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ORIGINAL ARTICLE

Exploring the link between antihypertensive drugs targets and pancreatitis risk through Mendelian randomization

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Background: Observational studies indicate an association between antihypertensive drugs and the risk of acute pancreatitis (AP) and chronic pancreatitis (CP). This study aims to utilize Mendelian randomization (MR) analysis to assess the causal impact of antihypertensive drugs on the risk of AP and CP.

Method: Protein target information for eight commonly used antihypertensive drugs was collected from the DrugBank database. The inverse variance-weighted (IVW) method was the primary approach used to investigate the association between genetic instruments from the discovery cohorts and the risk of AP and CP. The presence of heterogeneity was determined using Cochran's Q test.

Result: The genetic proxies of angiotensin-converting enzyme inhibitors (ACEIs) were identified as risk factors for AP. Genetic proxies for potassium-sparing diuretics (PSDs) were found to have a positive causal relationship with the occurrence of AP. In contrast, β-blockers (BBs) and loop diuretics were identified as protective factors against AP. Genetic proxies of ACEIs were identified as risk factors for CP, whereas BBs were found to be protective factors for CP. Additionally, genetic proxies for PSDs showed a protective effect on CP, while loop diuretics were identified as risk factors for CP.

Conclusion: BBs may have a protective effect on AP, whereas ACEIs and PSDs may have negative effects. The genetic proxies of PSDs and BBs are protective factors for CP, while the genetic proxies of ACEIs and loop diuretics are risk factors for CP.

KEYWORDS
acute pancreatitis, antihypertensive drugs, causal effect, chronic pancreatitis, Mendelian randomization

1 | BACKGROUND

Pancreatitis is a progressive, destructive inflammatory disease of the pancreas, characterized by high incidence and mortality rates. Inflammatory reactions play a major role in the development of pancreatitis, but it also has different clinical courses. The majority of patients mainly present with mild acute pancreatitis (AP). About 20%–40% of patients progress to moderate or severe AP, which causes necrosis of pancreatic or peripancreatic tissues or organ failure, or both, with a mortality rate of 20%–40%,[1–4] making it an extremely dangerous gastrointestinal disease.

Hypertension is a leading risk factor for cardiovascular complications, with approximately more than 10.8 million deaths attributed to it globally each year.[5] As a global health issue, hypertension affects

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approximately 31.1% of adults worldwide, characterized by high incidence, disability and mortality rates, yet with relatively low awareness.[6] Utilizing antihypertensive drugs to manage blood pressure is the most frequently employed clinical treatment. This approach is a well-established strategy to mitigate the risk of cardiovascular diseases.[7,8] In view of the diverse categories and mechanisms of action of antihypertensive drugs, the outcomes vary accordingly. Previous studies on drug-induced AP have reported that antihypertensive drugs such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs) and diuretics have been explicitly included as factors contributing to pancreatitis, excluding other causes.[9] There is, however, a lack of consistency and controversy regarding the relationship between antihypertensive drugs and pancreatitis. Variations in study populations, definitions of outcomes and unmeasured confounding biases could explain these inconsistent findings. It is widely recognized that observational designs are inadequate to establish causality. Despite being regarded as the gold standard for establishing causality, randomized clinical trials may face limitations due to feasibility issues, high costs and ethical challenges.[10]

Mendelian randomization (MR) is a popular method that utilizes the unique characteristics of genotypes to study causal relationships between exposure and outcomes.[11] It employs genetic variants closely associated with the exposure of interest as instrumental variables (IVs), and these variants are randomly allocated across the population during meiosis and conception, mimicking a randomized controlled setting. The MR design minimizes the influence of residual confounding factors and overcomes reverse causality.[12] To estimate causal relationships between exposure and disease outcomes, MR uses genetic variants as IVs for exposure.[13] Genetic variants are allocated randomly from parents to offspring, so common confounding factors cannot influence the association between genetic variants and outcomes, allowing causal inference to be drawn.

