

# Dietary Influences on Pancreatitis Risk Mediated by Gamma-glutamyltransferase: A Bidirectional Mendelian Randomization Analysis Using UK Biobank and Finnngen Datasets

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**Abstract** Pancreatitis is a destructive inflammatory condition with substantial morbidity. Although epidemiological studies link dietary patterns to pancreatitis, causality remains uncertain. This study applied bidirectional Mendelian randomization (MR) to examine the causal influence of dietary habits on pancreatitis and to identify potential mediating metabolites in blood and urine. Large-scale genetic datasets were analyzed, covering dietary intake patterns, relevant biomarkers, and multiple pancreatitis subtypes—including acute (AP), chronic (CP), alcohol-associated acute (AAP), and alcohol-associated chronic (ACP) pancreatitis. Results identified four dietary habits (dried fruit, fresh fruit, processed meat, and cereal intake) among the 15 tested that had significant causal effects on pancreatitis, without reverse causality. Notably, dried fruit consumption showed protective effects against AP ( $p < 0.00005$ ,  $\beta = -1.2401$ ) and CP ( $p = 0.0032$ ,  $\beta = -1.0084$ ), partially mediated by blood and urine gamma-glutamyltransferase (GGT). Mediation analysis revealed GGT showed the highest mediation proportion, accounting for 8.6% (CP,  $p = 0.0014$ ) and 4.6% (AP,  $p = 0.0261$ ) of this protective effect. Our MR study first discovered that the dried fruit intakes protect against pancreatitis, mediated by the blood and urine biomarkers GGT. These findings improve our understanding of how dietary patterns influence pancreatitis development and offer valuable insights for designing targeted nutritional prevention strategies.

**Keywords:** Mendelian randomization, food intakes, blood and urine biomarkers, pancreatitis, mediation analysis

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## 1. Introduction

Pancreatitis is a complex, progressive, and destructive inflammatory disease with high morbidity [1]. Acute pancreatitis (AP) is a common acute abdominal condition in the digestive system and one of the most common gastrointestinal diseases requiring acute hospitalization. Globally, the incidence of AP is 33.74 per 100,000 individuals, with a mortality rate of 1.16 per 100,000 individuals [2,3]. Chronic pancreatitis (CP) is a recurrent/persistent inflammatory change of the pancreas caused by a variety of reasons, such as a persistent pancreatic inflammatory response, pancreatic fibrosis, and progressive loss of endocrine and exocrine function [4]. The risk of developing recurrent acute pancreatitis (RAP)

after the first attack of AP is 17% -22%, and the risk of progression from RAP to CP is 32% - 36% [5,6]. Epidemiological studies have shown that the incidence of CP is 6.81 cases per 100,000 person-years [7]. Loss of pancreatic function leads to recurrent or persistent abdominal pain, diabetes, malnutrition, sarcopenia, and bone disease [8,9]. In addition, CP is an important risk factor for the development of pancreatic cancer, which is a highly fatal malignant tumor with few effective treatment options [10].

The common causes of pancreatitis include cholelithiasis, alcoholism, smoking, and hyperlipidemia [11]. Dietary habits are increasingly being recognized as a potential risk factor for pancreatitis [12]. Up to now, numerous studies have explored the correlation between dietary factors and the incidence of pancreatitis. Oskarsson has conducted a series of population-based

prospective cohort studies. Others believe that the incidence of non-gallstone-associated AP is related to the intake of vegetables, fish, and high glycemic load foods, but not to coffee intake [13,14,15,16]. Setiawan et al. analyzed the association between nine foods and nine nutrients and the incidence of acute pancreatitis using data from a multi-ethnic cohort study. The findings revealed that while numerous dietary factors are associated with gallstone-related episodes (such as red meat, eggs, saturated fat, dietary fiber, and milk), only dietary fiber intake was linked to non-gallstone-related episodes [17]. In addition to epidemiological association, studies have suggested causal effects of various potential exposures on pancreatitis. The genes driving smoking, alcohol consumption, cholelithiasis, autoimmune diseases, type 2 diabetes, elevated serum calcium levels, and triglycerides all increase the risk of pancreatitis [18,19]. Currently, serum parameters, including serum amylase [20], cholesterol [21], and C-reactive protein (CRP) [22], have been reported as potential biomarkers of pancreatitis. These studies offer new insights into novel strategies for the prevention and treatment of pancreatitis. However, the causal relationship between food intake and pancreatitis, particularly the underlying mediators, remains unclear.

Mendelian randomization (MR) is a powerful molecular epidemiological method for causal inference. [23]. It uses genetic variations (SNPs) associated with traits of interest and utilizes these SNPs as instrumental variables to simulate randomized experiments and assess causal effects between exposure and outcome traits. The causal relationship between specific genes and traits can be determined through statistical analysis, rather than merely relying on correlation. Despite challenges such as SNP selection and consideration of confounding variables, this method offers vital clues for comprehending the onset and treatment of diseases [24,25].

