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Genetic evidence causally linking gastroesophageal reflux disease to cholecystitis: a two-sample mendelian randomization study

Chao Wang^{1,3†}, Jia Wang^{2,3†}, Ming Fang^{2,3*} and Bojian Fei^{1,3*}

Abstract

Background Gastroesophageal reflux disease (GERD) and cholecystitis share overlapping symptoms, including belching, acid reflux, and heartburn. Despite this, the causal relationship between these two conditions remains unclear. This study aimed to investigate the causal link between GERD and cholecystitis using a Mendelian randomization (MR) approach.

Methods A two-sample MR analysis was conducted using the inverse variance weighted (IVW), weighted median, weighted mode, and MR-Egger method to assess the causal effects of GERD on the cholecystitis risk. Genome-wide association studies (GWASs) on GERD (N cases = 129080; N controls = 473524) and cholecystitis (N cases = 1930; N controls = 359264) were obtained from the IEU Open GWAS project. Various techniques were employed to assess pleiotropy and heterogeneity.

Results Seventy-seven single nucleotide polymorphisms from GERD GWASs were selected as instrumental variables (IVs). The primary IVW method revealed a significant association between GERD and an increased risk of cholecystitis (odds ratio = 1.004; 95% confidence interval = 1.003–1.005, $p = 2.68 \times 10^{-9}$). The absence of heterogeneity and pleiotropy in the data supports the reliability of the results.

Conclusions GERD was positively associated with the risk of cholecystitis. This study provides insights into potential avenues for the development of prevention strategies and treatment options for cholecystitis in patients with GERD. These findings contribute to our understanding of the complex interplay between GERD and cholecystitis.

Keywords Mendelian randomization, Gastroesophageal reflux disease, Cholecystitis, Single-nucleotide polymorphisms, Causal effect

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Background

Cholecystitis, a prevalent gallbladder disease, stands as a common cause of abdominal pain in Western countries. In the United States alone, gallbladder disease affects approximately 20 million people annually, with approximately 200,000 new diagnoses, imposing substantial physical and financial burdens on affected individuals [1]. Cystic ductal obstruction, mainly associated with gallstones, accounts for 90–95% of acute cholecystitis cases. The overall prevalence of gallstones is estimated at 10–15%, with 20–40% of patients facing gallstone-related complications and an annual incidence rate of 1–3% [2–4]. Typical clinical manifestations of cholecystitis include right upper abdominal pain, nausea, and malaise. Laparoscopic cholecystectomy stands as the preferred treatment for patients with symptomatic cholelithiasis due to its ability to reduce postoperative pain and shorten hospital stays [5, 6].

Various risk factors contribute to cholecystitis exist, including female sex, rapid weight loss, pregnancy, advanced age, obesity, consumption of high-fat or low-fiber diets, diabetes, and receipt of intravenous nutrition [7–9]. In clinical practice, gastroesophageal reflux disease (GERD) often coexists with cholecystitis, potentially leading to diagnostic challenges due to overlapping symptoms [10–12]. However, evidence regarding the causal relationship between GERD and cholecystitis remains inconclusive, underscoring the need for further investigation to prevent misdiagnosis and ensure timely interventions.

GERD, characterized by the backflow of gastric contents into the esophagus, presents distressing symptoms such as acid regurgitation, heartburn, and belching [13]. Over recent years, GERD has emerged as a prevalent clinical condition, affecting approximately 20% of adults in the Western world [14, 15]. The symptomatic similarities between GERD and cholecystitis exceed chance expectations, increasing the likelihood of diagnostic errors and compromising patient treatment and outcomes. Vagus nerve abnormalities lead to dyskinesia and paresthesia in the gastroesophageal and biliary systems, and some studies have reported an increased incidence of GERD after cholecystectomy, suggesting that there may be a connection between GERD and cholecystitis, or due to neurological or endocrine factors [16, 17]. Additionally, the direction and causative association between GERD and cholecystitis remain uncertain. Therefore, the objective of this study is to elucidate the causal relationship between these two conditions, and we have employed a Mendelian randomization (MR) analysis.

MR offers an alternative approach in epidemiology for inferring causality, utilizing single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to explore causal relationships between exposures and outcomes

[18, 19]. Given the random inheritance of alleles during gamete formation, genetic variants may serve as a means of controlling for reverse causation bias and confounding [20]. As a result, MR designs can be employed to address causal assumptions, with outcomes deemed comparable to those of randomized trials [21].

Therefore, we conducted a two-sample MR study utilizing single SNPs obtained from genome-wide association studies linked to exposure factor GERD as IVs in this study, in order to examine the causal impact of GERD on outcome factor cholecystitis risk, marking the first such attempt. And we found that GERD was positively associated with the risk of cholecystitis. These findings can serve as a fundamental basis for understanding the intricate interactions between GERD and cholecystitis, which can further provide new ideas for the prevention and treatment of cholecystitis in GERD patients.

Methods

Study design

MR is an epidemiological method that utilizes IVs which are highly linked with the exposures (e.g., GERD), such as SNPs, to establish causal relationships in statistical analyses [22]. Figure 1 presents a flowchart that provides a concise overview of the two-sample MR analysis employed in this study to investigate the causal associations between GERD and cholecystitis, utilizing genetic variants as IVs. Three key assumptions underlie MR analysis [23]: the IV must be strongly correlated with the exposure of interest, must not be associated with any confounders, and must exclusively influence outcomes through the exposure variable. Ethical approval was deemed unnecessary for the present study, which utilized aggregate-level genetic data sourced from publicly accessible repositories of extensive genome-wide association studies (GWASs).

