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Pancreatic cancer risk after acute and chronic pancreatitis

Evidence from Mendelian randomization and meta-analysis

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Abstract

Pancreatitis may be associated with the risk of developing pancreatic cancer (PC). Previous retrospective studies have shown that chronic pancreatitis (CP) may increase the risk of pancreatic cancer. However, the causal relationship between acute pancreatitis (AP) and pancreatic cancer remains unclear. We performed Mendelian randomization (MR) analysis to investigate the causal relationship between AP and PC and validate the effect of CP on PC identified in previous retrospective studies. Genome-wide association study data for AP, CP and PC were obtained from a public database. Inverse-variance weighting is the most important MR method for analyzing causality. Sensitivity analysis was used to evaluate the robustness of MR. Finally, a meta-analysis based on the inverse-variance weighting results was conducted to strengthen the robustness of the MR further. Four MR analyses were performed to investigate the effect of AP on PC. There was a result showing AP decreased the risk of PC (odds ratio [OR]: 0.773, 95% confidence interval [CI]: 0.612–0.975, $P = .030$), but other 3 results were not statistically significant ($P > .05$). The results of the meta-analysis revealed that AP did not increase the risk of PC (OR: 0.941, 95% CI: 0.861–1.029, $P = .182$). Three MR analyses were performed to validate the effect of CP on PC. There was a result showing CP increased the risk of PC (OR: 1.208, 95% CI: 1.037–1.406, $P = .015$), but the other 2 results were not statistically significant ($P > .05$). The results of the meta-analysis revealed CP increased the risk of PC (OR: 1.079, 95% CI: 1.011–1.152, $P = .023$). We confirmed that CP is associated with a greater risk of PC. However, there is no direct causal relationship between AP and PC. More clinical and experimental studies are needed to investigate the causal relationship.

Abbreviations: AP = acute pancreatitis, BAP1 = BRCA1-associated protein-1, CI = confidence interval, CP = chronic pancreatitis, GWAS = genome-wide association study, IVs = instrumental variables, IVW = inverse-variance weighted, MR = Mendelian randomization, MR-PRESSO = MR-pleiotropy residual sum and outlier, OR = odds ratio, PC = pancreatic cancer, RCTs = randomized controlled trials, SNPs = single nucleotide polymorphisms.

Keywords: acute pancreatitis, chronic pancreatitis, Mendelian randomization, meta-analysis, pancreatic cancer

1. Introduction

Pancreatitis, including acute and chronic pancreatitis, is a common admission diagnosis. The incidence rates of acute pancreatitis (AP) and chronic pancreatitis (CP) are 33.7 cases and 9.6 cases per 100,000 person-years, respectively, worldwide.[1–3] According to estimations, the incidence rate of pancreatitis will continue to rise and reach 123.7 cases per 100,000 person-years by 2050.[1–4] Despite its high incidence and mortality, advances in supportive care have increased the survival of patients with pancreatitis.[5,6] These survivors may experience long-term complications such as diabetes and exocrine pancreatic insufficiency.[7–9] However, whether an episode of pancreatitis increases the risk of pancreatic cancer (PC) in the future is also crucial for the long-term surveillance and prognosis of pancreatitis survivors.

Previous retrospective studies have shown that CP may be associated with an increased risk of PC.[10–15] However, whether AP predisposes patients to PC is still controversial, as there are differences among studies.[16–19] Currently, most previous studies

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were limited to adjusting for residual confounders, making findings on the causal relationship between pancreatitis and PC vulnerable to assessment. Although randomized controlled trials (RCTs) are generally considered the gold standard for making inferences on causation, they are unfeasible to conduct to investigate the causal relationship between pancreatitis and PC due to ethical constraints.

Mendelian randomization (MR), which employs genetic variants significantly correlated with exposure factors as instrumental variables (IVs) to assess the causal relationships between exposure factors and outcomes, is an increasingly popular method for assessing etiological inference in epidemiological investigations.[20] This approach could reduce residual confounding and mitigate reverse causation, which is a particular vulnerability in observational studies.[20–24] The evidence level of MR is equivalent to that of RCTs.[25]

Here, we employed MR analysis to investigate the causal relationship between AP and PC and validate the effect of CP on PC, as identified in previous retrospective studies.