Currently, MR studies have confirmed that diet influences the risk of pancreatitis; however, the mechanisms underlying different dietary pathways remain unclear. Further research is warranted to evaluate the potential mediating role of blood and urine biomarkers in this association. Therefore, this study aimed to elucidate the potential causal relationship among 15 food intake patterns, 35 blood and urine biomarkers, and four types of pancreatitis by performing a bidirectional MR analysis. Additionally, we sought to explore the mediating effects of these biomarkers to provide insights into the underlying mechanisms.

## 2. Methods

### 2.1. Study Design

Based on two-sample MR, our study was a preliminary assessment of the causal relationship between 15 dietary habits and pancreatitis. Taking pancreatitis disease as the exposure factor, we used the inverse variance weighted (IVW) method to select dietary habits as the outcome factor and conducted the reverse MR to determine the existence of reverse causality. Using two-step MR (TSMR) and multivariable MR methods, blood and urine biomarkers in 35 UKB databases were used as mediators.

We aimed to determine whether blood and urinary biomarkers play a mediating role in the causal pathway between dietary habits and pancreatitis.

### 2.2. Dietary Pattern Data Sources

GWAS summary data of 15 dietary patterns were obtained from the UK Biobank, a large prospective cohort, including about 500,000 participants with genetic and various phenotypic information [25]. Screen for SNPs significantly associated with each dietary pattern. A stringent genome-wide significance threshold of  $p < 1 \times 10^{-8}$  was applied to avoid bias from SNP correlations, followed by clustering of the identified significant SNPs. Using the parameter  $r^2 < 0.001$  and a window size of 10,000 Kb, only the most significant SNP was retained among those in close physical proximity, ensuring instrumental variables remained independent.

### 2.3. Pancreatitis Data Sources

Pooled genome-wide association study (GWAS) data for four types of pancreatitis were obtained from the FinnGen Consortium R10 database, based on European populations. Specifically, this includes acute pancreatitis (6,787 cases/361,641 controls), chronic pancreatitis (3,875 cases/361,641 controls), alcoholic acute pancreatitis (1,021 cases/411,160 controls), and alcoholic chronic pancreatitis (1,959 cases/410,222 controls). Subsequently, a rigorous genetic instrumental variable screening process was performed: Single nucleotide polymorphisms were initially screened based on a genome-wide significance threshold ( $p < 5 \times 10^{-8}$ ). Clustering and deduplication were then performed using linkage disequilibrium parameters ( $r^2 < 0.001$ , window size 10,000 kb). Ultimately, all strong instrumental variables with  $F$ -statistics  $> 10$  were retained, establishing a robust genetic foundation for subsequent Mendelian randomization analyses. All of which were related to European demography.

### 2.4. Biomarker Data Sources

The GWAS data of 35 blood and urine biomarkers sampled from 341,077 individuals of European descent were retrieved from the GWAS catalog. The genetic characteristics of 35 blood and urine biomarkers were investigated, and the genetic basis of these biomarkers was revealed. Through GWAS, multiple genetic loci significantly associated with these biomarkers were identified, indicating that most biomarkers have significant genetic components. Specifically, blood biomarkers such as glucose, cholesterol, inflammatory markers, and urine biomarkers such as uric acid and urinary protein have demonstrated various genetic associations and related genes. These findings help to understand the impact of genetics on biomarker levels, help to predict disease risk, and provide the basis for personalized medicine and precision medicine research. Specifically, the GWAS IDs of the 35 blood and urine biomarkers studied ranged from GCST90019492 to GCST90019526 [26]. The sources and detailed information regarding exposure, outcomes, and mediation

are provided in the supplementary materials (Table S1 and Table S2).

## 2.5. Instrumental Variable Selection

The selection of instrumental variables (IVs) needs to comply with several assumptions, with the primary setting being the robustness of IVs for exposures [27]. To obtain reliable IVs [28], we uniformly adopted the threshold of  $p < 1 \times 10^{-8}$  for defining dietary habits- and blood-and-urine-biomarkers- related SNPs [29,30]. Subsequently, SNPs showing linkage disequilibrium were filtered using the criteria of  $r^2 < 0.001$  and  $Kb = 10,000$  [31], and then the F-statistics of the selected SNPs were calculated to eliminate weak instrumental variables. F-statistics greater than 10 are considered to indicate the absence of instrumental variables [32,33].

## 2.6. MR Analysis

Five methods were used to evaluate causality: IVW, MR egger, weighted median, simple mode, and weighted mode methods, with IVW as the main method [34,35]. The Holm-Bonferroni method was used to correct for multiple comparisons and adjust significance thresholds, which were computed independently for dietary exposures ( $n = 15$ ) and mediators ( $n = 35$ ) [36]. The “leave one” method was used for sensitivity analysis and further tested for pleiotropy [37]. Using the TSMR method, we initially calculated the total effect (b) of dietary habits on pancreatitis, the effect of diet on blood and urine biomarkers (b1), and the effect of blood and urine biomarkers on pancreatitis (b2), and then calculated the mediated effect ( $b1 * b2$ ). The direct effect was the total effect minus the mediating effect [38]. All analyses were performed using R language (version 4.3.2) and TwosampleMR package (version 0.6.0).