Genetic variants in the targets of antihypertensive drugs can serve as surrogate indicators for studying the impact of their treatment on disease outcomes.[14] Drug target MR can simulate the potential effects of drug targets by utilizing genetic instruments near or within the target genes, thereby predicting the prospects for drug development and repurposing.[15] Because GWAS summary data are widely available, MR can assess causal relationships between exposure and disease outcomes effectively and economically.[16] Using genetic instruments located within or near drug targets, drug target MR can forecast opportunities for drug development and repurposing.[15]

In this study, we performed a comprehensive drug-targeted MR analysis, employing single nucleotide polymorphisms (SNPs) located in or near the target genes of antihypertensive drugs as genetic proxies. This approach allowed us to systematically investigate the causal relationship between categories of antihypertensive drugs and the onset of pancreatitis. The results of this study could offer valuable insights into the use of antihypertensive drugs for patients with hypertension, particularly those who have risk factors for pancreatitis. Additionally, in the future, antihypertensive drugs may be considered as a potential preventative strategy for pancreatitis in light of these findings.

What is already known about this subject

- Antihypertensive drugs are a type of medication that has been approved for clinical use to treat hypertension in patients.
- Known adverse events (AEs) associated with antihypertensive drugs exist, primarily documented from pre-approval clinical trials.
- There is limited detailed information regarding the association between antihypertensive drugs and the risk of pancreatitis.

What this study adds

- This drug target Mendelian randomization study suggests that certain antihypertensive agents may have a causal association with the risk of acute or chronic pancreatitis.
- The study suggests that ACE inhibitors may increase the risk of both acute and chronic pancreatitis, while β-blockers may offer protective effects against both and potassium-sparing diuretics are associated with a higher risk of acute pancreatitis but a protective effect against chronic pancreatitis.
- The findings of this study fill the gap in research on the association between antihypertensive drugs and the risk of pancreatitis, providing genetic evidence that may guide medication strategies for patients with pancreatitis.

2 | METHOD

2.1 | Study design

The study design flowchart is shown in Figure 1. All analyses were conducted using publicly available summary data from genetic association studies. Approval from ethics committees and consent from participants were secured in the initial studies that produced the data. Using the drug-targeted MR method, we assessed the causal relationship between genetic proxies of the occurrence of pancreatitis in relation to antihypertensive drugs. Initially, adhering to the directives outlined by the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines,[6] we considered eight frequently used antihypertensive drugs: alpha-adrenergic blockers, ARBs, ACEIs, β-blockers (BBs), thiazide diuretics, PSDs, loop diuretics and calcium channel blockers (CCBs). Genetic instruments were obtained from the International Consortium of Blood Pressure (ICBP). Furthermore, we applied the genetic instruments we constructed to investigate the effects of antihypertensive drugs on both AP and CP. Finally, we conducted independent data replication for validation.

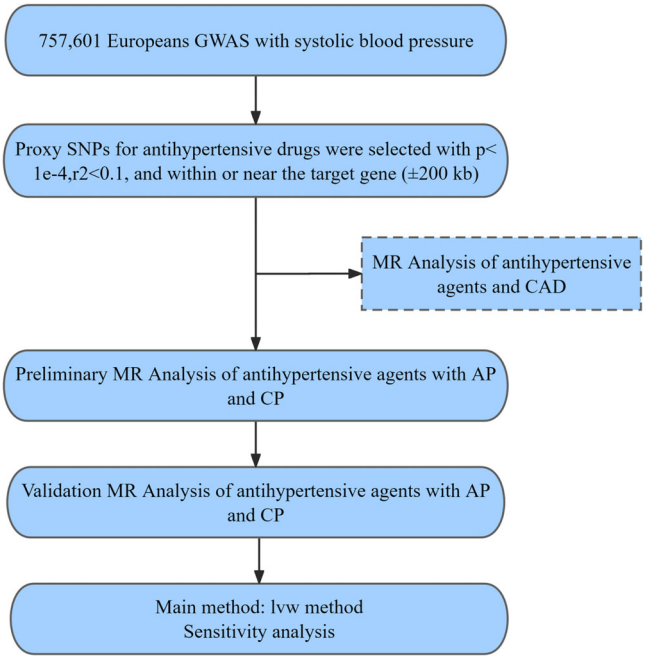

FIGURE 1 Diagram of the study design.