2. Methods

2.1. Study design

The overall study design is shown in Figure 1. Three core assumptions of the MR analysis are represented by A, B, and C. A indicates the selected single nucleotide polymorphisms (SNPs) that should be significantly associated with exposure (acute pancreatitis and chronic pancreatitis); B indicates the selected SNPs that are associated with the outcome (pancreatic cancer) only via exposure; and C indicates the selected SNPs that should be independent of confounders.

2.2. Data source

All of the information was obtained from openly accessible and publicly available summary statistics of genome-wide association studies (GWASs), which primarily included data on Europeans, both male and female. The GWAS summary statistics for AP were provided by Sakaue S (n = 479,902) and the FinnGen Consortium (n = 198,166); the GWAS summary statistics for CP were provided by Sakaue S (n = 477,528) and the FinnGen Consortium (n = 196,881); and the GWAS summary statistics for PC were provided by Sakaue S (n = 476,245) and the FinnGen Consortium (n = 218,792). We obtained data from the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/).

Since we utilized open and freely available GWAS summary statistics, additional ethical approval was not required.

2.3. Selection of IVs

In accordance with previous studies, 4 criteria were used to select SNPs.[26] First, we identified SNPs associated with AP and CP at the genome-wide threshold of significance ($P < 1 \times 10^{-5}$) to obtain a sufficient number of SNPs. Second, we eliminated linkage disequilibrium ($r^2 > 0.001$, clumping window = 10,000 kb). Third, we identified strong IVs on the basis of *F*-statistics ($F = \beta^2/SE^2$, $F > 10$).[27] Finally, we eliminated the SNPs related to outcome factors and confounding factors through the LDlink domain (https://ldlink.nih.gov/?tab=ldtrait). Before performing the MR analysis, we additionally conducted the data-harmonization steps, as the effects of a SNP on the exposure and the outcome had to correspond to the same allele.

2.4. MR and sensitivity analysis

The primary analysis was performed via the inverse-variance weighted approach.[26,27] If more than 50% of the information comes from valid instrumental variables, the weighted median method can provide a valid estimate.[28] MR-pleiotropy residual sum and outlier (MR-PRESSO) and MR-Egger were used for pleiotropy analysis. When $P < .05$, horizontal pleiotropy was

