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Original Article

Effects of gut microbiota and metabolites on pancreatitis: a 2-sample Mendelian randomization study

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ABSTRACT

Background: Acute pancreatitis (AP) and chronic pancreatitis (CP) have high incidences and poor prognoses. The early screening of at-risk populations still awaits further study. The limitation was mainly based on observational studies, with limited sample size and the presence of confounding factors. This study used a 2-sample Mendelian randomization (MR) analysis based on publicly available data from genome-wide association studies to reveal the causal effect of gut microbiota and metabolites on pancreatitis.

Methods: This study collected summary statistics on gut microbiota, metabolites, AP, and CP. A 2-sample MR analysis was performed using MR-Egger, inverse variance-weighted, MR Pleiotropy RESidual Sum and Outlier, maximum likelihood, and weighted median.

Results: The 2-sample MR showed that only *Eubacterium coprostanoligenes* was an independent protective factor for AP among all gut microbiota, and the other microbiota were not significant for pancreatitis. Unsaturated fatty acids in metabolites are protective factors for both AP (odds ratio [OR], 0.730; 95% CI, 0.593–0.899; P = .003) and CP (OR, 0.660; 95% CI, 0.457–0.916; P = .013). Furthermore, carnitine was a protective factor CP, and glucose was an independent risk factor for CP.

Conclusion: This study provides potential evidence of the causal role of gut microbiota and metabolites on pancreatitis, which may be conducive for designing microbiome and metabolite interventions on AP or CP in the future.

Introduction

Pancreatitis is a class of diseases involving inflammatory response leading to pancreatic tissue damage and includes acute pancreatitis (AP) and chronic pancreatitis (CP) [1]. AP is characterized by excessive activation of trypsin and autodigestion of the pancreas, which often results in dysfunction of the pancreas and important organs and systems of the body [2,3]. As the most common acute gastrointestinal disease requiring admission, AP has an annual incidence of 34 cases per 100,000 people in the general population annually (95% CI, 23–49) [4,5]. Approximately 20% of patients develop moderate AP or severe AP (SAP), and the mortality rate of these patients ranges from 20% to 40% [6]. CP is a chronic progressive inflammatory reaction that causes irreversible damage to pancreatic tissue and/or pancreatic function, leading to intrapancreatic and exocrine pancreatic insufficiency [7]. Although mortality is less than in SAP, the potential cancer predisposition of CP imposes a significant burden on patients.

The treatment of pancreatitis with multidisciplinary collaboration has been greatly advanced, but early screening of at-risk populations still awaits further study [8,9]. Among the current factors, the influence of gut microbiota and metabolites on pancreatitis has attracted considerable attention [10]. The gut microbiota is the most important active part of the gut microecosystem. In addition to the availability of synthetically essential vitamins and amino acids for absorption by the human body, they can participate in the regulation of host physiologic homeostasis through the production of endocrine-related hormones [11–13]. There are more than 1500 species of

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human gut microbiota, which are distributed differently in the gut of people with different eating habits [14]. The microecology of the gut microbiota and metabolites has an important influence on the body. In recent years, many studies have reported that specific gut microbiota, including *Escherichia-Shigella, Phascolarctobacterium, Candidatus Saccharimonas*, and *Bifidobacterium* [15], play important roles in the pathogenesis of pancreatitis. A meta-analysis of 11 trial studies with 930 patients suggested a lower risk of organ failure and shorter length of hospital stay in patients with AP after probiotic treatment [16]. In addition, microbiota analysis of 51 patients with CP identified CP to be associated with significant gut microbiota dysbiosis [17]. Currently, some scholars tried to explore the relationship between gut microbiota/metabolites and pancreatitis by regulating gut microbiota/metabolites in experimental animals. The evidence from the abovementioned studies of gut microbiota/metabolites in pancreatitis remains controversial because of the species differences among experimental animals. Moreover, this association primarily relied on observational studies, which had small sample sizes and were influenced by various confounding factors.

The Mendelian randomization (MR) has become an efficient method for identifying causal relationships between risk factors and diseases using genetic variants as instrumental variables (IVs) [18]. In MR, genetic variants are typically less affected by nondifferential measurement errors or confounding variables. Furthermore, MR satisfies the conditions essential for establishing causal inferences [19]. Here, we conducted a 2-sample MR analysis using publicly available data from genome-wide association studies (GWASs) to reveal the causal effects of gut microbiota and their metabolites on pancreatitis.