2.2 | Genetic instruments for proxying antihypertensive drugs

We identified SNPs related to reduced blood pressure, situated in or near the genes targeted by drugs, to serve as proxies for various antihypertensive drugs. These proxies were obtained from the ICBP, which includes GWAS data from 757 601 individuals and adjusts for age, age^2, BMI and sex.[17] We specifically gathered protein target data for eight frequently prescribed antihypertensive drugs from the DrugBank database.[18] When identifying SNPs associated with systolic blood pressure ($P < 1 \times 10^{-4}$), we chose SNPs within or nearby (±200 kb) the relevant target genes as proxies for the antihypertensive drugs.[19,20]

Additionally, we calculated the *F*-statistic. In this calculation, R2 as genetic tools was used to explain the proportion of trait variance, and R2 was computed using the formula: $R2 = 2 \times (1 - MAF) \times MAF \times \beta^2$ (where β = effect size and MAF is the minimum allele frequency for each SNP). Subsequently, we computed an *F*-statistic to assess the strength of selected SNPs in explaining phenotypic variance, with the formula: $F = (N - k - 1) / k \times R2 / (1 - R2)$ (where N = sample size, and k = number of SNPs). Variables with $F < 10$ were excluded to avoid weak instrument bias.[21] Following this, we employed the European reference panel from the 1000 Genomes Project to cluster these SNPs, using a lenient linkage disequilibrium (LD) threshold of $r^2 < 0.1$. Additionally, palindrome SNPs (minor allele frequency >0.1) were also removed from the analysis.

2.3 | Outcome data

Coronary artery disease (CAD) was chosen as the control outcome to validate the genetic proxies for antihypertensive drugs, given its critical role as a primary target of antihypertensive therapy. Data for CAD GWAS were sourced from the CARDIoGRAMplusC4D consortium, which comprises data from 60 801 cases and 123 504 controls drawn from the Coronary ARtery DIsease Genome-wide Replication and Meta-analysis (CARDIoGRAM) and the Coronary Artery Disease (C4D) Genetics Consortium.[22]

The main outcomes chosen were AP and CP. In the discovery cohort, we utilized GWAS data from the FinnGen database (version 9), with the AP data including 6223 cases and 330 903 controls, and the CP data including 3320 cases and the same 330 903 controls. In the validation cohort, GWAS data from the UK Biobank were used, with AP data covering 1215 cases and 461 795 controls, and CP data covering 361 194 participants.

2.4 | Statistical analysis

First, we assessed the suitability of SNPs as proxies for antihypertensive drugs, considering them as exposure factors and using CAD as the control outcome. Following this, we applied the inverse variance-weighted (IVW) method to estimate the impact of genetic instruments for antihypertensive drugs on CAD. As it is well known that antihypertensive drugs have a protective effect on CAD, we used CAD as the control to assess the effectiveness of proxy SNPs.

We utilized the IVW method as the primary approach to study the association between genetic instruments in the discovery cohort and AP and CP risk. To detect heterogeneity, we used Cochran's Q test. In addition to the IVW method, we also used four supplementary MR methods: weighted mode, weighted median, MR Egger and simple mode for our analyses.[23,24] Finally, we confirmed the effects of antihypertensive drugs on the risk of AP and CP by utilizing related GWAS data from the replication cohort. The results were reported as OR or beta coefficients, with a 95% confidence interval (95% CI), per 10-mmHg decrease in SBP. MR is a method for estimating causal effects under three core assumptions. The three core assumptions are as follows: the relevance assumption, where each variant must be linked to the exposure; the independence assumption, which states that each variant must not correlate with any confounding variables; and the exclusion restriction, requiring that each variant influences the outcome solely through the risk factor.[25]

We applied the Benjamini–Hochberg false discovery rate (FDR) correction to adjust for multiple comparisons among drug classes. Associations with FDR *q*-values <0.05 were considered statistically significant.

