough sensitivity analysis to validate the robustness of the results. Third, this study is the first to find an association between MDD and PUD in a population of European ancestry.

Causal association between major depressive disorder and gastroesophageal reflux disease

Using the MR study design, we found a positive relationship of genetically predicted MDD on GERD. We also found that genetically predicted GERD was associated with a higher risk of developing MDD. This finding was consistent with the result of a nested case-control study conducted in Korea by Kim et al. (OR 2.01, 95% CI 1.96–2.07, $p < 0.001$) (Kim et al., 2018). However, our findings contrast with those highlighted in Zhi, et al., an observational cohort study that used Men Androgen Inflammation Lifestyle Environment and Stress data (On et al., 2017). Nevertheless, it is possible that their analyses were underpowered, as their sample only included 221 GERD cases (13.7%). More importantly, the direction of the reported estimate is consistent with our findings and those previous observational study (Chen & Wang, 2020; Choi et al., 2018; You et al., 2015). MVMR analysis revealed that MDD had a direct causal effect on GERD independent of BMI, T2D and Insomnia, which was also found in these studies (Jansson et al., 2007; On et al., 2017).

There may be some biological mechanism to explain genetically predicted MDD increases the risk of GRED. Previous studies have shown a strong association between the brain and the gastrointestinal tract (Choi et al., 2018). Due to the gut-brain axis, psychological factors such as personal mood can influence gastrointestinal function and contribute to the progression of GID. Likewise, the state of the gastrointestinal tract may affect an individual's emotional state (Choi et al., 2018). MDD may precede GERD and increase the risk of GERD. First, depression can

Table 3. MR-CAUSE analysis, linking genetic predicted major depressive disorder (MDD) with gastrointestinal disorders (GID, based on UKB sample)

Model 1[a]	Model 2[a]	Δ ELPD[b]	s.e. Δ ELPD	*z* score	*p* value[c]
MDD → GERD					
Null	Sharing	−3.6	1.6	−2.2	0.015
Null	Causal	−8.5	3.6	−2.3	0.0096
Sharing	Causal	−4.9	2	−2.5	0.0071
MDD → IBS					
Null	Sharing	−0.3	0.53	−0.57	0.28
Null	Causal	−2.6	2.3	−1.10	0.13
Sharing	Causal	−2.3	1.8	−1.30	0.10
MDD → PUD					
Null	Sharing	−0.12	0.56	−0.22	0.41
Null	Causal	−1.10	2.00	−0.56	0.29
Sharing	Causal	−1.0	1.50	−0.67	0.25
MDD → NAFLD					
Null	Sharing	0.27	0.54	0.49	0.69
Null	Causal	1.10	1.00	1.10	0.86
Sharing	Causal	0.85	0.69	1.20	0.89

Abbreviations: CAUSE, causal analysis using summary effect; ELPD, expected log pointwise posterior density; MR, Mendelian randomization; GERD, gastroesophageal reflux disease; PUD, Peptic ulcer disease; IBS, Irritable bowel syndrome; NAFLD, Non-alcoholic fatty liver disease.
(MR-CAUSE parameter setting: r2_thresh = 0.01, pval_thresh = 1×10^{-3}).
[a]Model 1 and Model 2 refer to the models being compared (null, sharing, or causal).
[b]Model fit is measured by Δ Expected Log Pointwise Posterior Density (Δ ELPD); Negative values indicate that model 2 is a better fit.

lead to hypochondria and create a dread of reflux symptoms, which may increase an individual's perception of reflux symptoms (Kamolz & Velanovich, 2002). This may in turn reduce the body's sensory threshold and exaggerate the perception of reflux symptoms. Second, depression may cause physiological structural changes that increase reflux. MDD can decrease the pressure of the lower esophageal sphincter, alter esophageal motility, increase gastric acid secretion, and decrease acid clearance from the esophagus (Johnston, 2005; Kamolz & Velanovich, 2002). This mechanism has also been demonstrated in animal study. Rats subjected to psychological stress show disruption of the tight junctions of the esophageal epithelium and subsequent weakening of the barrier function of the esophageal mucosa, thereby increasing its vulnerability to reflux (Farré et al., 2007). Third, antidepressant medication may worsen reflux (Martín-Merino et al., 2010). Antidepressants have been shown to delay gastric emptying and inhibit esophageal peristalsis (Brahm & Kelly-Rehm, 2011).