Data source and IV selection

Publicly-available data were used for this study. Specifically, exposure data for GERD [24] were obtained from GWASs with larger sample sizes, comprising 602,604 individuals (N cases=129,080 cases; N control=473,524) of European ancestry, which were accessible through the IEU open GWAS project (<https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90000514/>). Additionally, the pooled statistics GWASs for cholecystitis (N cases=1,930; N control=359,264) were obtained from <https://gwas.mrcieu.ac.uk/datasets/ukb-d-K81/>. Table 1 provides a detailed overview of all GWASs that were included in this investigation.

Our study identified SNPs linked to GERD at a genome-wide significant level ($p < 5 \times 10^{-8}$), while also considering factors such as linkage disequilibrium (LD, $R^2 \leq 0.001$) and genetic clumping distance $< 10,000$ kb.

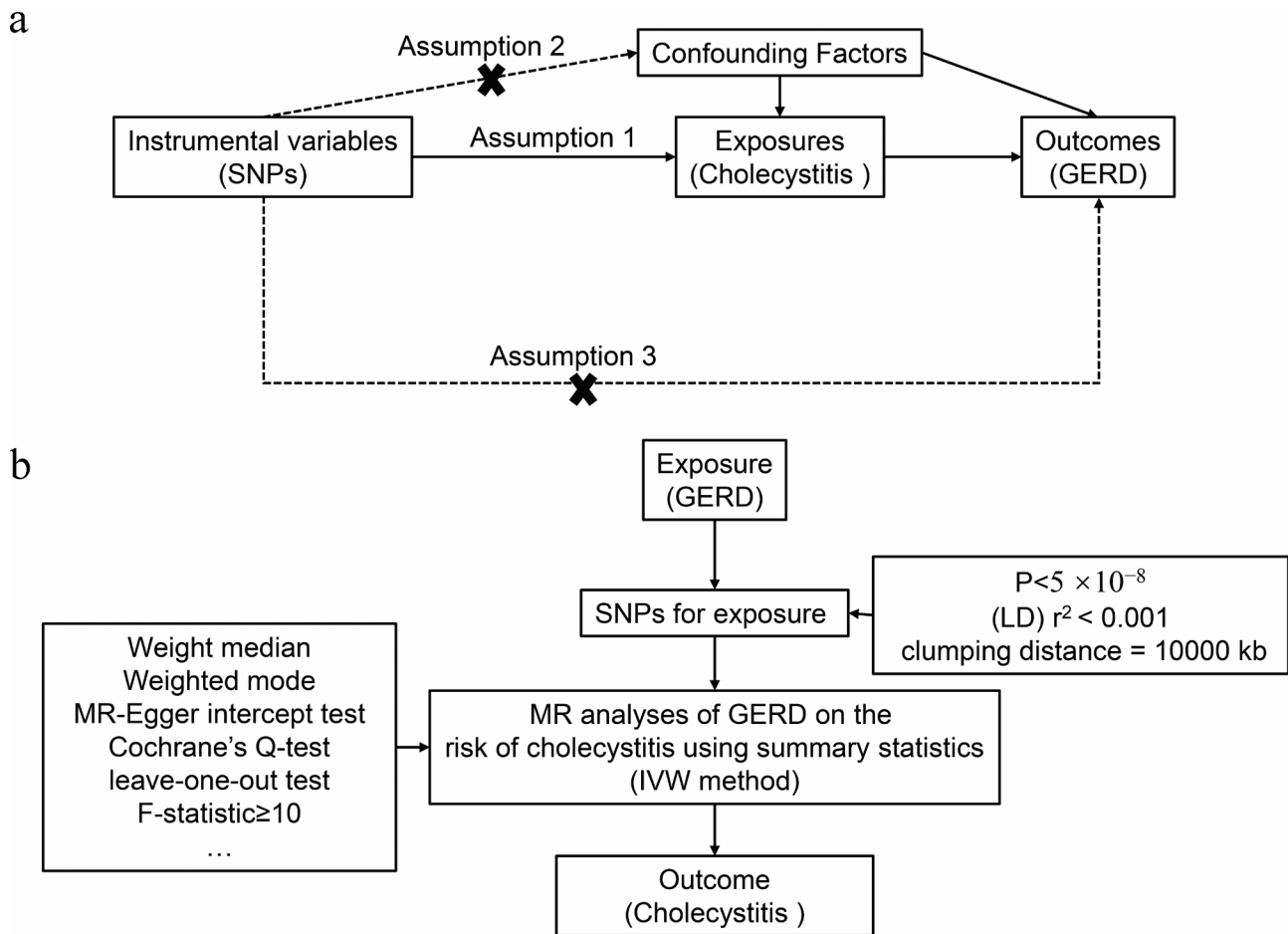


Fig. 1 Schematic representation of Mendelian randomization (MR) analysis. **(a-b)** Flow chart for the analytical assumptions **(a)** and how MR analysis was performed step-by-step **(b)**. The application of MR in this context relies on three fundamental assumptions: [1] Assumption 1, the genetic variants must exhibit associations with the exposures [2], Assumption 2, the genetic variants must not demonstrate associations with confounding factors, and [3] Assumption 3, the genetic variants must solely influence outcomes through the exposures, excluding alternative pathways. Abbreviations: MR, Mendelian randomization; SNP, single nucleotide polymorphism; LD, linkage disequilibrium; GERD, gastroesophageal reflux disease; IVW, inverse-variance weighted

Table 1 Details of studies and datasets included in the mendelian randomization

Exposure/Outcome	Sample Size	SNP Size	Year	Population	GWAS ID	First Author
GERD	602,604	2,320,781	2021	European	ebi-a-GCST90000514	Ong JS
Cholecystitis	361,194	10,491,778	2018	European	ukb-d-K81	Neale lab

Abbreviations: GERD, gastroesophageal reflux disease; SNP, single nucleotide polymorphisms; GWAS, genome-wide association study