## 3. Results

### 3.1. Genetic Causal Relationship between Dietary Habits and Pancreatitis: Significant Effects of Dried Fruit Intake

After linkage disequilibrium filtering and weak instrumental variables elimination, we finally identified 399 SNPs linked to 15 dietary habits, with a minimum F-value of 29.71. In the dietary exposure analysis of the study, the F-statistics for all obtained SNPs exceed the empirical threshold of 10, indicating that the results are unlikely to be biased by the influence of weak IVs.

In the main univariate MR analysis, after Bonferroni correction, three causal relationships were ultimately identified: the intake of dried fruits predicted by the gene was closely associated with a reduced risk of AP (OR = 0.2894; 95% CI, 0.1721-0.4864;  $p = 2.8800 \times 10^{-6}$ ) and CP (OR = 0.3648; 95% CI, 0.1866-0.7130;  $p = 0.0032$ ); the predicted cereal intake exhibited a protective effect on AP (OR = 0.4268; 95% CI, 0.2523-0.7220;  $p = 0.0015$ ) and CP (OR = 0.5016; 95% CI, 0.2577-0.9763;  $p = 0.0423$ ). In addition, we have identified several potential

causal relationships. Genetic tendency of preferred fresh fruit intake was also significantly associated with reduced risk of three types of pancreatitis: AP (OR = 0.4262; 95% CI, 0.1999-0.9085;  $p = 0.0272$ ), CP (OR = 0.4196; 95% CI, 0.1792-0.9822;  $p = 0.0454$ ) and ACP (OR = 0.2586; 95% CI, 0.0757-0.8833;  $p = 0.0309$ ). In contrast, genetically predicted processed meat intake levels were associated with increased risk of AP (OR = 1.9159; 95% CI, 1.0217-3.5926;  $p = 0.04277$ ), but not with CP (OR = 1.5339; 95% CI, 0.6698-3.5130;  $p = 0.3116$ ) and ACP (OR = 1.9869; 95% CI, 0.5007-7.8848;  $p = 0.3289$ ).

To exclude the reverse effect, we performed a reverse Mendelian randomization analysis with different types of pancreatitis as exposure factors and 15 dietary habits as outcomes. Our results did not show a reverse causal relationship between pancreatitis and any dietary habits ( $r$ - $p$  value  $> 0.05$ , Table S5). The sensitivity analysis by the leave-one-out test confirmed the robustness of the MR results (according to Cochran's Q test and mr-presso global test, and there is no evidence of potential pleiotropic bias (Figure 1, Table 1).

### 3.2. Genetic Causal Relationship between Dietary Habits and 35 blood/urine Biomarkers: Significant Effects of Dried Fruit Intake on Gamma-glutamyltransferase

To deeply explore the potential genetic causal effects of dietary habits on human blood and urine biomarkers, this study selected two dietary factors (dried fruit intake and grain intake) as core exposures. These factors were chosen based on prior analyses confirming their potential causal associations. 35 blood and urine biomarkers were set as outcome indicators. A TSMR analysis was systematically conducted. After Bonferroni corrections ( $p < 0.0014$ ), dried fruit intake showed significant genetic causal associations with nine biomarkers: apolipoprotein B, AST\_ALT\_ratio, C\_reactive\_protein, calcium, creatinine\_in\_urine, cystatin C, gamma-glutamyltransferase, LDL\_direct\_adjstatis, and sodium\_in\_urine (Figure 2). These findings indicate that dried fruit consumption may modulate various physiological processes through genetic pathways, including lipid metabolism, inflammation, hepatic/renal function, and electrolyte homeostasis. Meanwhile, grain consumption exhibited exclusive association with urinary sodium (sodium\_in\_urine), suggesting its primary influence centers on sodium metabolism regulation (Figure 2).

For the identified associations demonstrating robust causal relationships, we quantified effect sizes (b1) of dietary exposures on each biomarker (Table 2). These beta values represent the magnitude and direction of biomarker changes per unit increase in dietary intake, providing crucial genetic epidemiological evidence for understanding how nut and cereal consumption influences physiological processes. The results demonstrated that dried fruit intake exerted the most significant effects on three biomarkers (ST\_ALT\_ratio, C\_reactive\_protein, and gamma-glutamyltransferase) in blood and urine samples (Table 2).