2.5 | Sensitivity analysis

Pleiotropy testing was performed using MR Egger and MR Pleiotropy RESidualSum and Outlier (MR-PRESSO). $p > 0.05$ indicated that there was no pleiotropy. Heterogeneity analysis was performed using mr_egger and IVW in Cochran's Q statistic. $p > 0.05$ indicated that there was no heterogeneity analysis. In addition, we used 'leave-one-out' sensitivity analysis to demonstrate that the causal effect of exposure on outcomes is not affected by a single SNP.

3 | NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries online (http://www.guidetopharmacology.org) and are permanently archived in the Concise Guide to Pharmacology 2021/22 (Alexander et al., 2021).

4 | RESULTS

4.1 | Genetic instrument selection and validation

We identified 41 pharmacological target genes across the eight different categories of antihypertensive drugs (see Table S1). Genetic instruments positioned within or adjacent to these drug target genes were selected as proxies. According to the above criteria, a total of 545 SNPs were screened out, as detailed in Table S2. In summary, there were 8 SNPs for ACEIs, 7 SNPs for alpha-adrenergic blockers, 54 SNPs for BBs, 299 SNPs for CCBs, 64 SNPs for loop diuretics and 103 SNPs for PSDs. The *F*-statistics for all instrumental SNPs consistently exceeded 10, indicating that weak instrument bias is unlikely to impact the results (refer to Table S3). Demonstrating the protective impact of genetic proxies for antihypertensive drugs on CAD, Figure S1 highlights the efficacy of these instrumental SNPs.

4.2 | Drug-target MR analysis for AP

We first investigated the impact of genetic proxies of antihypertensive drug targets on AP using the FinnGen cohort (Figure 2 and Table S4). In this cohort, our study results revealed that the genetic proxy for ACEIs was a risk factor for AP (odds ratio [OR] = 1.100, 95% CI [1.048, 1.154]; $p = 0.0001$). Additionally, the genetic proxy for PSDs was also found to have a positive causal relationship with AP occurrence (OR = 1.029, 95% CI [1.009, 1.049]; $p = 0.0047$). Protective factors for AP were found to be BBs (OR = 0.907, 95% CI [0.887, 0.928]; $p = 7.79E\text{-}17$) and loop diuretics (OR = 0.908, 95% CI [0.890, 0.927]; $p = 3.25E\text{-}20$) However, it is worth noting that the method of the MR-Egger intercept for pleiotropy testing suggested that the results for loop diuretics might be unreliable (Table S5). No association was found between the genetic proxy for CCBs and AP. The FDR-corrected results maintained consistent significance.

Subsequently, in the UK Biobank cohort, consistent with the findings in the discovery cohort, the genetic proxy for PSDs was also identified as a risk factor for AP (OR = 1.0003, 95% CI [1.000002, 1.0006]; $p = 0.048$). Identified as a risk factor for AP, the genetic proxy for CCBs had an OR of 1.0002 (95% CI [1.00009, 1.0002]; $p = 1.07E\text{-}05$). However, the MR-Egger intercept method detected pleiotropy in this causal relationship. No heterogeneity or pleiotropy was found in the other results, and the MR-PRESSO method did not detect any outlier SNPs (see Table S5).

4.3 | Drug-target MR analysis for CP1

In the study of CP, we similarly first investigated the impact of genetic proxies of antihypertensive drug targets in the FinnGen cohort (Figure 3 and Table S4). In this cohort, similar to the results in AP, the genetic proxy for ACEIs was identified as a risk factor for CP (OR = 1.086, 95% CI [1.016, 1.160]; $p = 0.015$), while BBs were found to be protective factors for CP (OR = 0.963, 95% CI [0.933, 0.993]; $p = 0.016$). Interestingly, the genetic proxy for PSDs exhibited a protective effect in CP (OR = 0.951, 95% CI [0.927, 0.975];