If a specific exposure SNP did not exist in the outcome GWAS, a proxy SNP in linkage disequilibrium with the exposure SNP (minimum LD R^2 value of 0.8) was used. To avoid bias caused by weak proxies, the R^2 and F-statistics for each SNP were computed. The R^2 value denotes the fraction of variability in a risk factor accounted for by the IVs. The F-statistic, commonly employed as an indicator of the potency of the relationship between instruments and the exposure of interest, is deemed weak if it falls below a threshold of $F < 10$; such weak instruments are precluded from the MR analysis. The R^2 and F-statistics were derived using the following formulae [19]:

$$R^2 = 2 \times (1 - \text{EAF}) \times \text{EAF} \times \beta^2$$

$$F = \left(\frac{R^2}{1 - R^2} \right) \left(\frac{N - k - 1}{k} \right)$$

Where N represents sample size, β represents the genetic estimation of each SNP on the exposure, k represents the number of SNPs, and EAF refers to effect allele frequency.

MR statistical methods

Seventy-seven SNPs were utilized as IVs following the coordination of effect alleles (EAs) from GWAS in both

GERD and cholecystitis. Several MR analysis methods were employed to determine the causal relationship between GERD and cholecystitis, including the inverse-variance weighted (IVW), MR-Egger, weighted median, and weighted mode approaches. The random-effects model of IVW was the primary statistical method used in the MR analysis [25]. The IVW method, which combines Wald ratio estimates through inverse variance weighting, was employed to evaluate the causal effect of exposure on the outcomes. MR-Egger regression was used to address potential issues of the causal effects and the directional pleiotropy, which are robust to invalid IVs. Additionally, the weighted median method was employed to provide a consistent estimate of causality, even when up to 50% of the genetic IVs used were invalid [26]. The robustness of the significant findings was further tested by applying the weighted mode method, which accommodated more than 50% of the invalid IVs.

Sensitivity analysis

The potential pleiotropic effects of the instrumental SNPs were evaluated using MR-Egger regression. To assess heterogeneity among the various genetic variations, the Cochran's test and the I^2 test [27] were employed. Furthermore, a leave-one-out sensitivity analysis was conducted to verify the conformity of each SNP. Funnel plots were used to present the heterogeneity of the results, and asymmetric plots indicated the absence of heterogeneity.

Statistical analysis

Statistical analyses were conducted with R software version 4.2.1, utilizing the R-based package "TwoSampleMR (0.5.5)" for MR analysis. For the methods of MR Egger, weighted median, IVW, weighted model, Cochran's Q test, and I^2 test, the results with a P value of less than 0.05 were significant.

Results

Detail information on the IVs

This study incorporated 77 SNPs in GERD as IVs. To mitigate the risk of weak instrumental bias, SNPs with an F -statistic lower than 10 were also removed, and all these SNPs were significantly associated with GERD at the genome-wide level ($p < 5 \times 10^{-8}$). Additional file 1–2 provide detailed information on each SNP, including the EA and effect allele frequency (EAF), as well as

estimations of their associations with GERD and cholecystitis, including the beta, SE, and P values. The details of the SNPs we have covered in this article can be found in the <https://gwas.mrcieu.ac.uk/>.

Causal effect of GERD on cholecystitis

Table 2 presents the results of the IVW analysis, indicating an elevated risk of cholecystitis in patients with GERD (odds ratio [OR]=1.004; 95% confidence interval [95%CI] 1.003–1.005, $p=2.68 \times 10^{-9}$). Meanwhile, the estimates derived from the weighted median (OR=1.005; 95%CI 1.003–1.006; $P=2.35 \times 10^{-6}$) and weighted mode (OR=1.007; 95%CI 1.002–1.012; $p=0.01044$) aligned with the direction of the IVW estimates. However, the MR-Egger analysis (OR=1.005; 95%CI 0.998–1.013; $p=0.1841$) suggested no causal relationship between GERD and cholecystitis. These findings are further supported by the forest plot (Fig. 2) and scatter diagram (Fig. 3).

Sensitivity test

Subsequently, the Cochran's Q test did not detect the existence of heterogeneity in the causality of cholecystitis, and the I^2 values in our results showed low heterogeneity, indicating increased reliability of the MR estimates. Table 3 summarizes the results of the sensitivity analysis. In addition, there was no evidence that the result was affected by horizontal pleiotropy (MR-Egger regression intercept = -3.6×10^{-5} ; SE=0.00012; directionality $p=0.772$). Asymmetry in the funnel plot indicated directional horizontal pleiotropy; however, there was no evidence of asymmetry (Fig. 4). Moreover, the leave-one-out analysis results were stable when each SNP was discarded one by one (Fig. 5).

Discussion

Cholecystitis and GERD are prevalent pathological conditions that result in dyspepsia of the upper gastrointestinal tract. These diseases exhibit comparable clinical symptoms, including epigastric pain, heartburn, abdominal distension, and early satiety [12, 28, 29]. Consequently, a significant number of patients remain undiagnosed or misdiagnosed with stomach disease, and the causal relationship between GERD and cholecystitis remains uncertain. In this study, we conducted a two-sample MR analysis to evaluate the causal association

Table 2 MR estimates from each method of assessing the causal effect of GERD on the risk of cholecystitis

Method	nSNP	β	SE	P	OR	Low95%	Up95%
MR Egger	77	0.005102	0.003805	0.1841	1.005115	0.997647	1.012639
Weighted median	77	0.004497	0.000953	2.35E-06	1.004507	1.002633	1.006385
IVW	77	0.004011	0.000674	2.68E-09	1.004019	1.002693	1.005346
Weighted mode	77	0.006676	0.002542	0.01044	1.006698	1.001695	1.011727

Abbreviations: IVW, inverse variance weighted; SNP, single-nucleotide polymorphism; SE, standard error; OR, odds ratio