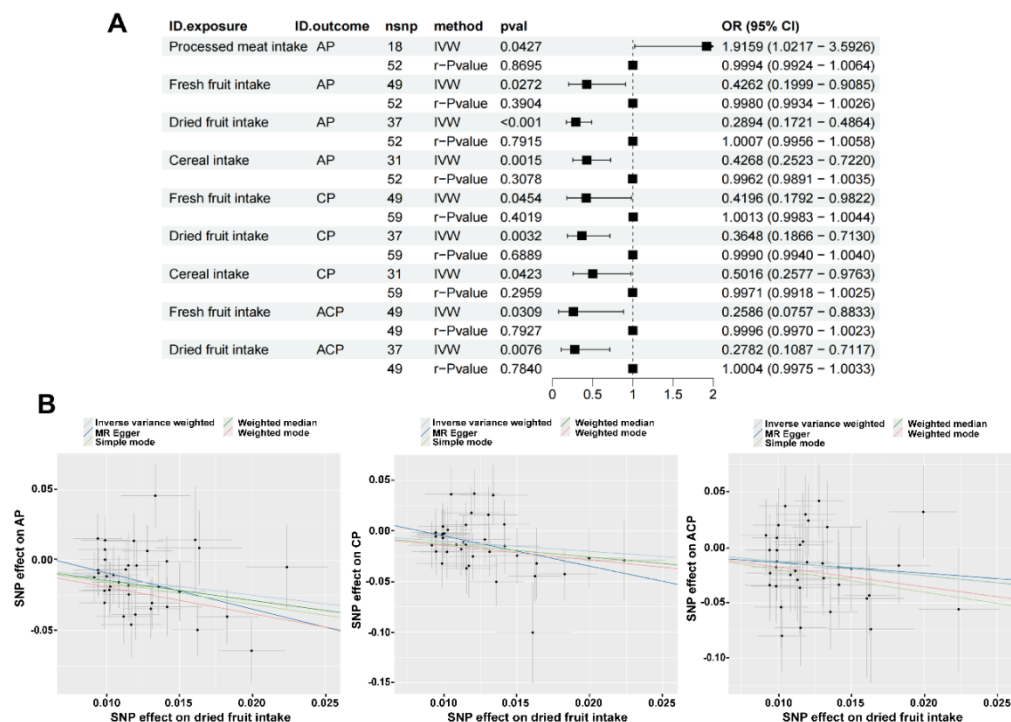
### 3.3. Genetic Causal Relationship between Blood/urine Biomarkers and Pancreatitis: Gamma-glutamyltransferase as a Risk-associated Biomarker

By selecting instrumental variables, we conducted an association analysis to eliminate linkage disequilibrium and weak instrumental variables, ultimately identifying 20,467 SNPs associated with hematuria biomarkers, with a minimum F-statistic of 10.0014 (Table S6).

Through MR analysis of 35 hematuria biomarkers and 4 different types of pancreatitis, IVW analysis and Bonferroni correction identified three hematuria biomarkers with a causal relationship to pancreatitis. Gamma-glutamyltransferase (GGT) was associated with an increased risk of AP (OR = 1.1564; 95% CI, 0.0737-1.2455;  $p = 0.0001$ ); Insulin-like growth factor 1 (IGF-1)

was associated with a reduced risk of AP (OR = 0.8758; 95% CI, 0.8120-0.9447;  $p = 0.0006$ ). GGT was also associated with an increased risk of CP (OR = 1.2497; 95% CI, 1.1356-1.3752;  $p = 5.0600 \times 10^{-6}$ ). For alcoholic pancreatitis, triglycerides increased the risk of AAP and ACP. Specifically, AAP (OR = 1.3535; 95% CI, 1.1265-1.6263;  $p = 0.0012$ ) and ACP (OR = 1.2627; 95% CI, 1.0981-1.4518;  $p = 0.0011$ ) (Figure 3, Table 3).

In our final analysis, based on the positive results obtained after Bonferroni correction, we conducted a mediation analysis to elucidate the causal relationship between dietary habits, mediated by hematuria biomarkers, and pancreatitis. Our findings revealed that gamma-glutamyltransferase was the sole hematuria biomarker mediating the protective effect of dry fruit intake on pancreatitis. Specifically, the mediated effect on CP was 8.6% ( $p = 0.0014$ ), while for AP, it was 4.6% ( $p = 0.0261$ ) (Figure 4, Table 4).