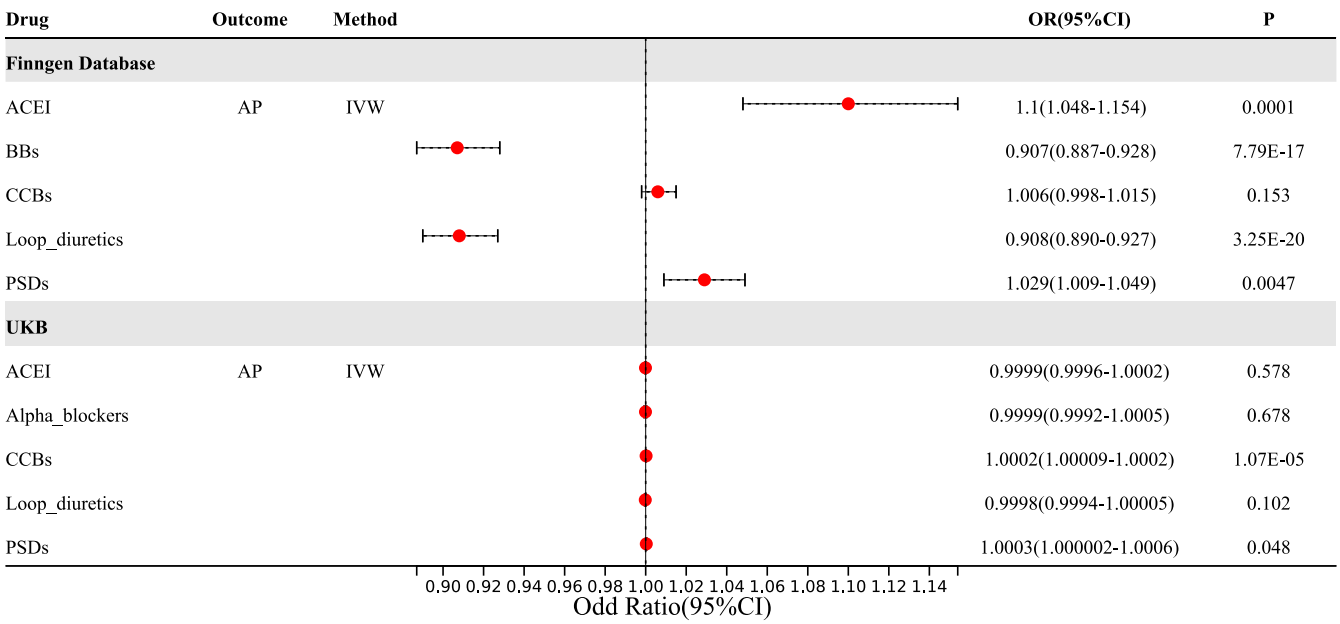

FIGURE 2 Forest diagram of MR analysis of antihypertensive drugs with AP.