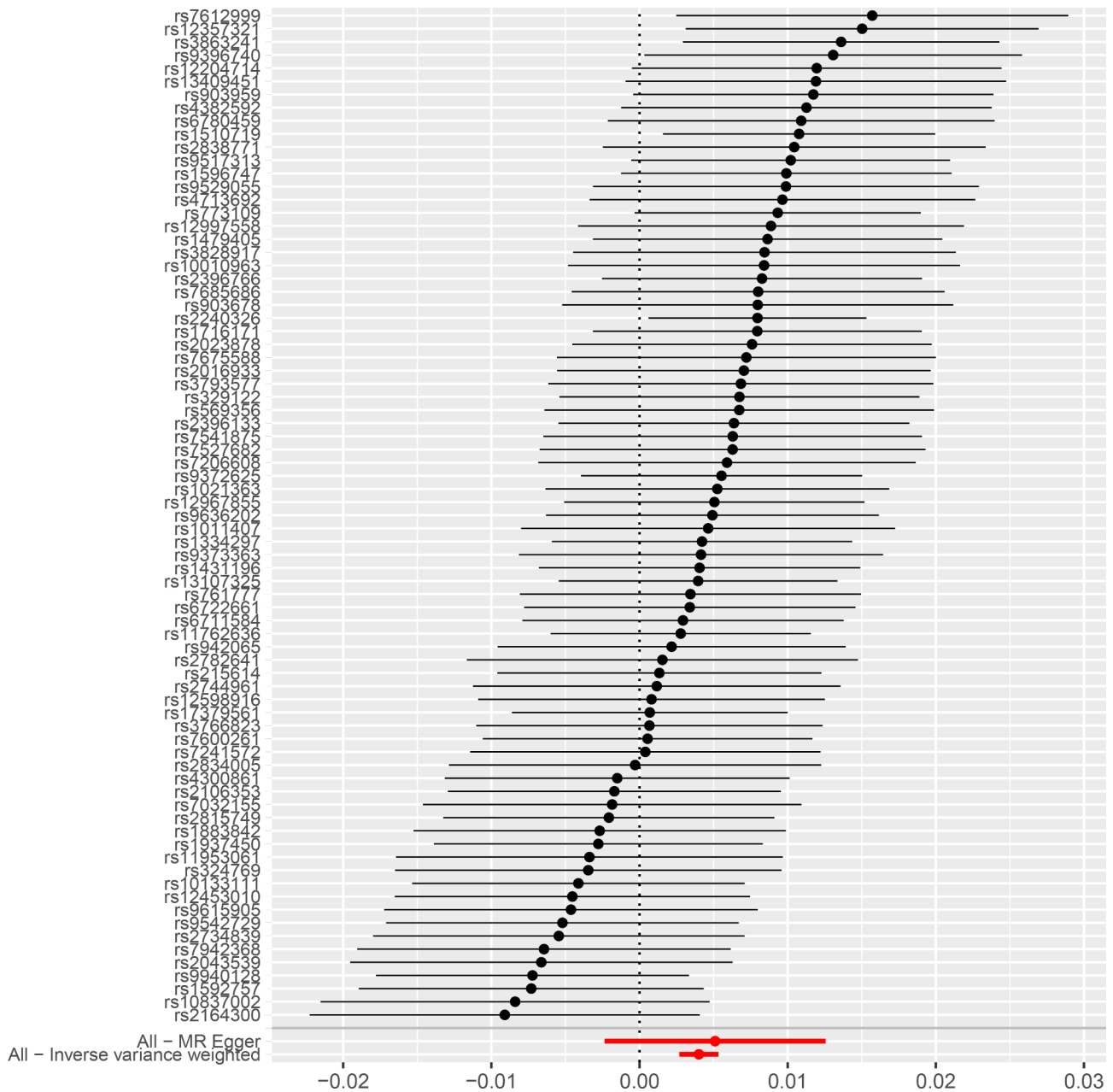


Fig. 2 Forest plot of the causal effects of SNPs associated with GERD on cholecystitis. The logarithmic odds ratio (OR) for cholecystitis per standard deviation (SD) increase in GERD is denoted by black dots. The combined causal estimate using all SNPs together as a single instrument is represented by red dots, generated via two different methods: the inverse variance weighted (IVW) method and MR-Egger. The MR results of the MR-Egger test and IVW method are indicative of the significance of red lines. The 95% confidence intervals of the estimate are represented by the horizontal line segments

between GERD and cholecystitis. Our analysis demonstrated that genetically-predicted GERD was significantly associated with an increased risk of cholecystitis.

We conducted the study utilizing four distinct estimation methods for MR analysis: the IVW, weighted mode, MR-Egger, and weighted median analyses. Our analysis, which employed large-scale GWASs data, demonstrated that genetically predicted GERD was significantly associated with an increased risk of cholecystitis. While the

results of the four MR analysis methods were inconsistent, the IVW, weighted mode, and weighted median analyses provided evidence of a causal link between GERD and cholecystitis. Unlike observational studies, MR analyses are less likely to be affected by confounding bias and reverse causality. Our investigation, being the first of its kind on a large scale, is less prone to bias and reverse causation, thereby enhancing our comprehension