Materials and methods

Study design

Here, we attempted to determine the causality of gut microbiota and metabolites with pancreatitis based on a 2-sample MR approach [20]. A schematic diagram of causal inference in this study is shown in Fig. 1.

Data collection for gut microbiota, metabolites, and pancreatitis

It is important to emphasize that the exposure data used in our study originated from Kurilshikov et al. [21], which included 16S ribosomal RNA (rRNA) gene sequencing profiles and genotyping data from 18,340 participants across 24 cohorts in the United States, Canada, Israel, South Korea, Germany, Denmark, the Netherlands, Belgium, Sweden, Finland, and the United Kingdom (UK). This microbial analysis encompasses 211 taxonomic units (composed of 131 genera, 35 families, 20 orders, 16 classes, and 9 phyla). In this research, the MiBioGen consortium conducted a large-scale, multiethnic, genome-wide meta-analysis of the associations between human autosomal genetic variation and the gut microbiome. Furthermore, biologic interpretations of the GWAS results were performed using gene set enrichment analysis, phenome-wide association studies, and MR methods. Pooled data on metabolites (amino acid, carbohydrate, cofactors and vitamin, energy, lipid, nucleotide, peptide, and xenobiotic metabolism) were obtained from GWASs, including summary data on the human metabolome of 33,244 European participants Table. Considering that GWAS loci for gut metabolites rarely reached genome-wide significance, single-nucleotide polymorphisms (SNPs) with suggestive genome-wide significance thresholds were selected for IVS ($P < 5.0 \times 10^{-8}$) in our study.

Table
Description of gut microbiota, metabolites, and neuropsychiatric disorders.

Traits	Author	Case	Control	Sample size	Year
Expose					
Gut microbiota [21]	Kurilshikov	NA	NA	14,306	2021
Metabolites [22]	Shin	NA	NA	7822	2014
Metabolites [23]	Roederer	NA	NA	497	2015
Metabolites [24]	Kettunen	NA	NA	24,925	2016
Pancreatitis					
Acute pancreatitis [25]	NA	1215	461,795	463,010	2018
Chronic pancreatitis [26]	Kurki	1737	195,144	196,881	2021

NA, not available.

Leading SNPs as genetic IVs were from the current largest available GWAS meta-analysis on AP and CP among individuals with European ancestry, performed by the UK Biobank and the Finn Consortium. The identification of AP or CP in the database would at least meet one of the following requirements: discharge record, pathologic diagnosis, death registration, or doctor's diagnosis.

Selection of IVs

First, in the GWAS of gut microbiota and metabolites, SNPs were selected using Plink software conditional on $P < 5 \times 10^{-8}$, genetic distance of 10,000 kb, and linkage disequilibrium parameter (r^2) of < 0.001. Second, we analyzed these SNPs using Catalog (https://www.ebi.ac.uk/gwas/) and PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/). Some SNPs were excluded from the study if they were associated with known confounding factors (dyslipidemia and biliary tract infection). Third, we calculated the F

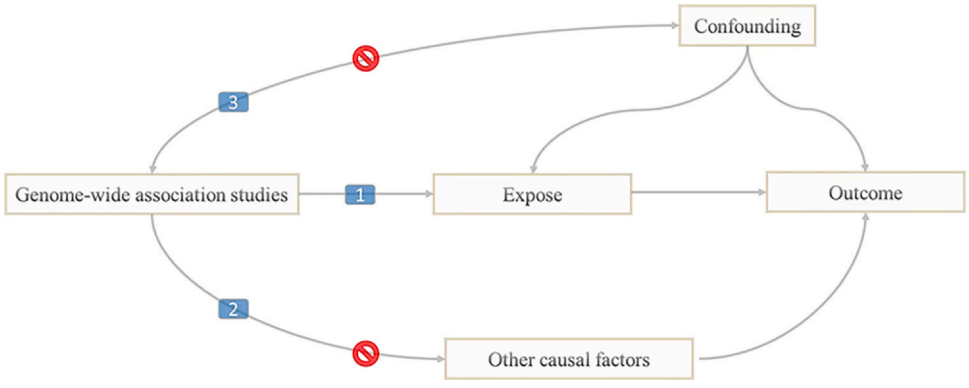

Figure 1. The basic principles of Mendelian randomization (directed acyclic graphs). The following conditions are required to establish that the target exposure is causally related to the outcome: (1) genetic variants are associated with exposure, (2) the association between genetic variant and outcome must be confirmed by exposure, and (3) genetic variants are independent of any confounding factors. The connecting line of the red symbol must be absent for the genetic variant to be a valid instrumental variable.

statistics for each SNP to determine the weak IV bias in this study. More specifically, we excluded F statistics of SNP of < 12.13 to eliminate the influence of weak IV bias on our results.