Conversely, GERD may also increase the risk of MDD. First, persistent reflux symptoms can be annoying and upsetting and may precipitate depression (Kamolz & Velanovich, 2002). Previous studies have shown that those patients who do not respond well to medication are more likely to exhibit higher levels of depression, and this group is most common in the NERD group of GERD subtypes (Kimura et al., 2016). Second, the esophageal mucosa of GERD patients contains high levels of cytokines such as interleukin IL-6, IL-8, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) (Altomare, Guarino, Cocca, Emerenziani, & Cicala, 2013). Increased levels of these immune mediators may lead to chronic inflammation in the

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central nervous system (Lampa et al., 2012). This chronic inflammation plays a vital role in the pathophysiology of MDD and may lead to the development of depression (Berk et al., 2013; Goldstein, Kemp, Soczynska, & McIntyre, 2009). Again, the frequent arousal of GERD may affect sympathetic activation (Jansson et al., 2009). Frequent reflux of gastric acid stimulates the vagus nerve and triggers bronchoconstriction (Demeter & Pap, 2004), which may lead to sleep disturbances and further affect MDD (Altena et al., 2016).

The relationship between MDD and GERD involves a complex interaction of various mechanisms. The results of bidirectional MR corroborate the potential pattern of co-morbidity between MDD and GRED. A recent study showed that treatment of GERD with a proton-pump inhibitor also slightly improved the symptoms of MDD (Wu, Chen, & Wen, 2021a). Therefore, it is necessary to pay careful attention to the degree of depression in GERD patients or the symptoms of GERD in MDD patients to make the disease treatment more effective.

Causal association between major depressive disorder and irritable bowel syndrome

In the case of IBS, our study suggests that genetically predicted MDD increased the risk of IBS, and genetically predicted IBS increased the risk of MDD. This finding was consistent with those reported in Janssens, Zijlema, Joustra, and Rosmalen, 2015, a cohort study that used LifeLines data (OR 1.87, 95% CI 1.67–2.10) (Janssens et al., 2015). Additionally, evidence from numerous studies, including systematic reviews (Aziz, Kumar, Muhammad Nawawi, Raja Ali, & Mokhtar, 2021) and meta-analyses (Nikolova et al., 2022; Sibelli et al., 2016; Zamani, Alizadeh-Tabari, & Zamani, 2019), case reports (Li et al., 2022), and animal study (Takajo et al., 2019), suggest a co-morbid state of MDD and IBS. Additionally, MVMR analysis revealed that MDD had a direct causal association on IBD independent of BMI, T2D and Insomnia.

A potential mechanism might explain MDD may lead to higher IBS risk. Drossman et al., found by functional magnetic resonance imaging that depression can activate the cingulate region of the limbic system of the cerebral cortex (Drossman et al., 2003); and the emotional activity center of the limbic system is in the same anatomical site as the vegetative center and the endocrine regulatory center, which govern the movement and secretion of the digestive tract; thus, the function of the vegetative center and the endocrine regulatory center is altered, and then the information is transmitted to the enteric nervous system through the brain-gut axis, causing changes in neurotransmitters and adrenocorticotropin-releasing factors, which affect visceral sensation, intestinal movement and endocrine function (Tan et al., 2021). In addition, study has shown that depression can lead to increased levels of expression of cytokines such as IL-1β and TNF-α in the peripheral serum of patients (Miller, Maletic, & Raison, 2009). Elevated levels of IL-1β can stimulate inflammation, affect visceral sensitivity and ultimately lead to the development of IBS. TNF-α can contribute to the development of IBS by affecting the activation and expression of myosin light chain kinase, leading to impaired tight junction function and disruption of intestinal epithelial barrier function (Al-Sadi, Guo, Ye, Rawat, & Ma, 2016).

As for the causal association of genetically predicted IBS on MDD, a recent review by Mayer et al., showed that sensory input from the gut implicates the activity of a number of brain regions that are associated with various brain functions such as sensory, cognitive and emotional (Mayer, Ryu, & Bhatt, 2023); Drossman et al., suggested that intestinal symptoms such as abdominal pain in IBS patients can induce activation of areas related to the limbic system of the cerebral cortex, which affects patients' depressive mood (Drossman, 2005). IBS may also worsen symptoms of depression by affecting behavior (Ballou et al., 2019). Concerns about bowel movements or IBS symptoms may lead patients to seek isolation and avoid social activities. These changes in behavior may cause psychological symptoms such as loneliness and helplessness, which can lead to feelings of depression.