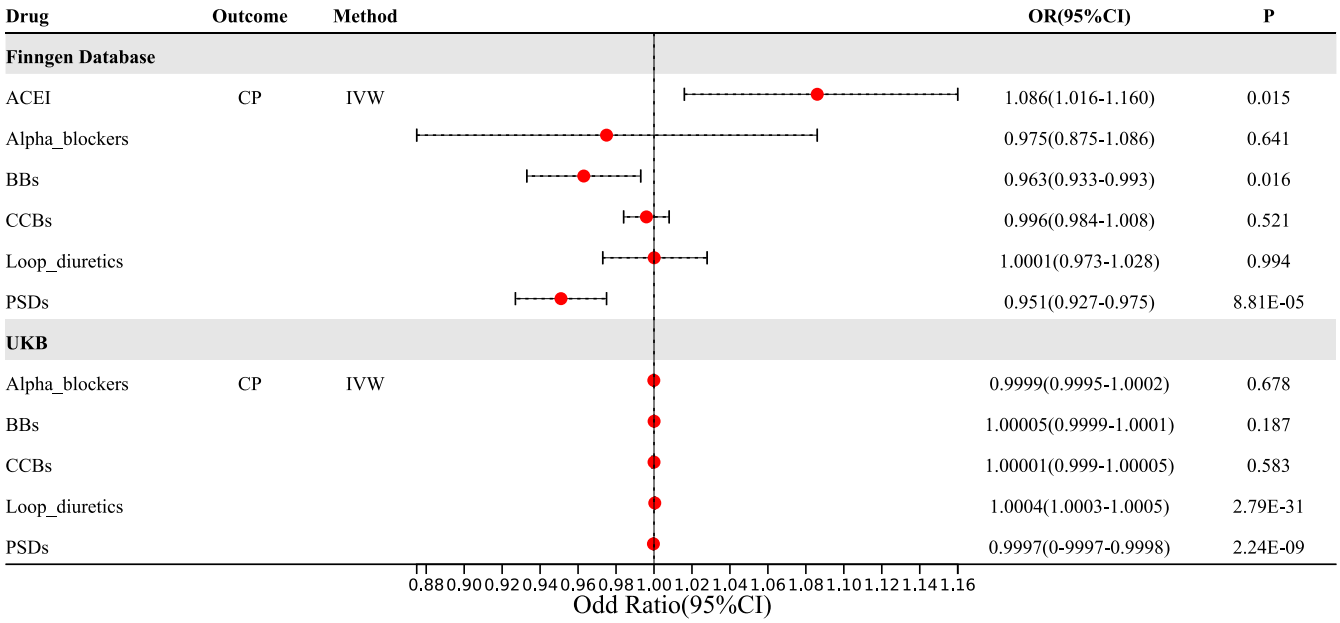

FIGURE 3 Forest diagram of MR analysis of antihypertensive drugs with CP.

$p = 8.81E-05$). The FDR-corrected results maintained consistent significance. Then, in the UK Biobank cohort, the genetic proxy for PSDs repeated the protective effect observed previously in CP (OR = 0.9997, 95% CI [0.9997, 0.9998]; $p = 2.24E-09$). Loop diuretics were found to be risk factors for CP, conversely, with an OR of 1.0004 (95% CI [1.0003, 1.0005]; $p = 2.79E-31$). No heterogeneity or pleiotropy was found in the other results, and the MR-PRESSO method did not detect any outlier SNPs (Table S5).

5 | DISCUSSION

In this study, we utilized MR analysis of drug targets to investigate the potential causal effects of antihypertensive drugs on pancreatitis. In the FinnGen cohort, genetic instruments for ACEIs and PSDs were positively associated with AP, whereas those for BBs and loop diuretics were found to be protective against AP. No significant association was found between genetic instruments for CCBs and AP. Notably, the multiplicative test MR-Egger intercept suggested that the results for loop diuretics might be subject to debate. Subsequently, in the UK Biobank cohort, consistent with the previous findings, genetic instruments for PSDs were also positively associated with AP, and those for CCBs were found to be positively correlated with AP. The MR-Egger intercept method revealed the multiplicative nature of this causal relationship. We conducted a similar analysis for CP using the same methods. Initially, in the FinnGen cohort, we studied the effects of genetic instruments for antihypertensive drug targets on CP, yielding results similar to those for AP. Genetic instruments for ACEIs were positively correlated with CP whereas those for BBs showed a negative correlation. However, PSDs' genetic instruments exhibited a protective effect against CP. In the UK Biobank cohort, genetic instruments for PSDs were found to be negatively correlated with CP, whereas those for loop diuretics were positively correlated with CP. These findings provide genetic evidence supporting antihypertensive drugs as potential therapeutic targets for improving and preventing pancreatitis.