Sensitive analysis

We assessed the effect of variants on the association between the exposure and the outcome variable using leave-one-out sensitivity analysis, and the essence of this method was to delete a single SNP every time. In addition, when the intercept term was statistically significant in MR analysis, the MR-Egger regression test was used to estimate the horizontal multiplicity. Finally, the detection of heterogeneity was achieved by calculating the Cochran Q statistic [27].

Statistical analysis

This study focused primarily on the inverse variance-weighted (IVW) approach. The IVW fixed effect model was used when there was a lack of potential horizontal multiple heterogeneity, and the random effect model was used in the presence of heterogeneity [28].

In addition, we performed estimation using MR-Egger, weighted median, maximum likelihood, and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) for sensitivity analysis of IVW results to further validate the reliability of the IVW results [29–31]. The essence of the maximum likelihood method was to evaluate the causal effect by directly maximizing the likelihood given the SNP exposure and SNP outcome effects. It was assumed that there was a linear relationship between the exposure and the results. The MR-Egger method is characterized by weighted linear regression of exposure results based on the Individualized, Networked, Situated, Integrated, and Dynamic Environment hypothesis, but the results are vulnerable to IV. In addition, the ability to detect causal effects can be significantly improved using the weighted median method. In the current study, $P < .05$ indicated statistical significance. All statistical analyses were performed using R (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria) with the 2-sample MR and MR-PRESSO packages.

Results

IVs selection

Of the data embodied in this study, a total of 9,853,596 independent genome-wide significant SNPs associated with gut bacterial traits and metabolites were included to construct IVs. The *F* values were all > 12.13, indicating that the study was not sensitive to weak IVs. In the MR analysis of gut microbiota and AP, the number of SNPs with positive results was 1, whereas gut microbiota with CP had no positive results.

Gut microbiota for AP and CP

There were several gut microbiotas strongly associated with the risk of AP (Fig. 2). For instance, the relative risk (RR) of AP decreased by 59.8% for each unit increase in *Eubacterium coprostanoligenes* (odds ratio [OR], 0.402; 95% CI, 0.167–0.970; $P = .042$). There were no significant differences between *Oxalobacteraceae* (OR, 0.718; 95% CI, 0.447–1.154; $P = .171$), *Intestinibacter* (OR, 1.739; 95% CI, 0.831–3.639; $P = .142$), *Ruminococcus* (OR, 2.072; 95% C I, 0.845–5.081; $P = .111$), and *Tyzzerella3* (OR, 1.397; 95% CI, 0.894–2.183; $P = .142$) and AP from IVW results (Fig. 2).

Here, the effects of 5 gut microbiota on CP were analyzed, including *Oxalobacteraceae* (OR, 0.607; 95% CI, 0.325–1.130; $P = .116$), *Peptostreptococcaceae* (OR, 0.368; 95% CI, 0.122–1.112; $P = .076$), *Erysipelatoclostridium* (OR, 0.453; 95% CI, 0.201–1.021; $P = .056$), *Faecalibacterium* (OR, 2.633; 95% CI, 0.912–7.601; $P = .735$), and *Romboutsia* (OR, 0.371; 95% CI, 0.124–1.110; $P = .076$), and no significant differences were found (Fig. 3).