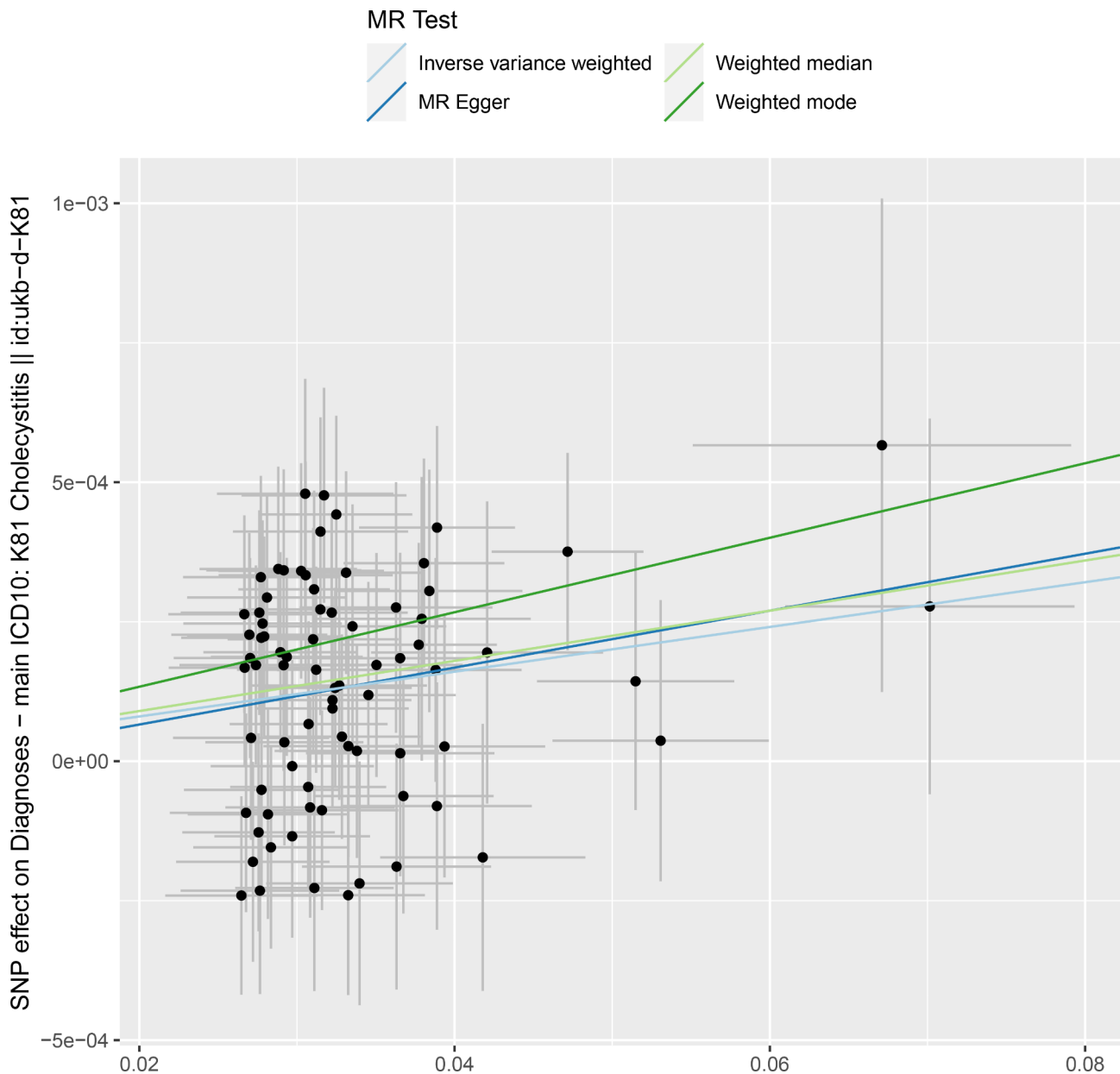


Fig. 3 Scatter plots of SNPs associated with GERD and cholecystitis. The causal associations for each Mendelian randomization (MR) method, namely the IVW method, weighted median estimator, weighted mode estimator, and MR-Egger, are represented by the slopes of each line. The plot illustrates the effect sizes of the SNP-cholecystitis association (y-axis, log (OR)) and the SNP-GERD association (x-axis, SD units) along with their respective 95% confidence intervals

Table 3 The analysis of the heterogeneities between SNPs

method	Q	Q_df	Q_P	I ²
MR Egger	75.79	75	0.4527	0.010424
IVW	75.88	76	0.4824	0.001581

Abbreviations: SNP, single-nucleotide polymorphism; IVW, inverse variance weighted; Q, Cochran’s Q test; df, degree of freedom; I² = (Q - df)/Q [27]

of the potential risk factors for Cholecystitis among patients with GERD.

The etiology of cholecystitis is complex and it is an independent risk factor for extrahepatic biliary tract

malignancies, including gallbladder cancer [30]. Given the unfavorable prognosis associated with gallbladder cancer, with an overall 5-year survival rate of less than 10% [31], proactive measures to prevent cholecystitis assume paramount importance in the prevention of gallbladder cancer. Numerous risk factors associated with cholecystitis in the general population have been identified, including prolonged fasting, rapid weight loss, total parenteral nutrition, and somatostatin (-analog) treatment, which significantly increase the risk of