Previously, there have been seven reported cases of ACEIs-induced pancreatitis. Patients developed AP due to the use of enalapril.[26–30] Most patients were taking 20 mg of enalapril daily, with an incubation period ranging from 5 days to 10 years. There are still several case reports suggesting other ACEIs as the cause of AP: two cases of captopril,[31,32] six cases of lisinopril (incubation period ranging from 3 h to 5 years),[33–38] one case of benazepril[39] and one case of ramipril.[40] By modulating the renin–angiotensin–aldosterone system (RAAS), ACEIs exert their pharmacological effects. Beyond its systemic impacts, RAAS also contributes to the function of the intestinal mucosal barrier. The renin–angiotensin system (RAS) is an important mediator of AP. Angiotensin-(1-7) is a member of the ACE2/Ang-(1-7)/Mas receptor axis, which antagonizes the classical RAS axis (ACE/Ang II/AT1 receptor). Previous studies have shown that Angiotensin-(1-7) can significantly improve pancreatic injury and reduce pancreatic acinar cell apoptosis. ACEIs can alter the function of the intestinal mucosal barrier by regulating angiotensin, leading to the occurrence of acute and CP. Furthermore, ACEI-mediated inhibition of bradykinin degradation results in elevated systemic levels of this peptide. Bradykinin, a powerful vasodilator, also enhances capillary permeability. This physiological effect can, under certain conditions, precipitate localized vascular oedema. When such oedema forms in the vicinity of the pancreatic head or the duodenal papilla, it may exert pressure on the pancreatic duct or the terminal portion of the common bile duct. This compression impedes pancreatic fluid outflow, thereby culminating in acute obstructive pancreatitis.[41] This is consistent with the results of our cohort study at the genetic level, indicating that ACEIs

exacerbate pancreatic injury by inhibiting angiotensin-(1-7), making them a risk factor for both AP and CP.

Although there have been reports of five cases of loop diuretics-induced pancreatitis, with one case confirmed to have received 40 mg/day of furosemide treatment for 5 weeks before developing AP, contradicting the results of our cohort study. The depletion of potassium ions due to excessive use of furosemide may be attributed to this discrepancy, leading to hypokalaemia, pancreatic cell dysfunction, and impaired pancreatic circulation, resulting in pancreatitis. However, from a genetic perspective, we found it to be protective, indicating the need for further exploration of this issue. There have been few reports of pancreatitis caused by PSDs, but at the genetic level, in both the FinnGen and UK Biobank cohorts, PSDs were recognized as a risk factor for AP, as we found. This may be due to accelerated water metabolism and reduced blood volume in the body after using PSDs such as spironolactone, indirectly affecting pancreatic blood circulation, leading to pancreatic ischaemia and hypoxia. Additionally, while spironolactone retains potassium, it also lowers other ion levels, potentially increasing the risk of AP. Interestingly, in both the FinnGen and UK Biobank cohorts, PSDs act as a protective factor for CP, as we discovered. Drugs of the same class have opposite effects on organ inflammation in chronic and acute states, suggesting complex and diverse mechanisms that warrant further investigation.

In both the FinnGen and UK Biobank cohorts, we found that genetic indicators for BBs were protective factors for both AP and CP. AP precipitates a state of extreme physiological stress, which in turn leads to excessive activation of the sympathetic nervous system and a consequent surge in circulating catecholamines (e.g., adrenaline and noradrenaline). This phenomenon, often termed a 'sympathetic storm', exacerbates pancreatic and systemic damage via three principal pathophysiological mechanisms. First, it promotes pancreatic ischaemia and necrosis. Catecholamines, being potent vasoconstrictors, induce intense constriction of the pancreatic microvasculature. This rapidly results in severe local ischaemia and hypoxia, culminating in parenchymal necrosis. Second, it potentiates the systemic inflammatory response. The binding of catecholamines to β2-adrenergic receptors expressed on immune cells stimulates a massive release of pro-inflammatory cytokines, thereby initiating systemic inflammatory response syndrome (SIRS). Third, it imposes a significant burden on the cardiovascular system. Catecholamine activation of cardiac β1-receptors leads to tachycardia and increased myocardial contractility, which markedly elevates myocardial oxygen consumption and cardiac workload, thus accelerating the progression to multiple organ dysfunction syndrome (MODS). The therapeutic rationale for beta-blockers lies in their ability to competitively antagonize the binding of catecholamines to their receptors. By doing so, they counteract these deleterious.[42] There have been previous case reports of patients developing pancreatitis due to excessive use of CCBs. Excessive use of CCBs may lead to hypercalcemia in the body, further causing pancreatic duct calcification, promoting premature release of pancreatic enzymes, and triggering AP. In the UK Biobank cohort, where CCBs were identified as a risk factor for AP, this aligns with our findings.