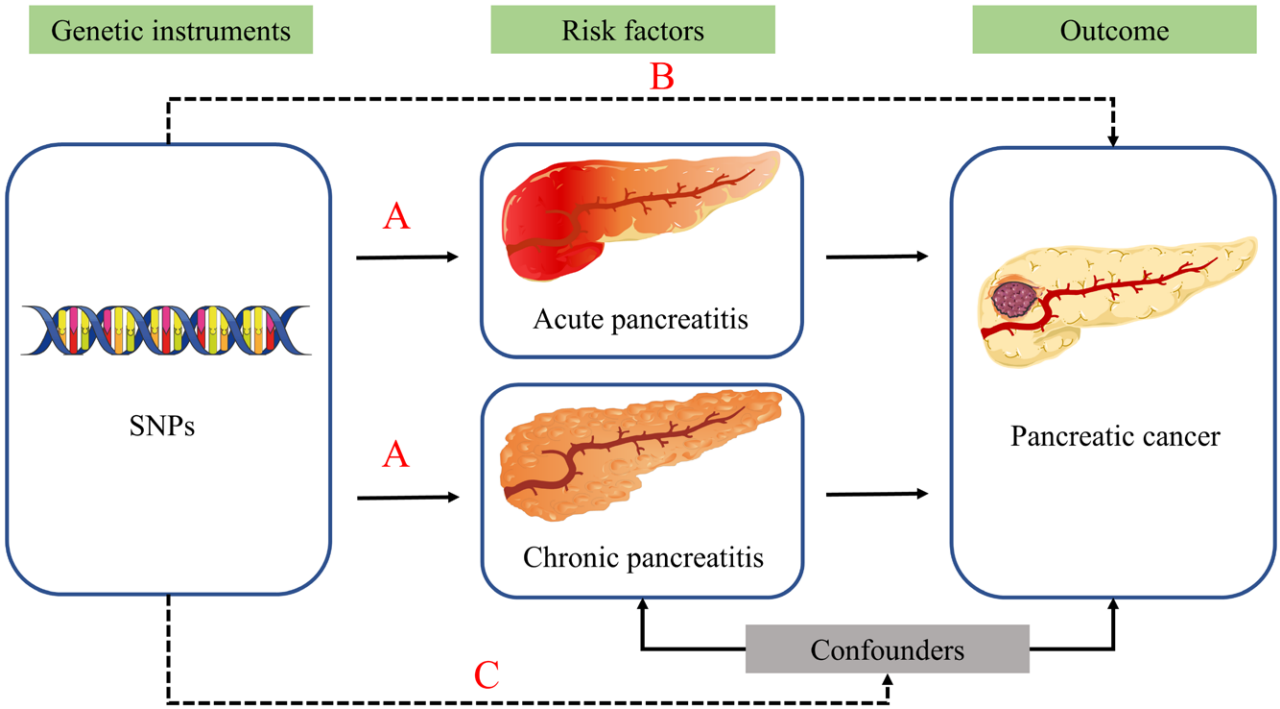

Figure 1. Three core assumptions of the Mendelian randomization analysis. (A) The selected SNPs that should be significantly associated with exposure (acute pancreatitis and chronic pancreatitis); (B) The selected SNPs that are associated with the outcome (pancreatic cancer) only via exposure; (C) The selected SNPs that should be independent of confounders. SNPs = single nucleotide polymorphisms.

indicated, and IVs with horizontal pleiotropy were deleted.[28] Cochrane Q test was used for the heterogeneity test. When $P < .05$ indicated heterogeneity, the inverse-variance weighted method with a random effects model was used for analysis.[26–28] $P < .05$ was considered statistically significant. MR analyses were performed via the "TwoSampleMR" package in R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

2.5. Meta-analysis

To increase the confidence of the results, we selected multiple exposure and outcome datasets, which is equivalent to conducting multiple RCTs. We subsequently performed a meta-analysis on the inverse-variance weighted (IVW) results to further strengthen the robustness of the results. When there was no heterogeneity ($P > .05$), the common effects model was used; otherwise, the random effects model was employed. $P < .05$ was considered statistically significant. The meta-analysis was performed via the "meta" package in R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Results of IVs selection

The characteristics of the data used in our MR study are summarized in Table 1 and Table S1, Supplemental Digital Content, https://links.lww.com/MD/Q340.

The results of IVs selection are summarized in Table S2, Supplemental Digital Content, https://links.lww.com/MD/Q340. We selected 2 GWAS datasets for AP and PC, which are equal to 4 RCTs. The number of selected SNPs was 21, 19, 14, and 14, respectively. We also selected 2 GWAS datasets for CP, however, we ultimately had to eliminate the GWAS dataset for CP provided by Sakaue S and PC provided by Sakaue S due to the presence of horizontal pleiotropy. The number of SNPs employed for the remaining 3 results was 23, 24, and 24, respectively.

3.2. Acute pancreatitis and pancreatic cancer

We used MR analysis to explore the effect of AP on PC, and the results are summarized in Table 2.

AP was not associated with an increased risk of pancreatic cancer, according to IVW results from several studies: AP (Sakaue S) on PC (odds ratio [OR]: 1.080, 95% confidence interval [CI]: 0.929–1.254, $P = .317$); AP (Sakaue S) on malignant pancreatic neoplasm (OR: 0.923, 95% CI: 0.732–1.164, $P = .499$); and AP (FinnGen) on PC (OR: 0.897, 95% CI: 0.772–1.042, $P = .155$). However, there was a result showing acute pancreatitis decreased the risk of pancreatic cancer: AP (FinnGen) on malignant neoplasm of the pancreas (OR: 0.773, 95% CI: 0.612–0.975, $P = .030$) (Fig. 2).

All weighted median values were not statistically significant ($P > .05$). The results of the sensitivity analysis are summarized in Table S3, Supplemental Digital Content, https://links.lww.com/MD/Q340. The absence of statistical significance ($P > .05$) was observed for all pleiotropy, MR-Egger, and MR-PRESSO data, indicating the presence of horizontal pleiotropy. As the heterogeneity tests lacked statistical significance ($P > .05$), the IVW results under the common effect model were certainly reliable. The results of the leave-one-out, forest plot, scatter plot, and funnel plot analyses demonstrated that the SNPs were properly selected and that the MR results were robust (Figure S1, Supplemental Digital Content, https://links.lww.com/MD/Q339).

Because the 4 results were not entirely consistent, we conducted a meta-analysis to strengthen the robustness of MR further. The results of the meta-analysis, based on the 4 studies from the IVW method, are presented in Figure 3. The heterogeneity tests were not statistically significant ($P = .090$), indicating that the common effect model should be adopted. According to the meta-analysis results (OR: 0.941, 95% CI: 0.861–1.029, $P = .182$), AP did not increase the risk of PC.