Causal association between major depressive disorder and peptic ulcer disease

As for PUD, we found evidence that genetically predicted MDD increased the risk of PUD, while genetically predicted PUD had no causal association with MDD. Several previous observational studies were consistent with the present results but were based on East Asian populations (Fang et al., 2019; Hsu et al., 2015; Kim, Min, Oh, & Choi, 2020; Lee et al., 2015). In contrast, the association between MDD and PUD has not been studied in European ancestry. Therefore, the present study partially fills this gap. Additionally, MVMR analysis showed no direct causal association of MDD on PUD after adjustment for BMI, T2D or insomnia, implying a potential mediating role for BMI, T2D or insomnia in this association.

Previous research has proposed many pathways involving different organ systems via which depression may elevated the development of PUD. A seemingly plausible explanation involves the function of the gut-brain axis. The gut-brain axis functions through mechanisms such as intestinal permeability, intestinal endocrine signaling and immune activation, which are important for regulating the GI and intestinal immune systems (Carabotti, Scirocco, Maselli, & Severi, 2015). However, chronic depression can interfere with the normal functioning of the gut-brain axis (Zhu et al., 2017), which may increase the susceptibility of the gastrointestinal tract to ulcer-causing agents such as *H. pylori* (Liu et al., 2018). Additionally, depression can affect sympathetic-adrenal stress response mechanisms, leading to dysregulation of the hypothalamic-pituitary-adrenal axis (Scott et al., 2013). This neuroendocrinological abnormality may further affect gastroduodenal function by increasing cortisol levels and gastric acid secretion, potentially leading to an elevated risk of PUD (Lee et al., 2017). Moreover, the relationship between depression and PUD may involve the immune system (Lee et al., 2015). Depression-related stress may activate the release of certain pro-inflammatory cytokines, which may activate inflammatory cells in patients with H. pylori-induced ulcers (Sugimoto, Yamaoka, & Furuta, 2010).

Causal association between major depressive disorder and non-alcoholic fatty liver disease

We found evidence that genetically predicted MDD increased the risk of NAFLD, while genetically predicted NAFLD had no causal association with MDD. MVMR analysis showed no direct causal effect of MDD on NAFLD after adjustment for BMI, T2D or insomnia, implying that a large proportion of this association was mediated by BMI, T2D or insomnia. Previous studies have reported inconsistent results (Kim et al., 2019; Lee et al., 2013; Tomeno et al., 2015; Youssef et al., 2013). Additionally, Labenz et al., found that NAFLD constituted an independent risk factor

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for emerging depression after controlling for confounding comorbidities, whereas the current MR analysis did not support this finding (Labenz et al., 2020).

Several mechanisms support the association of genetically predicted MDD increased risk of NAFLD. First, systemic inflammation plays an important role in the pathogenesis of MDD and NAFLD. Increased overall body stress due to underlying obesity, diabetes, or metabolic syndrome leads to increased production of pro-inflammatory cytokines, cortisol, and epinephrine, which is further amplified by depression, increasing the propensity for NAFLD development (Chan, Cathomas, & Russo, 2019; Huang, Liu, & Yu, 2017). Pathophysiological factors associated with depression, such as increased monoamine oxidase-A enzyme activity, may enhance cellular oxidative stress and thus adversely affect NAFLD (Bhanji, Narayanan, Allen, Malhi, & Watt, 2017; Youssef et al., 2013). Another possible explanation is the association between NAFLD and obesity or diabetes, both of which are strongly associated with depression (Bica, Castelló, Toussaint, & Montesó-Curto, 2017). After further adjustment for diabetes and obesity, the association was attenuated to null, suggesting that a large proportion of the association between depression and NAFLD is mediated by diabetes and obesity. New evidence for the involvement of insulin signaling in brain mechanisms associated with depression suggests that insulin resistance may be one of the major causal factors in NAFLD and that it may develop in the brains of depressed patients (Lyra et al., 2019).

Summary of the above findings

The co-morbid mechanisms and development of MDD and GID have a mutually subtle character in that depression is characterized by somatic symptoms of gastrointestinal dysfunction, which in turn exacerbates depression with somatic visceral perception and other upstream symptoms of the central nervous system. The co-morbid neurobiological pathways may involve four major dimensions, including negative feedback impairment of the hypothalamic-pituitary-adrenal axis (HPA) (Dinan et al., 2006), imbalance of gut microecology (Tillisch, 2014) and dysregulation of inflammatory cytokine ratios (Dowlati et al., 2010). These potential neurobiological pathways will have important implications for the diagnosis and treatment of both disorders, improving the accuracy and sensitivity of therapeutic strategies adopted by clinicians and providing an entry point for research into the pathogenesis and pharmacological mechanisms of action of depression in combination with GID.