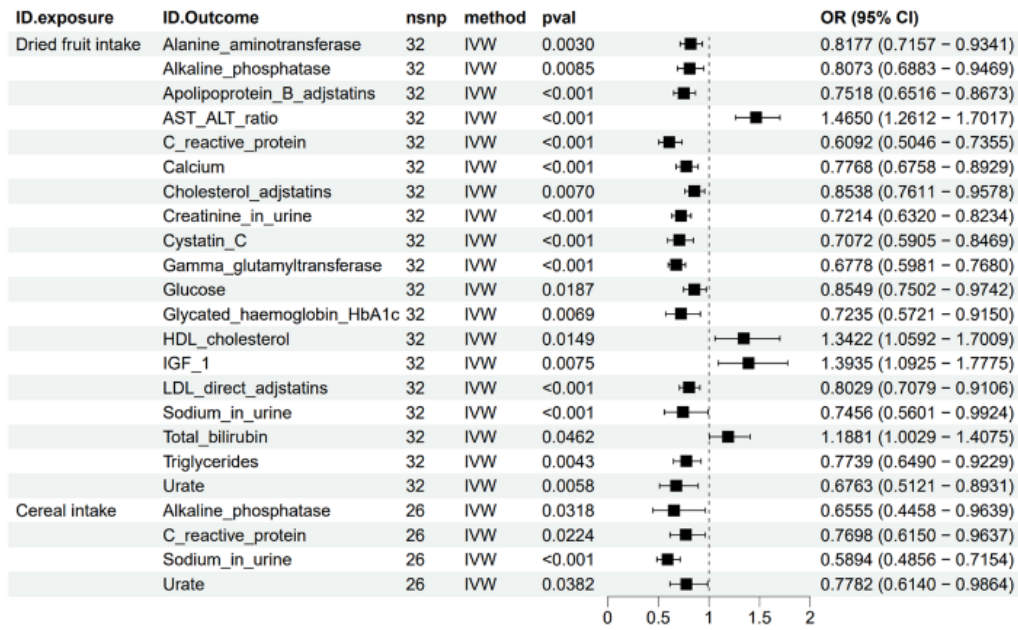
**Figure 1.** The causal effects between dietary habits and different types of pancreatitis. A. Forest plot of causality between four dietary habits and pancreatitis (r-Pvalue is the result of reverse Mendelian randomization); B. Scatter plot of dried fruit intake and cereal intake reducing pancreatitis risk. Nsnp, the number of single nucleotide polymorphisms; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval

**Table 1. Causal effects of dietary on pancreatitis**

| Outcome | Exposure              | Method | Nsnp | Beta    | Se     | P-val    | Pleiotropy |
|---------|-----------------------|--------|------|---------|--------|----------|------------|
| AP      | Processed meat intake | IVW    | 18   | 0.6502  | 0.3208 | 0.0427   | 0.3908     |
|         | Fresh fruit intake    | IVW    | 49   | -0.8530 | 0.3862 | 0.0272   | 0.1681     |
|         | Dried fruit intake    | IVW    | 37   | -1.2401 | 0.2650 | <0.00005 | 0.2676     |
|         | Cereal intake         | IVW    | 31   | -0.8515 | 0.2683 | 0.0015   | 0.0626     |
| CP      | Fresh fruit intake    | IVW    | 49   | -0.8686 | 0.4340 | 0.0454   | 0.0793     |
|         | Dried fruit intake    | IVW    | 37   | -1.0084 | 0.3419 | 0.0032   | 0.2061     |
|         | Cereal intake         | IVW    | 31   | -0.6900 | 0.3398 | 0.0423   | 0.9328     |
| ACP     | Fresh fruit intake    | IVW    | 49   | -1.3525 | 0.6267 | 0.0309   | 0.0209     |
|         | Dried fruit intake    | IVW    | 37   | -1.2796 | 0.4793 | 0.0076   | 0.8834     |

AP, acute pancreatitis; CP, chronic pancreatitis; ACP, alcohol-induced chronic pancreatitis; IVW, inverse variance weighted; Nsnp, the number of single nucleotide polymorphisms; Se, standard error.



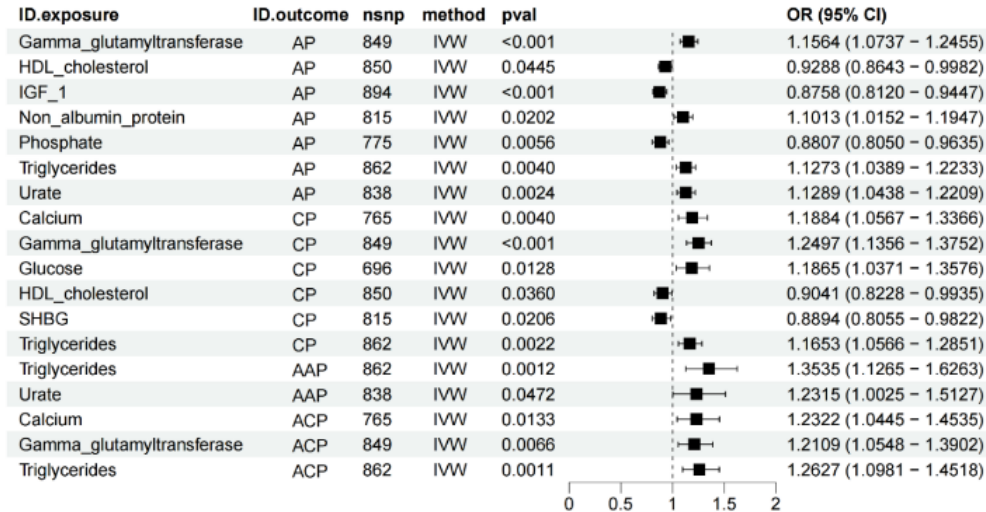


**Figure 2.** Forest plot of causality between four dietary habits and blood and urine biomarkers. Nsnp, the number of single nucleotide polymorphisms; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval