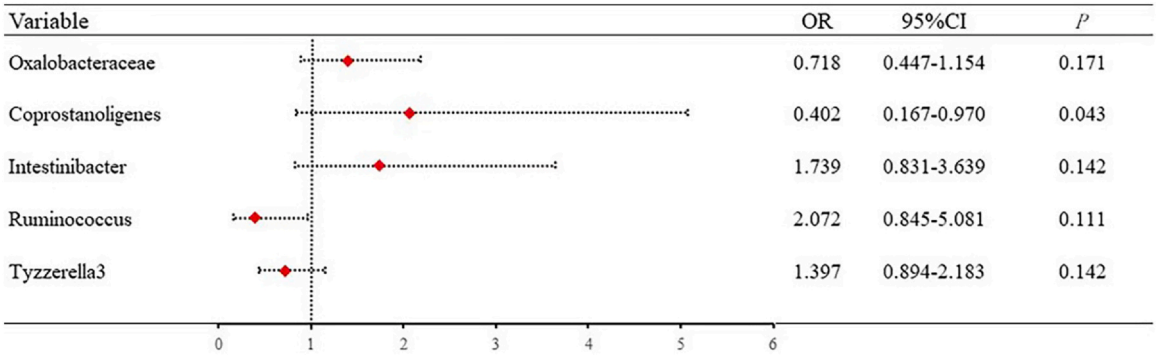

Figure 2. Forest plot showing the causal effect of gut microbiota on the risk of acute pancreatitis. OR, odds ratio.

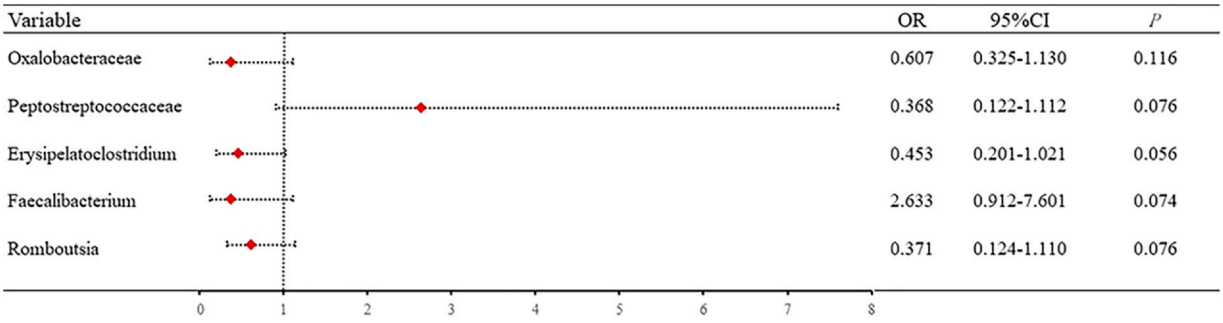

Figure 3. Forest plot showing the causal effect of gut microbiota on the risk of chronic pancreatitis. OR, odds ratio.

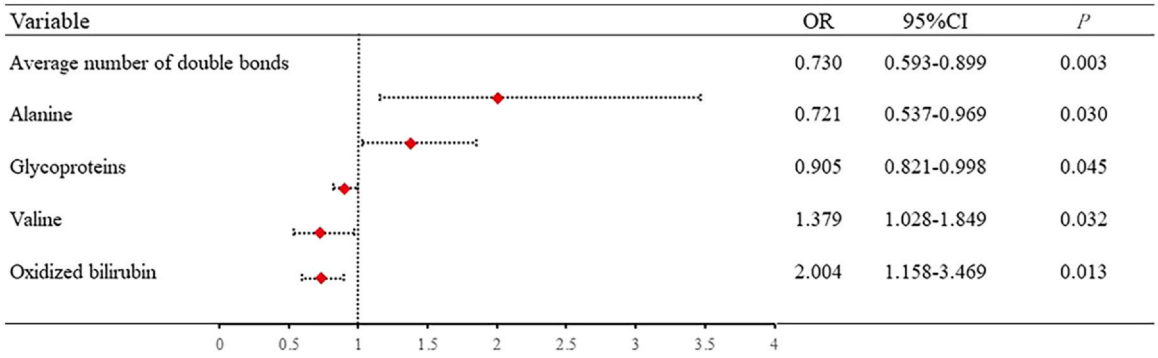

Figure 4. Forest plot showing the causal effect of metabolites on the risk of acute pancreatitis. OR, odds ratio.