Strengths and limitations

The most significant highlight of this study is the pooling of results from multiple sources using fixed-effect meta-analysis to improve the precision of the effect size estimates. Thorough sensitivity analyses, such as MR of negative control outcomes, MR of GID risk factors, Steiger filtering and CAUSE analyses, were conducted to assess the validity of the MR assumptions. Moreover, we performed MVMR, reversed MR and LDSC as secondary analyses to validate the robustness of MR results. Additionally, our findings contribute to the identification of modifiable targets for future interventions aimed at MDD for the prevention of GID. The current study is well-powered (online Supplementary Table S4) and the relatively high F statistic ($\geqslant$167) of the genetic instruments involved in the main primary MR analyses of depression implied a lower chance of weak instrument bias.

This study also has limitations. First, there was partial sample overlap between MDD and GID. However, the relatively high F statistic ($\geqslant$167) of the genetic instruments involved in the main primary MR analyses of depression and MR-RAPS analysis results implied a lower chance of weak instrument bias. The relative bias from sample overlap is also very small (<0.002). Second, some of our sensitivity analyses, such as the MR-Egger intercept test used to detect uncorrelated horizontal pleiotropy, had low power, resulting in imprecise estimates. The weighted mode method may also be misleading in this context, as its use is limited in the presence of very few SNPs. Although these limitations potentially undermine the validity of our results, it is reassuring that point estimates for the genetically predicted effect of MDD on GID were consistent across MR methods. Third, partial cases of GID are derived from self-reporting, which may be affected by recall bias and response bias. Another limitation is that we did not have access to individual-level data. Therefore, we were unable to stratify the analyses by potential effect modifiers, such as sex, smoking, and sleep quality. Finally, to reduce bias due to population stratification, this study is limited to individual of European ancestry and cannot be generalized to other ancestral backgrounds. Furthermore, our MR of negative control outcomes suggests that our MR results are unlikely to be biased by residual population stratification. Despite this, confounding due to population stratification, dynastic effects and assortative mating cannot be ruled out completely.

Clinical implications

We highlight certain aspects here that may advance the field; however, we advise that due to numerous limitations, the current findings should not be overinterpreted.

From a public health perspective, our work provides potentially relevant findings. Observational and MR studies suggest that MDD may be influenced by some GID risk factors, such as obesity and smoking (Tyrrell et al., 2019; Yao et al., 2021). If MDD is a causal mediator between these risk factors and GID, then MDD may be a manageable mediator when targeting the underlying risk factors is not feasible or too difficult to accomplish. However, we believe that it may be premature to make claims about the clinical utility of our findings. From a treatment perspective, the associations between MDD and GID comorbidities appear to be bidirectional. When treating patients with MDD, clinicians should focus on their GID symptoms; for patients with gastrointestinal symptoms, physicians should also focus on their emotional problems simultaneously, which may help in the choice of treatment measures or in reducing comorbidities. In addition, exploring drugs that can both treat MDD and improve GID will better advance clinical care; however, this study could not provide confirmatory evidence. Notably, a small clinical trial reported that Probiotics treatment of IBS resulted in improvement of MDD symptoms (Pinto-Sanchez et al., 2017).

Future directions

Although promising in terms of consistency and biological plausibility, further research is required to confirm our findings. For example, MVMR could be used to disentangle the causal effects of MDD on GID from other shared heritable factors (e.g. Gut microbiota, *H. pylori* infection, education level, neuroticism, dietary intake, physical activity, c-reactive protein, insulin resistant, etc.). Moreover, we did not have sex-specific instruments for

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MDD. Given the higher prevalence of MDD in women, the genetic structure of MDD may differ between the sexes. We also didn't have access to summary statistics of GID subtypes. The clinical features and genetic components differ between GID subtypes. Further studies should focus on sex-specific and GID subtypes based on individual data. Despite these suggestions, we acknowledge that it may be challenging to get access to suitable datasets for replication purposes in the short term.

Conclusions

In conclusion, genetically predicted MDD may increase the risk of GERD, IBS, PUD and NAFLD. Genetically predicted GERD or IBS may increase the risk of MDD. The findings may help elucidate the mechanisms underlying the co-morbidity of depression and GID and may have clinical implications. However, further clinical studies are required to replicate the findings and investigate the effects of comorbidity therapies. Further investigations are also warranted to elucidate the mechanism involved.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723000867

Acknowledgements. Not applicable.