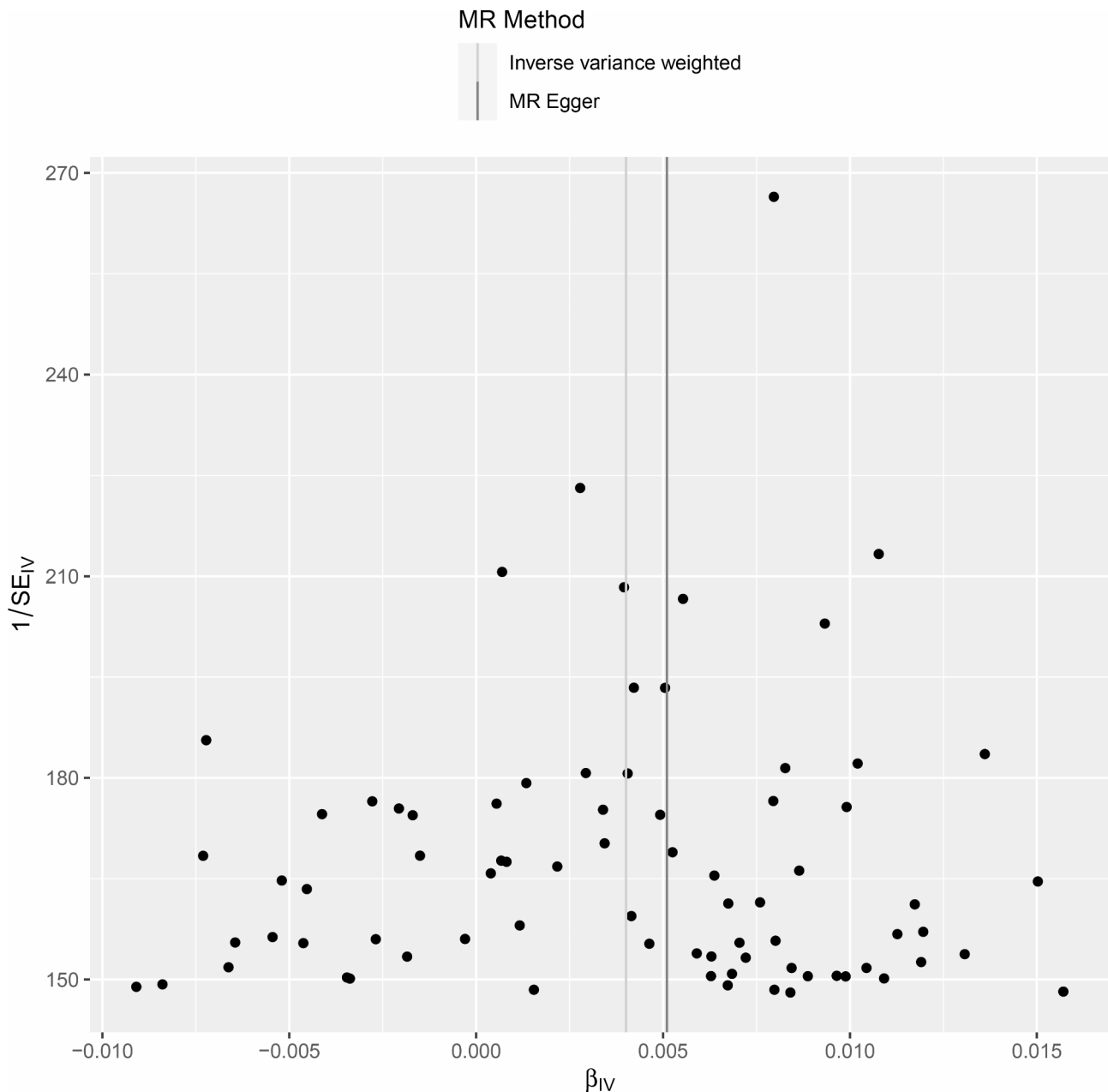


Fig. 4 Funnel plots from genetically predicted GERD on cholecystitis. The estimate the inverse-variance weighted estimate is depicted by the blue line, while the MR-Egger estimate is represented by the dark blue line

developing the condition [32]. Additionally, female sex, estrogen levels, and obesity have also been identified as risk factors [33–35]. In clinical practice, patients diagnosed with cholecystitis frequently present with varying degrees of belching, acid reflux, heartburn, and other reflux symptoms. Belching, acid reflux, and heartburn are also recognized as typical symptoms of GERD. Therefore, the correlation between GERD and cholecystitis has attracted considerable interest.

The roles of gastric acid and bile as direct causative factors in the pathogenesis of GERD have been widely

acknowledged. Typically, the esophagus maintains a state of equilibrium between its anti-reflux defense mechanism and the erosive effects of reflux substances on the esophageal mucosa. However, this balance is disrupted when the defense mechanisms of the esophagus are weakened, or when the harmful effects of reflux substances are intensified, ultimately resulting in the development of GERD. The principal pathophysiological mechanism underlying GERD is the compromised function of the anti-reflux barrier, primarily characterized by reduced pressure in the lower esophageal sphincter,