3.3. Chronic pancreatitis and pancreatic cancer

We subsequently used MR analysis to validate the effect of CP on PC, and the results are summarized in Table 3.

CP did not increase the risk of PC according to the IVW results from several studies: CP (Sakaue S) on malignant neoplasm of the pancreas (OR: 1.156, 95% CI: 0.999–1.339, $P = .052$) and CP (FinnGen) on PC (OR: 1.020, 95% CI: 0.938–1.1109, $P = .648$). However, there was a result showing CP increased the risk of PC: CP (FinnGen) for malignant neoplasm of the pancreas (OR: 1.208, 95% CI: 1.037–1.406, $P = .015$) (Fig. 4).

All weighted median values were not statistically significant ($P > .05$). The results of the sensitivity analysis are shown in Table S3, Supplemental Digital Content, https://links.lww.com/MD/Q340. According to the results of pleiotropy, MR-Egger, and MR-PRESSO, none of which were statistically significant ($P > .05$), there was no horizontal pleiotropy. Heterogeneity tests were not statistically significant ($P > .05$), indicating that the IVW results under the common effect model were reliable. The results of the leave-one-out, forest plot, scatter plot, and funnel plot analyses demonstrated that the SNPs were properly selected and that the MR results were robust (Figure S2, Supplemental Digital Content, https://links.lww.com/MD/Q339).

Similarly, we conducted a meta-analysis to strengthen the robustness of MR further, as the 3 results were not entirely consistent. The results of the meta-analysis, based on the 3 studies using the IVW method, are presented in Figure 5. Heterogeneity tests were not statistically significant ($P = .100$), indicating that the common effect model should be adopted. The results of the meta-analysis (OR: 1.079, 95% CI: 1.011–1.152, $P = .023$) revealed that CP increased the risk of PC.

Table 1

The characteristics of the data used in the Mendelian randomization study.

Trait	GWAS ID	Consortium	Year	Author	Population
Acute pancreatitis	ebi-a-GCST90018789	–	2021	Sakaue S	European
Acute pancreatitis	finn-b-K11_ACUTPANC	FinnGen	2021	–	European
Chronic pancreatitis	ebi-a-GCST90018821	–	2021	Sakaue S	European
Chronic pancreatitis	finn-b-K11_CHRONPANC	FinnGen	2021	–	European
Pancreatic cancer	ebi-a-GCST90018893	–	2021	Sakaue S	European
Malignant neoplasm of pancreas	finn-b-C3_PANCREAS	FinnGen	2021	–	European

GWAS = genome-wide association study.

Table 2

Results of MR by IVW, MR-Egger, and weighted median regarding the causal relationship between AP and PC.

		IVW		MR-Egger		Weighted median	
Exposure	**Outcomes**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Acute pancreatitis (Sakaue S)	Pancreatic cancer	1.080 (0.929–1.254)	.317	1.188 (0.887–1.591)	.262	0.975 (0.793–1.198)	.808
Acute pancreatitis (Sakaue S)	Malignant neoplasm of pancreas	0.923 (0.732–1.164)	.499	1.049 (0.660–1.667)	.843	0.960 (0.696–1.324)	.803
Acute pancreatitis (FinnGen)	Pancreatic cancer	0.897 (0.772–1.042)	.155	1.112 (0.839–1.476)	.474	0.942 (0.770–1.153)	.565
Acute pancreatitis (FinnGen)	Malignant neoplasm of pancreas	0.773 (0.612–0.975)	.030	0.883 (0.566–1.377)	.593	0.876 (0.637–1.203)	.412

AP = acute pancreatitis, CI = confidence interval, IVW = inverse-variance weighted, MR = Mendelian randomization, OR = odds ratio, PC = pancreatic cancer.