Authors' contributions. ZH, JJ and TH designed the study. DC performed the statistical analysis. DC and YZ wrote the manuscript. All authors helped interpret the data, reviewed, and edited the final paper, and approved the submission. The corresponding author had full access to all the data.

Financial support. Not applicable.

Conflict of interest. The authors declare that they have no competing interests.

Author(s)	Year	Dataset title	Dataset URL	Database and Identifier
Wray, et al.	2018	Genome-wide association studies identify 44 loci for major depressive disorder	https://doi.org/10.6084/m9.figshare.14672085	PGC, mdd2018
An, et al.	2019	Gastroesophageal reflux disease	https://doi.org/10.6084/m9.figshare.8986589	Online URL
Eijsbouts, et al.	2021	Irritable bowel syndrome	https://www.ebi.ac.uk/gwas/	GWAS Catalog, GCST90016564
Wu, et al.	2021	Peptic ulcer disease	https://cnsgenomics.com/content/data	Complex Trait Genomics, PUD
Fairfield, et al.	2022	Nonalcoholic fatty liver disease	https://www.ebi.ac.uk/gwas/	GWAS Catalog, GCST90054782
FinnGen consortium	2021	Gastroesophageal reflux disease	http://r5.finngen.fi/	IEU OpenGWAS, finn-b-K11_REFLUX
FinnGen consortium	2021	Irritable bowel syndrome	http://r5.finngen.fi/	IEU OpenGWAS, finn-b-K11_IBS
FinnGen consortium	2021	Peptic ulcer disease	http://r5.finngen.fi/	IEU OpenGWAS, finn-b-K11_GASTRODUOULC
FinnGen consortium	2021	Nonalcoholic fatty liver disease	http://r5.finngen.fi/	IEU OpenGWAS, finn-b-NAFLD
Ben Elsworth, et al.	2018	Skin colour	https://gwas.mrcieu.ac.uk/datasets/ukb-b-19560/	IEU OpenGWAS, ukb-b-19560
Ben Elsworth, et al.	2018	Ease of skin tanning	https://gwas.mrcieu.ac.uk/datasets/ukb-b-533/	IEU OpenGWAS, ukb-b-533
Ben Elsworth, et al.	2018	Pack years of smoking	https://gwas.mrcieu.ac.uk/datasets/ukb-b-10831/	IEU OpenGWAS, ukb-b-10831
Ben Elsworth, et al.	2018	Time spent doing vigorous physical activity	https://gwas.mrcieu.ac.uk/datasets/ukb-b-13702/	IEU OpenGWAS, ukb-b-13702
Okbay, et al.	2016	Years of schooling	https://gwas.mrcieu.ac.uk/datasets/ieu-a-1001/	IEU OpenGWAS, ieu-a-1001
Ben Elsworth, et al.	2018	Alcohol intake frequency	https://gwas.mrcieu.ac.uk/datasets/ukb-b-5779/	IEU OpenGWAS, ukb-b-5779
Locke AE, et al.	2015	Body mass index	https://gwas.mrcieu.ac.uk/datasets/ieu-a-835/	IEU OpenGWAS, ieu-a-835
Locke AE, et al.	2015	Waist circumference	https://gwas.mrcieu.ac.uk/datasets/ieu-a-61/	IEU OpenGWAS, ieu-a-61
Ligthart, S, et al.	2018	C-Reactive protein level	https://gwas.mrcieu.ac.uk/datasets/ieu-b-35/	IEU OpenGWAS, ieu-b-35
Ben Elsworth, et al.	2018	Townsend deprivation index at recruitment	https://gwas.mrcieu.ac.uk/datasets/ukb-b-10011/	IEU OpenGWAS, ukb-b-10011
Ben Elsworth, et al.	2018	Average total household income before tax	https://gwas.mrcieu.ac.uk/datasets/ukb-b-7408/	IEU OpenGWAS, ukb-b-7408
Scott, et al.	2017	Type 2 diabetes	http://diagram-consortium.org/downloads.html	DIAGRAM, DIAGRAM 1000 G GWAS meta-analysis Stage 1 Summary statistics
Jansen, et al.	2019	Insomnia	https://ctg.cncr.nl/software/summary_statistics	CTGlab, Summary statistics for Insomnia, wave 2 from Philip Jansen et al., 2019

Ethical standards. Not applicable.

Data availability. The following publicly available datasets of summary statistics were used:

Code availability. Custom ***R*** scripts used to generate results in this study can be found in: https://github.com/Rick-Chen-PKU/Depression_GI.

Patient and public involvement. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

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