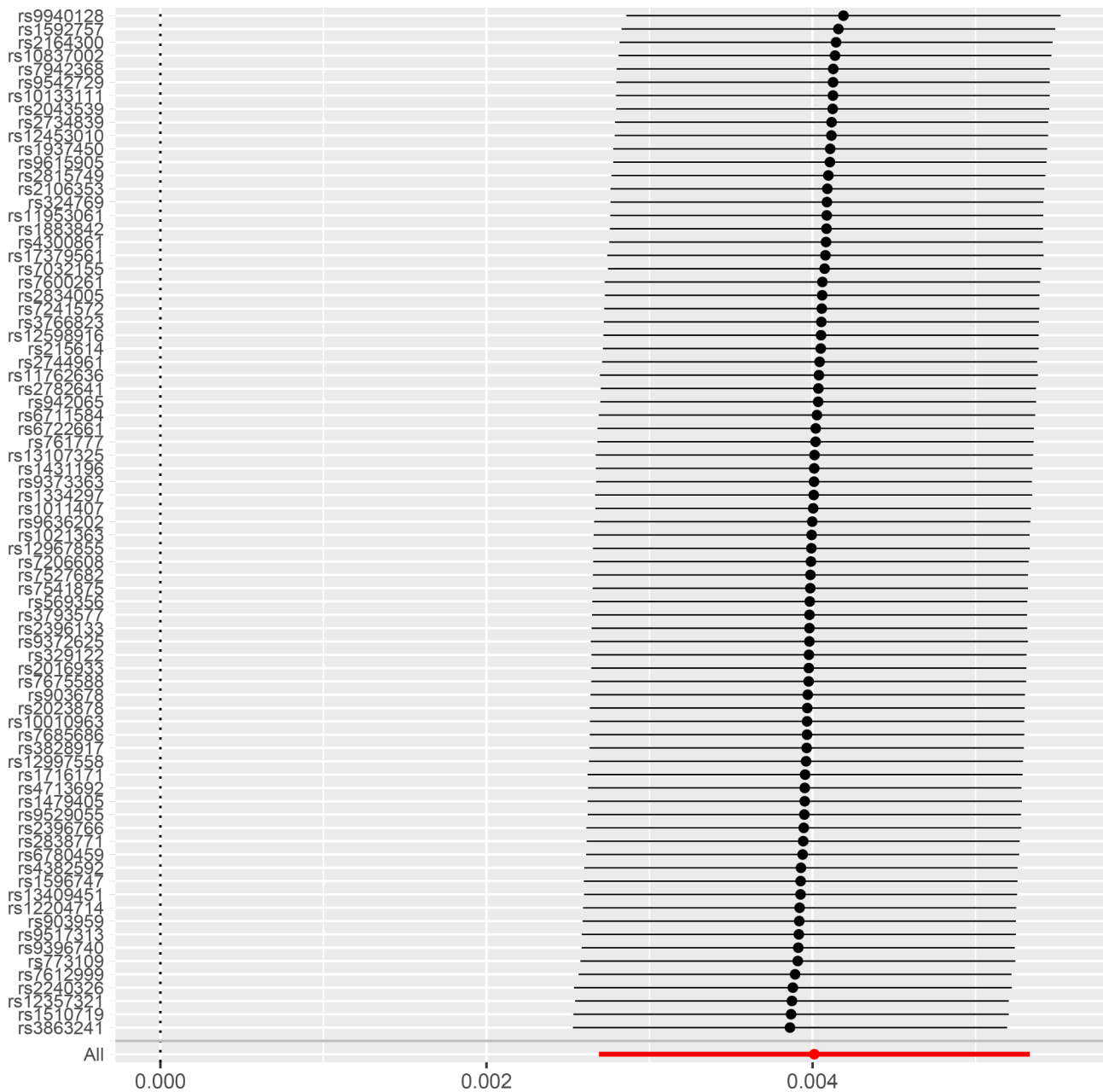


Fig. 5 Leave-one-out of SNPs associated with GERD and their risk of cholecystitis. Each black dot represents the outcome of the IVW MR method employed to evaluate the causal impact of GERD on cholecystitis. Conversely, each red dot illustrates the IVW estimate obtained by incorporating all SNPs. Notably, no SNPs were identified as having a significant influence on the relationship between GERD and cholecystitis in this leave-one-out sensitivity analysis

transient relaxation of the lower esophageal sphincter, dysfunction of the crural diaphragm, presence of hiatal hernia, and impaired esophageal clearance, which is mainly attributed to ineffective esophageal motility and multiple rapid swallowing [15]. GERD and cholecystitis are both common motility disorders, and the relationship between GERD and cholecystitis is intricate, involving complex mechanisms.

Research has demonstrated that compared to healthy individuals, patients with esophagitis and Barrett’s esophagus exhibit substantially elevated levels of bile acid, which is linked to acid reflux [36, 37]. Bile reflux-induced chemical damage has been identified as a significant contributor to esophageal mucosal rupture and refractory GERD. Abnormal gallbladder function and anatomical structure contribute to cholestasis, resulting in impaired gallbladder function in terms of bile concentration and

biliary pressure regulation. This, in turn, can accelerate bile enterohepatic circulation, elevate bile acid content, and ultimately compromise the regulatory function of the sphincter of Oddi, leading to bile reflux into the stomach [38]. Stimulation of mucosal receptors at the distal end of the esophagus by GERD can expedite the vagus nerve reflex, leading to anomalous peristalsis of the digestive tract [39]. The motor function of the gastroesophageal and biliary tract systems is regulated by nervous and humoral factors, among which the enteric nervous system (ENS), which is mainly composed of peptitineural nerves, plays the most important role. The ENS-interstitial cells of Cajal (ICC)-smooth muscle cells (SMC) network structure is the basic functional unit of gastrointestinal motility [40–43]. Therefore, GERD and cholecystitis are closely related to vagus nerve abnormalities and ICC abnormalities. This may exacerbate cholestasis, resulting in the onset of cholecystitis, accompanied by intractable dyspepsia. Patients with cholecystitis are prone to bile reflux, and the main damage caused by bile reflux to the esophageal mucosa is bile acids. When the concentration of bile acids exceeds the physiological level or the action time is prolonged, the intracellular bile acid concentration is too high, which destroys the intracellular membrane system and leads to cell necrosis, while the stimulation of bile salts can cause the expression of oxidative stress-related genes, induce DNA damage, and eventually lead to mucosal erosion and ulceration [44]. From the summary of clinical practice experience, the application of ursodeoxycholic acid can be used to treat GERD [45]. Bile reflux is present in GERD, and esophageal inflammation becomes more severe as the incidence of bile reflux increases. High concentrations of bile, deoxycholic acid, and trypsin can reduce the expression of cadherin, an interepithelial tight junction protein, and disrupt the esophageal epithelial barrier [46]. Treatment of GERD with ursodeoxycholic acid in combination with PPIs and/or prokinetic agents is associated with a higher rate of symptom remission [47]. Ursodeoxycholic acid has been reported to be effective in reducing the frequency and duration of reflux and significantly alleviating heartburn and acid reflux [48]. In addition, cholecystitis can be treated with gastrointestinal motility drugs, and Dhiman et al. [49] found that cisapride can inhibit stone formation. By promoting the movement of the gallbladder and intestines, cisapride enhances the intestinal and hepatic circulation, normalizes the lipid composition of bile, increases the secretion of bile salts, prolongs the nucleation time, and reduces the concentration of cholesterol in bile [50, 51]. There may be a positive synergistic effect between acid reflux and bile reflux, and in-depth study of the relationship between GERD and cholecystitis is of great value for the diagnosis and treatment of clinical diseases. In this study, the causal relationship

between GERD and cholecystitis was explored from the perspective of genetics, and a number of SNPs of great significance were screened. Therefore, GERD should be considered as a risk factor for cholecystitis in clinical practice, and early intervention in GERD may reduce the avoidance of gallbladder resection. Understanding the underlying mechanisms may be valuable in preventing and treating cholecystitis symptoms in patients with GERD, therefore, further research should be conducted to better elucidate the mechanisms, and intervention targets can be studied through the relevant SNPs that we have screened.