Although the World Health Organization (WHO) database lists over 500 drugs that can cause pancreatitis, there is a lack of evidence indicating that the majority of these drugs are aetiological factors in AP.[43] Currently, there are only a small number of case reports and retrospective studies on the relationship between antihypertensive drugs and pancreatitis, with a lack of RCTs and MR studies to clearly establish causality. Understanding the causal relationship between the two is of great significance for studying the mechanisms of disease occurrence and guiding clinical practice. Therefore, we designed an experiment to conduct a MR study on both. This study has several advantages. It utilizes simulated genetic variations in antihypertensive drugs to test their effects through drug target MR. First, by avoiding the time and resource constraints associated with randomized controlled trials, this approach mitigates the limitations of observational studies, such as reverse causality and potential confounding factors. Second, by utilizing GWAS data from the largest genetic investigations to date, the study enhances the statistical robustness of the findings and conclusions. Third, to identify genetic variations associated with systolic blood pressure as surrogate markers of antihypertensive drugs, a stringent screening process is implemented, followed by a positive control analysis to verify the efficacy of the genetic instruments. Fourth, to confirm the reliability and consistency of the findings, various sensitivity analyses are conducted. Compared with traditional observational studies, MR can minimize the influence of

TABLE 1 The dataset employed for the MR analysis in this research.

Phenotype	Ancestry	Sample size (case/control)	Sources
Exposure			
SBP	European	757 601	ICBP
Outcome			
CAD	European	547 261 (122 733/424 528)	CARDIoGRAMplusC4D Consortium
AP	European	337 126 (6223/330 903)	FinnGen Database R9
AP	European	463 010 (1215/461 795)	UK Biobank
CP	European	334 223 (3320/330 903)	FinnGen Database R9
CP	European	361 194	UK Biobank

Abbreviations: AP, acute pancreatitis; CAD, coronary artery disease; CARDIoGRAMplusC4D, Coronary ARtery DIsease Genome-wide Replication and Meta- analysis (CARDIoGRAM) plus the Coronary Artery Disease (C4D) Genetics; CP, chronic pancreatitis; ICBP, International Consortium of Blood Pressure; SBP, systolic blood pressure.

confounding factors on experimental results. Additionally, the sample size is larger compared with previous studies, ensuring the strength of the results in the MR analysis through a meta-analysis of the largest available GWAS datasets. MR-Egger and MR-PRESSO regression intercept tests are used to detect and eliminate horizontal pleiotropy, ensuring the robustness of the results. However, our study also has certain limitations. First, assessing the long-term effects of drugs, MR analysis targeting drug targets may hold more substantial significance than the short-term effects observed in clinical trials. Thus, the primary importance of this study might be in offering guidance regarding the causal association of drugs. Second, the drug effects observed in MR analysis could be affected by potential horizontal pleiotropy. To mitigate this possibility, we utilized IVs proximal to the genes encoding drug targets.

In summary, we have confirmed a causal relationship between antihypertensive drugs and both AP and CP. This finding can provide new insights for the prevention and treatment of both acute and CP.

6 | CONCLUSIONS

This study provides evidence for the causal relationship between antihypertensive drugs and pancreatitis. The findings indicate that genetic markers for ACEIs and PSDs might have a harmful effect on AP, whereas those for BBs and loop diuretics might have a protective effect. Furthermore, genetic indicators for ACEIs and PSDs are identified as risk factors for CP, whereas genetic indicators for BBs are protective factors for CP. This study advocates for the repositioning of antihypertensive drugs in pancreatitis treatment and contributes to the creation of effective antihypertensive regimens for individuals at high risk of pancreatitis in clinical practice.

AUTHOR CONTRIBUTIONS

Zhiwei Du and Jiachen Li designed the study, analysed the data and wrote the manuscript. Xuxu Liu, Yi Zheng, Tianming Liu, Yuanhang He and Ziang Meng prepared the images and tables. Jing Wang, Dali Zhao and Liyi Wang reviewed and revised the manuscript. Dongbo Xue and Liyi Wang supervised the research. All authors approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

We declare that there are no conflicts of interest in this study.

DATA AVAILABILITY STATEMENT

The datasets supporting the conclusions of this article are publicly available. The specific data sources are shown in Table 1

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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