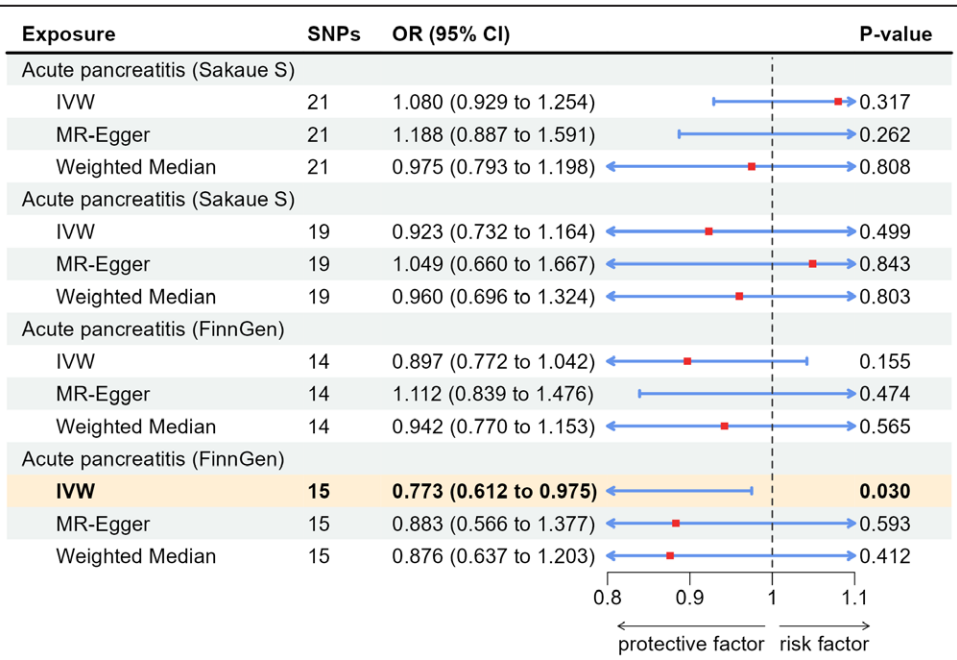

Figure 2. Forest plot of MR by IVW, MR-Egger, and weighted median regarding the causal relationship between AP and PC. AP = acute pancreatitis, CI = confidence interval, IVW = inverse-variance weighted, OR = odds ratio, PC = pancreatic cancer, SNPs = single nucleotide polymorphisms.

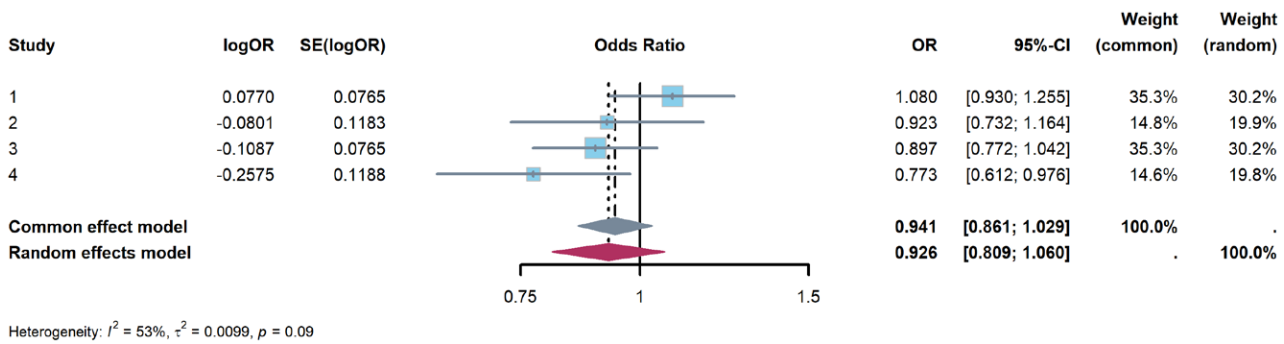

Figure 3. Meta-analysis of MR by IVW regarding the causal relationship between AP and PC. AP = acute pancreatitis, CI = confidence interval, IVW = inverse-variance weighted, OR = odds ratio, PC = pancreatic cancer.

4. Discussion

In the past decade, pancreatitis-related mortality has decreased due to improvements in life support and care. Long-term complications are increasingly affecting the prognosis and quality of life of pancreatitis survivors.[14,15] Whether pancreatitis is a causal factor for PC directly affects physicians' choices for monitoring and long-term follow-up for pancreatitis survivors. Several retrospective studies have explored whether acute and chronic pancreatitis are risk factors for PC. The findings of retrospective studies, however, are susceptible to reverse causation and confounding bias, which makes establishing the causal relationship between pancreatitis and PC challenging. Moreover, ethical concerns limit the potential of RCTs to validate these findings.[16–19] Mendelian randomization analysis is not subject to ethical restrictions and ensures a reasonable time sequence between exposure and outcome. Therefore, its evidentiary strength is comparable to that of RCTs, which provides the possibility for a solution to this clinical dilemma.[20–25]

In this study, we used MR to analyze the effects of acute and chronic pancreatitis on PC. When investigating the relationship

Table 3

Results of MR by IVW, MR-Egger, and weighted median regarding the causal relationship between CP and PC.