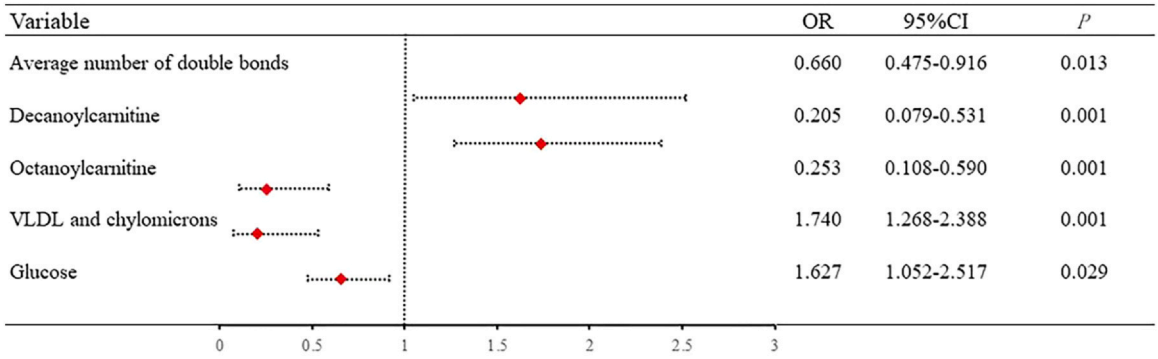

Figure 5. Forest plot showing the causal effect of metabolites on the risk of chronic pancreatitis. OR, odds ratio.

Metabolites for AP and CP

We observed that some gut microbial metabolites were strongly associated with AP using the IVW approach (Fig. 4). For the protective factors, the most significant is the average number of double bonds in a fatty acid chain. When the average number of double bonds increases by 1 unit, the RR of AP decreases by 27% (OR, 0.730; 95% CI, 0.593–0.899; $P = .003$). In addition to the effects of lipids, the RR of AP decreased by 27.9% for every unit increase in alanine (OR, 0.721; 95% CI, 0.537–0.969; $P = .030$). Furthermore, glycoproteins are protective factors for AP, and each unit increase leads to a 9.5% reduction in the RR of AP (OR, 0.905; 95% CI, 0.821–0.998; $P = .045$). In addition, we found suggestive evidence of risk factors for AP. For every unit increase in valine, the RR of AP increased by 37.9% (OR, 1.379; 95% CI, 1.028–1.849; $P = .032$). Meanwhile, oxidized bilirubin was a risk factor, and each unit increase will double the AP RR (OR, 2.000; 95% CI, 1.158–3.469; $P = .013$).

Similarly, some gut microbial metabolites were strongly associated with CP in the IVW approach (Fig. 5). Among the relevant factors of CP, the most significant factor is the average number of double bonds in a fatty acid chain. In addition, the protective effect of the average number of double bonds in a fatty acid chain was significant. When the average number of double bonds increases by 1 unit, the RR of CP decreases by 34.0% (OR, 0.660; 95% CI, 0.457–0.916; $P = .013$). Moreover, carnitine metabolites related to fat metabolism are important protective for CP, and 2 carnitines with protective effects were confirmed in this study: decanoylcarnitine and octanoylcarnitine. For every unit increase in decanoylcarnitine, the RR of CP decreased by 79.5% (OR, 0.205; 95% CI, 0.079–0.531; $P = .001$). The RR of AP decreased by 74.7% for every unit increase in octanoylcarnitine (OR, 0.253; 95% CI, 0.108–0.590; $P = .001$). It is noteworthy that very low-density lipoprotein and chylomicrons were significant risk factors for CP (OR, 1.740; 95% CI, 1.268–2.388; $P = .001$). Most importantly, glucose was a significant risk factor for CP, with each unit elevation resulting in a 34.6% higher RR for CP (OR, 1.346; 95% CI, 1.033–0.756, $P = .028$).

Sensitive analysis

Significant statistical results were detected in this study, and further sensitivity analysis yielded similar results. There were no directional pleiotropies. However, there were potential heterogeneities in the analysis results. To perform further analyses, we replaced with random effect model on heterogeneous results and found consistent results. Importantly, the leave-one-out analysis revealed no significant effect of IVs on outcomes. Funnel plots indicated a point symmetrical distribution representing the causal association effect when individual SNPs were used as IVs, indicating that the causal association was unlikely to be affected by underlying biases. MR-PRESSO results showed that there was no outlier in our MR analysis (all $P > .05$).