**Table 2. Causal effects of dietary on blood and urine biomarkers**

| Exposure           | Outcome                    | Method | Nsnp | Beta    | Se     | P-val    | Pleiotropy |
|--------------------|----------------------------|--------|------|---------|--------|----------|------------|
| Dried fruit intake | Alanine_aminotransferase   | IVW    | 32   | -0.2013 | 0.0679 | 0.0030   | 0.5700     |
|                    | Alkaline_phosphatase       | IVW    | 32   | -0.2141 | 0.0814 | 0.0085   | 0.0430     |
|                    | Apolipoprotein_B_adjstatis | IVW    | 32   | -0.2853 | 0.0729 | 0.0001   | 0.3701     |
|                    | AST_ALT_ratio              | IVW    | 32   | 0.3819  | 0.0764 | <0.00005 | 0.0021     |
|                    | C_reactive_protein         | IVW    | 32   | -0.4956 | 0.0961 | <0.00005 | 0.8162     |
|                    | Calcium                    | IVW    | 32   | -0.2526 | 0.0711 | 0.0004   | 0.4706     |
|                    | Cholesterol_adjstatis      | IVW    | 32   | -0.1581 | 0.0587 | 0.0070   | 0.7753     |
|                    | Creatinine_in_urine        | IVW    | 32   | -0.3266 | 0.0675 | <0.00005 | 0.5763     |
|                    | Cystatin_C                 | IVW    | 32   | -0.3465 | 0.0920 | 0.0002   | 0.7528     |
|                    | Gamma_glutamyltransferase  | IVW    | 32   | -0.3889 | 0.0638 | <0.00005 | 0.9657     |
|                    | Glucose                    | IVW    | 32   | -0.1568 | 0.0667 | 0.0187   | 0.2344     |
|                    | Glycated_haemoglobin_HbA1c | IVW    | 32   | -0.3236 | 0.1198 | 0.0069   | 0.3102     |
|                    | HDL_cholesterol            | IVW    | 32   | 0.2943  | 0.1208 | 0.0149   | 0.2393     |
|                    | IGF_1                      | IVW    | 32   | 0.3318  | 0.1242 | 0.0075   | 0.5949     |
|                    | LDL_direct_adjstatis       | IVW    | 32   | -0.2196 | 0.0642 | 0.0006   | 0.5150     |
|                    | Sodium_in_urine            | IVW    | 32   | -0.4192 | 0.0746 | <0.00005 | 0.4251     |
| Cereal intake      | Total_bilirubin            | IVW    | 32   | 0.1724  | 0.0865 | 0.0462   | 0.0690     |
|                    | Triglycerides              | IVW    | 32   | -0.2563 | 0.0898 | 0.0043   | 0.8865     |
|                    | Urate                      | IVW    | 32   | -0.3912 | 0.1419 | 0.0058   | 0.7715     |
|                    | Alkaline_phosphatase       | IVW    | 26   | -0.4223 | 0.1967 | 0.0318   | 0.4731     |
|                    | C_reactive_protein         | IVW    | 26   | -0.2616 | 0.1146 | 0.0224   | 0.6801     |
|                    | Sodium_in_urine            | IVW    | 26   | -0.5286 | 0.0988 | <0.00005 | 0.4568     |
|                    | Urate                      | IVW    | 26   | -0.2507 | 0.1210 | 0.0382   | 0.9006     |

IVW, inverse variance weighted; Nsnp, the number of single nucleotide polymorphisms; Se, standard error

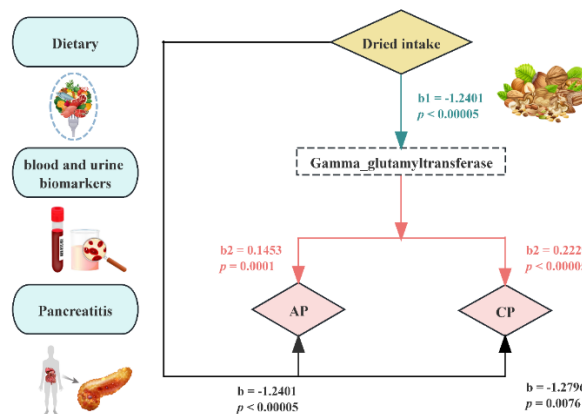


**Figure 3.** Forest plot of causality between blood and urine biomarkers and pancreatitis. Nsnp, the number of single nucleotide polymorphisms; IVW, inverse variance weighted; OR, odds ratio; CI, confidence interval