MR was employed to address the inherent limitations of observational studies, thereby reducing the likelihood of confounding or inherent biases [52]. One of the fundamental assumptions of MR is that the genetic variants utilized as instruments do not affect the outcome other than via the exposure of interest [53]. The incorporation of pleiotropic variation in the MR analysis leads to distorted causal effect estimates and a higher likelihood of type I errors when testing of causal hypotheses [54]. To identify any potential imbalances in pleiotropy, the weighted median approach was used to generate reliable estimates in instances where over 50% of the weight was derived from valid IVs [55]. The MR-Egger regression method was used to produce estimates after accounting for horizontal pleiotropy. In contrast to the outcomes obtained from the other three methods, the MR-Egger approach resulted in reduced in precision and statistical power. However, our weighted median estimator findings aligned with the IVW estimator, thereby offering supplementary support for a causal association. The present MR study provides compelling evidence that the mechanisms underlying the effects of GERD on cholecystitis risk are noteworthy. Further investigations are warranted to gain a more comprehensive understanding of these mechanisms. However, we continue to emphasize the need for independent MR studies, large prospective trials, and basic experiments in relevant laboratories to validate our findings using more accurate population data on cholecystitis and GERD.

However, this study had several limitations. First, the reliance on self-reported GERD diagnosis may have affected the reliability of the MR results. The lack of a detailed classification of GERD in the current GWAS study limits our ability to investigate the causal relationship between GERD and cholecystitis. To address this issue, future investigations should use GWAS data for GERD diagnosis based solely on the ICD criteria to validate the findings presented herein. In addition, due to the lack of sufficient IVs for GERD subtypes, the inverse causal relationship between GERD subtypes and GM needs to be further explored in the future. Second, the summary GWAS data for GERD and cholecystitis

were obtained exclusively from individuals of European descent, thereby limiting the generalizability of our findings to the broader population. Considering the potential influence of race and selection bias on causality, additional MR studies involving diverse populations are warranted. Furthermore, genetic variants may have a negligible impact on a given exposure (GERD), because they may account for only a small proportion of the variance. Therefore, this study may have been underpowered in terms of detection of such associations. Third, two-sample MR studies may involve over-identification, leading to an overestimation of the association between SNP and exposure. Additionally, the causal effects of GERD on cholecystitis appeared modest, indicating a relatively low risk of cholecystitis as a secondary outcome of GERD. The absence of pleiotropy in the modest MR estimates provides reassurance of the robustness of the MR estimates, nevertheless, our understanding of the biological functions of genetic tools is still evolving, which introduces the potential risk of violating the assumptions of independence and exclusion restrictions of MR, especially with regard to pleiotropy. Lastly, while this study has identified SNPs that have a causal effect of GERD on the risk of cholecystitis, these findings are primarily based on statistical analyses. Experimental research is required to elucidate the exact roles of these SNPs in the pathogenesis of cholecystitis and to validate our results further. Notably, this study is the first to investigate of the causal relationship between GERD and cholecystitis.

Conclusions

In summary, we found that genetically predicted GERD is causally associated with a higher risk of cholecystitis from the general population. GERD can stimulate the mucosal receptors distal to the esophagus and accelerate the vagus nerve reflex to cause abnormal peristalsis of the digestive tract, thereby aggravating cholestasis, and cholecystitis with intractable dyspepsia symptoms may occur. There may be a positive synergistic effect between acid reflux and bile reflux, and in-depth study of the relationship between the two is of great value for the diagnosis and treatment of clinical diseases. Clinicians should pay more attention to the development of cholecystitis in patients with GERD. The pathophysiological mechanism of cross-talk between GERD and cholecystitis needs to be further studied.

Abbreviations

GERD	Gastroesophageal reflux disease
SE	Standard error
CI	Confidence interval
GWAS	Genome-wide association study
IV	Instrumental variable
IVW	Inverse-variance weighted
LD	Linkage disequilibrium
MR	Mendelian randomization

MR-PRESSO	MR pleiotropy residual sum and outlier
OR	Odds ratio
SNP	Single nucleotide polymorphism

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12876-024-03390-w>.

Additional File 1: Instrument variables of the causal effect of GERD on cholecystitis in MR analysis (Description: Instrument variables of the causal effect of GERD on cholecystitis in MR analysis)

Additional File 2: Instrumental variables (IVs) used in MR analysis of the association between GER and Cholecystitis among European populations (Description: Instrumental variables (IVs) used in MR analysis of the association between GER and Cholecystitis among European populations)

Additional File 3: STROBE-MR-checklist

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Author contributions

CW: conceptualization, data curation, writing of the original draft, methodology, formal analysis. JW: investigation, data curation, and formal analysis. MF: methodology, writing, review and editing. BJF: conceptualization, methodology, writing – review, and editing. All the authors have read and approved the final version of this manuscript.

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Data availability

The datasets utilized in this study, namely the GWAS for GERD and cholecystitis, were obtained from publicly accessible databases of large-scale genome-wide association studies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare no competing interests.

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