Discussion

This is the first MR analysis to examine the genetically predictive ability of gut microbiota and metabolites in pancreatitis (AP and CP). Our results indicated that there were parts of the gut microbiota and metabolites to promote or prevent pancreatitis. The most interesting finding was that metabolites rather than gut microbiota play the most important role in the development of pancreatitis. This combination of findings provides powerful support for the conceptual premise that early diagnosis and intervention for pancreatitis are based on metabolite screening.

It is essential to identify potential deviations that violate MR assumptions and evaluate the consistency of the results with the observational literature in the application of MR research to conclude causality. Consequently, we compared the results of previous observation studies to evaluate the reliability of MR results. A clinical

study that enrolled 165 adult patients found that gut microbiota disturbance directly contributes to the development of AP [32]. In our study, *Eubacterium* may be a protective factor for AP. These results reflect those of Yu et al. [33], who also found that *Eubacterium* was the most decreased species in SAP. In the human gut, *Eubacterium* can regulate the homeostasis of microbial metabolism, inhibit pathogens, and exert anti-inflammatory effects in the gut [34]. Although no significant influence of gut flora was identified in CP, *Eubacterium* should also be cautioned for recurrent episodes of AP leading to CP.

Furthermore, a recently published prospective study identified key bacteria predictive of SAP and revealed a significant association between increased short-chain fatty acids (SCFAs) and SAP [35]. Among the 16 key bacteria identified, many belong to the Clostridia class. In our study, *Intestinibacter* (OR, 1.739; 95% CI, 0.831–3.639; $P = .142$), *Ruminococcus* (OR, 2.072; 95% CI, 0.845–5.081; $P = .111$), and *Tyzzerella3* (OR, 1.397; 95% CI, 0.894–2.183; $P = .142$) were also classified within Clostridia. Although these 3 bacterial taxa did not show statistically significant differences in our analysis, they were considered potential risk factors. In addition, this study underscored the role of SCFAs as significant risk factors, noting that SCFAs are predominantly saturated fatty acids, further supporting our findings that unsaturated fatty acids have a protective effect against AP.

The metabolites of pancreatitis are an area of research with great potential, and lipids have received the most attention. The protective effect of unsaturated fatty acids in inflammatory diseases has been observed, and a meta-analysis of 49 randomized controlled trials (RCTs) showed that unsaturated fatty acid emulsions significantly reduced inflammatory indicators in hospitalized patients [36]. In a meta-analysis involving 8 RCTs with a total of 364 patients with AP, the treatment of unsaturated fatty acid could be beneficial for decreasing mortality, infectious complications, and length of hospital stay [37]. In this research, we observed a potential association between genetically increased unsaturated fatty acids and a lower risk of AP, and the underlying mechanism may be related to the regulation of Toll-like receptor 4 downstream signaling [38]. In addition, severe hypertriglyceridemia (> 500 mg/dL) is a risk factor for pancreatitis, and unsaturated fatty acids may contribute to improving hyperlipidemia by inhibition of diacylglycerol acyltransferase, increased plasma lipoprotein lipase activity, decreased hepatic lipogenesis, and increased hepatic β-oxidation [39]. In summary, these studies support the protective role of unsaturated fatty acids against pancreatitis.

Further studies take certain carnitine metabolites into account, because carnitine plays important roles in the relationship between lipid class and inflammation. A clinical trial involving 50 patients found that the administration of carnitine significantly improved lipid metabolism and attenuated inflammation [40]. Further animal tests found a significant decrease in pancreatic tissue oxidation and indicators of inflammation in rats administered carnitine [41]. In general, we found that unsaturated fatty acids can reduce the incidence of AP and CP. It suggested that adjusting the dietary structure of the risk population and reducing saturated fatty acid intake could help reduce the incidence of pancreatitis, thereby reducing disability and mortality.

Amino acids are the component of gut microbial metabolites, and some amino acids play an important role in pancreatitis. A study based on metabolomic analysis of pancreatic tissue from Wistar rats with AP found increased levels of leucine, isoleucine, and valine but decreased levels of glycine and alanine [42]. The results of our MR analysis were consistent with the abovementioned studies. Valine was a risk factor for AP, whereas alanine was a protective factor. A valine tracing study found that elevated valine levels predicted impaired local circulation, tissue damage, and diminished protein synthesis in the pancreas [43]. Alanine may play a protective role by inhibiting pancreatic secretory proteases by affecting the membrane potential of pancreatic acinar cells [44]. A study that included 35 male patients with CP and 21 healthy male patients found that serum concentrations of glutamine, histidine, tyrosine, proline, tryptophan, and threonine were significantly decreased in patients with CP. However, there were no potential amino acids affecting CP in our study, and the role of amino acids in CP remained to be further explored.