**Table 3. Effect of blood and urine biomarkers on pancreatitis**

| Outcome | Exposure                  | Method | Nsnp | Beta    | Se     | P-val    | Pleiotropy |
|---------|---------------------------|--------|------|---------|--------|----------|------------|
| AP      | Gamma-glutamyltransferase | IVW    | 849  | 0.1453  | 0.0379 | 0.0001   | 0.0259     |
|         | HDL-cholesterol           | IVW    | 850  | -0.0738 | 0.0367 | 0.0445   | 0.2913     |
|         | IGF_1                     | IVW    | 894  | -0.1326 | 0.0386 | 0.0006   | 0.6445     |
|         | Non-albumin protein       | IVW    | 815  | 0.0965  | 0.0415 | 0.0202   | 0.7884     |
|         | Phosphate                 | IVW    | 775  | -0.1271 | 0.0459 | 0.0056   | 0.9289     |
|         | Triglycerides             | IVW    | 862  | 0.1199  | 0.0417 | 0.004    | 0.238      |
|         | Urate                     | IVW    | 838  | 0.1212  | 0.04   | 0.0024   | 0.417      |
| CP      | Calcium                   | IVW    | 765  | 0.1726  | 0.0599 | 0.004    | 0.6519     |
|         | Gamma-glutamyltransferase | IVW    | 849  | 0.2229  | 0.0489 | <0.00005 | 0.1454     |
|         | Glucose                   | IVW    | 696  | 0.171   | 0.0687 | 0.0128   | 0.6739     |
|         | HDL-cholesterol           | IVW    | 850  | -0.1008 | 0.0481 | 0.036    | 0.339      |
|         | SHBG                      | IVW    | 815  | -0.1172 | 0.0506 | 0.0206   | 0.0957     |
| AAP     | Triglycerides             | IVW    | 862  | 0.3027  | 0.0937 | 0.0012   | 0.7978     |
|         | Urate                     | IVW    | 838  | 0.2082  | 0.1049 | 0.0472   | 0.0252     |
| ACP     | Calcium                   | IVW    | 765  | 0.2088  | 0.0843 | 0.0133   | 0.4766     |
|         | Gamma-glutamyltransferase | IVW    | 849  | 0.1914  | 0.0704 | 0.0066   | 0.1333     |
|         | Triglycerides             | IVW    | 862  | 0.2332  | 0.0712 | 0.0011   | 0.396      |

AP, acute pancreatitis; CP, chronic pancreatitis; AAP, alcohol-induced acute pancreatitis; ACP, alcohol-induced chronic pancreatitis; IVW, inverse variance weighted; Nsnp, the number of single nucleotide polymorphisms; Se, standard error.



**Figure 4.** The role of mediators in the relationship between dietary habits and pancreatitis. b, total effect of dried intake on pancreatitis; b1, the effect of dried intake on Gamma-glutamyltransferase; b2, the effect of Gamma-glutamyltransferase on pancreatitis; AP, acute pancreatitis; CP, chronic pancreatitis

**Table 4. Potential metabolite mediators accounting for the causal effect of dried fruit intake on pancreatitis**

| Dietary            | Mediating biomarkers      | Pancreatitis | Mediated effect | Mediated proportion | Beta Direct | P-val  |
|--------------------|---------------------------|--------------|-----------------|---------------------|-------------|--------|
| Dried fruit intake | Gamma-glutamyltransferase | AP           | 0.05652409      | 0.0456              | 1.1835      | 0.0261 |
|                    |                           | CP           | 0.08668427      | 0.0860              | 0.9217      | 0.0014 |

## 4. Discussion

The pancreas is a crucial organ in the human body that regulates nutrient metabolism. It secretes insulin and glucagon into the blood circulation system to control the body's glucose metabolism [39]. It also produces a number of digestive enzymes, including trypsin and lipase, which are released into the duodenum via the pancreatic duct to aid in food digestion [40]. On the one hand, these digestive enzymes break down carbohydrates, proteins, and fats into their fundamental components, enabling the body to absorb and utilize them [41]. On the other hand, the composition of pancreatic juice is influenced by dietary composition. Different nutrient substrates trigger the secretion of specific enzymes, and dietary composition affects the development of pancreatic function and the secretion patterns of digestive enzymes [42]. Furthermore, inappropriate dietary habits may lead to metabolic changes or disorders, ultimately resulting in pancreatitis. However, there is currently limited data on the impact of dietary habits mediated by blood and urine biomarkers on the risk of pancreatitis.