		IVW		MR-Egger		Weighted median	
Exposure	**Outcomes**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95%CI)**	***P***
Chronic pancreatitis (Sakaue S)	Malignant neoplasm of pancreas	1.156 (0.999–1.339)	.052	1.051 (0.816–1.354)	.703	1.177 (0.964–1.438)	.109
Chronic pancreatitis (FinnGen)	Pancreatic cancer	1.020 (0.938–1.109)	.648	1.013 (0.884–1.161)	.852	1.001 (0.896–1.118)	.987
Chronic pancreatitis (FinnGen)	Malignant neoplasm of pancreas	1.208 (1.037–1.406)	.015	1.075 (0.802–1.441)	.633	1.183 (0.965–1.451)	.106

CI = confidence interval, CP = chronic pancreatitis, IVW = inverse-variance weighted, MR = Mendelian randomization, OR = odds ratio, PC = pancreatic cancer.

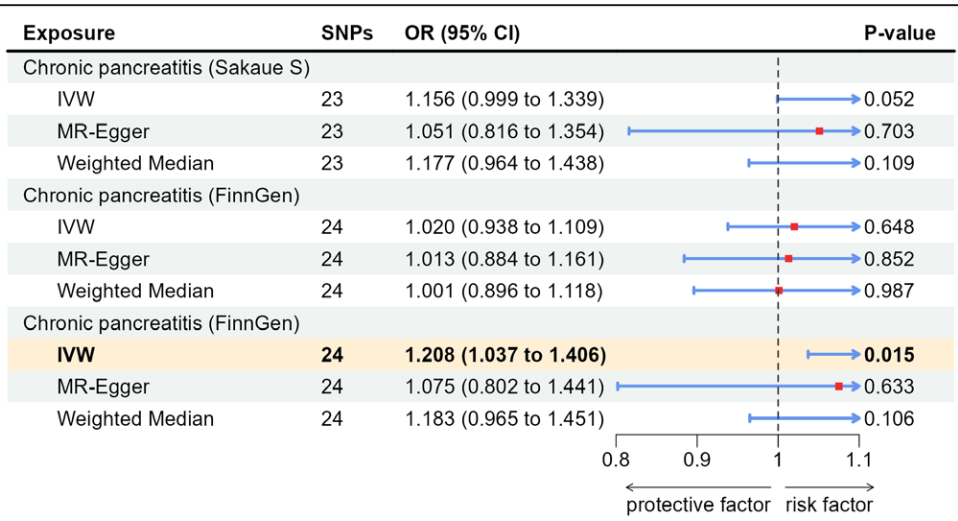

Figure 4. Forest plot of MR by IVW, MR-Egger, and Weighted median regarding the causal relationship between CP and PC. CI = confidence interval, CP = chronic pancreatitis, IVW = inverse-variance weighted, OR = odds ratio, SNPs = single nucleotide polymorphisms, PC = pancreatic cancer.

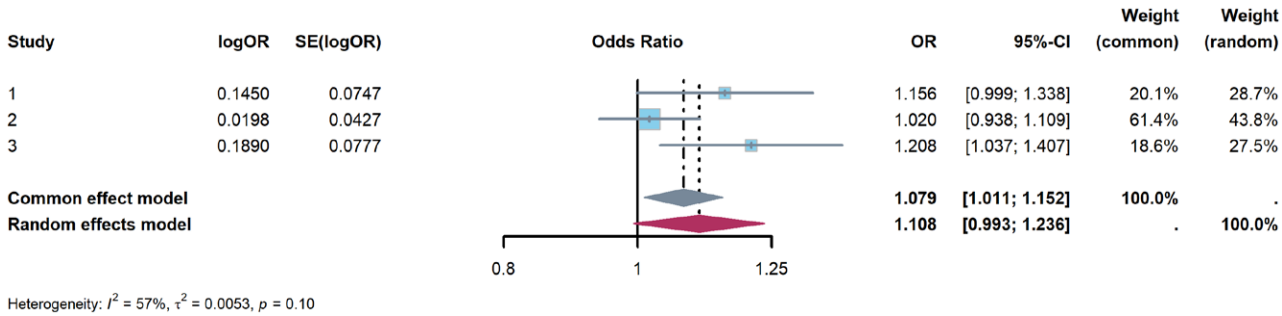

Figure 5. Meta-analysis of MR by IVW regarding the causal relationship between CP and PC. CP = chronic pancreatitis, IVW = inverse-variance weighted, PC = pancreatic cancer.