It is well recognized that pancreatitis impairs exocrine function mainly by affecting pancreatic acinar cells. However, the effect of pancreatitis on pancreatic endocrine function has not been clarified, specifically the causal relationship between glycemic control and pancreatitis is not clear [45]. Of note, 1 study found that the positive rate of glucose breath test in patients with CP was higher than that in controls by analyzing 43 patients with CP and the same number of controls [46]. Our study similarly identified glucose as an independent risk factor for CP, further supporting this viewpoint. Quantitative detection of intestinal glucose is the most common method, which is attributed to glucose being the most abundant metabolite among the metals in the gut microbiota. In patients with elevated blood glucose, besides the diagnosis of diabetes mellitus, the early diagnosis of underlying CP will also significantly improve patient outcomes. An analysis of serum markers from 157 patients found that serum bilirubin levels were predictive of AP and significantly superior to gamma-glutamyl transferase, lactate dehydrogenase, and C-reactive protein [47]. A similar conclusion was found in our study that for every unit increase in oxidized bilirubin levels, the incidence of AP doubles. The underlying mechanism may be attributed to the promotion of oxidative stress and activation of inflammatory response by bilirubin [48].

The study of the association between metabolites and pancreatitis has several potential benefits. First, the common detection methods in the clinic for pancreatitis mainly rely on imaging findings, and significant changes tend to appear in the advanced stages. Second, with the development of metabonomics in various medical fields, the cost of metabolite detection has decreased dramatically. Third, there is currently no single biomarker for the diagnosis of CP, and the comprehensive metabolite combination has excellent sensitivity for CP diagnosis. Finally, the MR analysis of pancreatitis with metabolites could guide high-risk patients to exert a preventive effect by controlling the metabolite diet.

There are several limitations in our study. First, although the main body of GWAS is White, a small number of Mongoloid individuals existed in the GWAS, and the inconsistent distribution of ethnicities may have affected the accuracy of the results. Second, we cannot completely exclude the potential influence of diet gene or gene environment on the study, which may have biased our results. Third, the cross-sectional nature of the data may not capture the dynamic changes in gut microbiota and metabolites over time, which is particularly relevant in chronic conditions, such as pancreatitis. Fourth, not all studies included in the analysis were subjected to rigorous quality control. Finally, IVW-based estimates can be easily biased when some instrumental SNPs exhibit horizontal pleiotropy. Although we performed the sensitivity analysis of our results using MR-PRESSO and other methods, it is possible that our results were less stable because of the intestinal flora having a P value of $< 5 \times 10^{-8}$ in this analysis.

Despite some limitations, our study has the following advantages. The GWAS associated with pancreatitis that we included in this study had the largest known sample size, and the large amount of data allowed us to perform a comprehensive analysis of incident pancreatitis. In addition, the consistent causal estimation across 5 methods (MR-Egger, IVW, MR-PRESSO, maximum likelihood, and weighted median) suggests the excellent stability of our conclusions. Finally, we comprehensively analyzed the classic form of pancreatitis, which facilitates the coordinated management of AP and CP.

Conclusion

Our study provides potential evidence regarding the causal role of gut microbiota and metabolites in pancreatitis. However, additional support from original research studies is needed to determine the exact relationship between gut microbiota and metabolites and pancreatitis. Future studies should explore the more precise mechanism of this association.

Ethics approval

All authors have read the article and agreed to publish it.

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Author contributions

Zhirong Zhao: conceptualization, methodology, and writing of the original draft; Li Han: software, validation, and data curation; Baobaonai Tuerxunbieke: writing of the original draft and visualization; Lan Ming: conceptualization; Jiamin Ji: conceptualization; Yuan Chen: writing - review and editing; Ran Sun: writing of the original draft and visualization; Weiliang Tian: writing of the original draft; Fan Yang: writing - review and editing; Qian Huang: writing - review and editing, project administration, and supervision.

Data availability

All data generated or analyzed during this study are included in this published article.

Declaration of competing interest

The authors declare no competing interests.

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