In current study, we analyzed 15 dietary habits, 35 blood and urine biomarkers, and pancreatitis by using summary data from genome-wide association studies. We conducted a TSMR analysis to investigate the causal relationship between dietary intake and pancreatitis, complemented by a two-step mediation analysis and multivariable MR to identify potential biomarkers mediating blood and urine. And found a causal relationship between four of the 15 dietary habits (dried fruit, fresh fruit, cereal, and processed meat) and various types of pancreatitis. Reverse MR analysis revealed no causal relationship between these four dietary habits and different types of pancreatitis. Consistent with previous studies demonstrating that fruit intake is associated with a reduced risk of pancreatitis [16], we discovered that the intake of genetically predicted dried fruits was inversely correlated with the risk of AP and CP, indicating a protective effect against these three distinct types of pancreatitis. This result is acceptable because fruits are abundant in vitamins, minerals, dietary fiber, and antioxidants, including vitamin C, vitamin A, vitamin K, potassium, magnesium, calcium, flavonoids, phenolic acids, carotenoids, and tannins [43,44]. Dried fruits have a similar nutrient profile to fresh fruits and are a shelf-stable form of fresh fruits obtained by various drying techniques, but overcome the latter's short shelf life [45]. Over the past two decades, experimental and human clinical studies have consistently reported that dried fruits are rich in health-promoting essential substances and nutrients, which have a positive impact on human health [46,47]. Dried fruits have antioxidant, anticancer, and anti-aging properties [48,49,50,51]. In addition, intake of dried fruits has beneficial effects on reducing inflammation, weight, blood pressure, and glycosylated hemoglobin levels [52,53].

GGT is a common bioassay marker found in numerous human organs. Its concentration levels have been significantly correlated with a variety of diseases, including alcoholic liver disease, cardiovascular disease, hypertension, metabolic syndrome, type II diabetes, and certain cancers [54,55]. Considerable evidence indicates that the expression of the GGT in both animals and humans is regulated by redox mechanisms and by activating oxidative stress signaling pathways [56]. GGT plays a role in the metabolism of the antioxidant glutathione (GSH), and plasma GGT activity can be used as an indicator of the metabolic level of GSH in the body [57,58]. An abnormal increase in GGT can hinder the normal function of GSH. GGT has become one of the most recent serological markers for the assessment of oxidative stress [62]. GSH is a crucial antioxidant in the human body with physiological functions such as delaying chronic inflammatory reactions and reducing LDL oxidation. Abnormal increases in GGT can hinder these normal functions of GSH. GGT has emerged as one of the latest biological serological markers for assessing oxidative stress [59].

We found that Gamma-glutamyltransferase is the sole blood and urine biomarker mediating the protective effect of dried fruit intake on pancreatitis. Specifically, the mediated effect on chronic pancreatitis (CP) is 8.6% ( $p = 0.0014$ ), while the mediated effect on acute pancreatitis (AP) is 4.6% ( $p = 0.0261$ ). We hypothesize that the high antioxidant content in fruits could attenuate GGT-induced oxidative stress, thereby reducing basal oxidative stress levels and potentially preventing pancreatitis. However, functional studies on GGT-mediated fruit intake and pancreatitis are still lacking. Therefore, the results obtained from MR need further verification in the future. Nonetheless, the present study has some limitations, mainly due to limitations in data collection, as the sample was restricted to a European population, which may limit the generalizability of our findings to other populations. Additional researches are needed to validate our observations in non-European populations.

## 5. Conclusion

In summary, the present study assessed the causal relationship among dietary habits, blood and urine biomarkers, and pancreatitis. We have identified that dried fruit intake exhibits protective effects against pancreatitis, mediated by the blood and urine biomarkers GGT. We speculate that the high antioxidant content in fruits may prevent pancreatitis by influencing the oxidative stress induced by GGT, thereby reducing the basic level of oxidative stress. These findings underscore the significance of potential mechanisms linking dietary intake, blood and urine biomarkers, and pancreatitis. Our research contributes to a better understanding of the potential role of dietary patterns in the development of

pancreatitis and aids in the formulation of more targeted dietary strategies for preventing pancreatitis.

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## Author Contributions

Yalan Han and Ling-Yan Su conceived and designed the study. Miao Xiong, Hejiang Zhou, and Dan Xu analyzed the data. Miao Xiong and Xin Gan wrote the manuscript. All authors reviewed the content and approved the final version for publication.

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## Data Availability

The GWAS summary statistics data of dietary, blood and urine biomarkers, and pancreatitis used in this study are all publicly available. All R scripts used in the MR analysis are available from the authors upon request.

## Ethical Approval

There were no patients directly involved in the overall process of our study. This study was performed based on publicly available data and no ethical approval was required.

## Competing Interests

The authors declare no competing interests.

## Supplementary Material

Supplementary data for this article can be accessed on the publisher's website.

## Abbreviations

**AAP:** alcohol-induced acute pancreatitis; **ACP** alcohol-induced chronic pancreatitis; **AP:** acute pancreatitis; **CP:**

chronic pancreatitis; **CRP:** C-reactive protein **GGT:** gamma-glutamyltransferase; **GSH:** glutathione; **GWAS:** Genome wide association study; **IGF\_1:** Insulin-like growth factor 1; **IVs:** instrumental variables; **IVW:** inverse variance weighted; **MR:** Mendelian randomization; **MVMR:** multivariable mendelian randomization; **RAP:** recurrent acute pancreatitis; **SNP:** Single nucleotide polymorphism; **TSMR:** two-step mendelian randomization

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