between CP and PC, one of the results showed that CP increased the risk of PC (OR: 1.208, 95% CI: 1.037–1.406, *P* = .015; Fig. 4). However, the other 2 results were not statistically significant. Considering the inconsistencies of the 3 results, a further meta-analysis was conducted to strengthen the robustness of the MR. The meta-analysis of the 3 results revealed that CP increased the risk of PC (OR: 1.079, 95% CI: 1.011–1.152, *P* = .023; Fig. 5). These results in our study are consistent with those of previous retrospective studies. A retrospective study with a 10-year follow-up revealed that individuals with CP had a higher incidence of PC; during the 10-year follow-up, the highest risk of PC was observed in the second year.[11] Additionally, the findings from a meta-analysis revealed that CP increases the risk of pancreatic ductal adenocarcinoma, which is the most common pathological type.[13,29] A possible explanation might be that shared gene mutations accelerate the development of both pancreatitis and PC. For example, BRCA1-associated protein-1 is highly expressed in both CP and PC, and BRCA1-associated protein-1 inhibition can prevent the development of CP into PC.[30] Multiple experimental studies have also demonstrated that epithelial mesenchymal transformation, which promotes pancreatic fibrosis, plays a crucial role in the mechanism of transformation from CP to PC.[31–36]

According to the MR analysis of the effect of AP on PC, one of the results showed that AP was associated with a decreased risk of PC (OR: 0.773, 95% CI: 0.612–0.975, *P* = .030; Fig. 2). However, the results for the other 3 variables were not statistically significant. Similarly, we further conducted a meta-analysis to strengthen the robustness of MR. The results of the meta-analysis revealed that AP did not increase the risk of PC (OR: 0.941, 95% CI: 0.861–1.029, *P* = .182; Fig. 3). There has been debate over the results derived from retrospective studies on the relationship between AP and PC. Kirkegård et al reported an increased risk of PC within 10 years following AP.[37] Further

studies indicated that recurrent AP and its progression into CP were the primary contributors to the increased risk of PC following AP.[19,38] In contrast, a meta-analysis suggested that AP may not be a long-term risk factor for PC.[39] This difference might be attributed to several factors. Importantly, differences in AP severity result in changes in the recommended procedure for therapy. Patients with severe AP are more likely to require surgery or endoscopic procedures, which increases the risk of developing CP and, eventually, PC. Additionally, the sequence of AP and PC cannot be fully determined, which renders the results biased. Cancer formation is a chronic process. However, in some retrospective studies, PC was diagnosed within 2 years after the diagnosis of AP, and in some cases, it was diagnosed even within a few months after the diagnosis of AP.[16–18] In these studies, it is worth considering whether any individuals suffer AP following PC.

This study has several strengths. To the best of our knowledge, this is the first large MR study to investigate the causal relationship between AP and PC and validate the effect of CP on PC. In this study, we selected multiple exposure and outcome datasets, which is equivalent to conducting multiple RCTs. Furthermore, we performed a meta-analysis based on the IVW results to strengthen the robustness of the MR results. In brief, our results are more reliable and convincing than those of retrospective studies.

This study also has limitations. First, since all of the data we used included only Europeans, our results were limited to the European population. Therefore, caution should be taken when extending our results to other populations. Second, due to the lack of information about the etiology and severity of AP, an investigation into the risk of PC based on the cause and severity of AP could not be carried out. Third, because information about the frequency of episodes and whether AP recurred was unavailable, a subgroup analysis could not be performed.

5. Conclusions

In summary, this MR study is based on a large-scale population to investigate the causal relationship between AP and PC and validate the effect of CP on PC identified in previous retrospective studies. We confirmed that CP is associated with a greater risk of PC. However, there is no direct causal relationship between AP and PC. More clinical and experimental studies are needed to investigate the causal relationship.

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Author contributions

Data curation: Xiaohua Ma.
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Writing – review & editing: Chang Liu, Kai Qu.

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