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RESEARCH ARTICLE

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Impact of college completion and mediating factors on the risk of acute pancreatitis: a Mendelian randomization study

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ABSTRACT

This study aimed to investigate the causal relationship between college completion and incidence of acute pancreatitis (AP). We assessed the impact of various factors, such as smoking, alcohol consumption, triglyceride levels, type 2 diabetes, and cholelithiasis, on this causal association. We conducted a genome-wide association study (GWAS) summary statistics from European populations using a two-sample Mendelian randomization (MR) approach to analyze the causal link between college completion and AP. Two-step MR was further applied to evaluate potential mediating pathways. College completion was associated with a reduced risk of AP (odds ratio [OR] = 0.29, 95% confidence interval [CI] 0.10–0.80), as well as protective effects against smoking status (OR = 0.78, 95% CI 0.69–0.89), total triglyceride levels (OR = 0.67, 95% CI 0.53–0.85), and cholelithiasis (OR = 0.46, 95% CI 0.32–0.66). Smoking status (OR = 2.54, 95% CI 1.58–4.10), alcohol consumption (OR = 7.30, 95% CI 2.62–20.22), cholelithiasis (OR = 1.58, 95% CI 1.48–1.70), and type 2 diabetes (OR = 1.10, 95% CI 1.03–1.16) were identified as risk factors for AP. The mediating percentages of smoking status and cholelithiasis in the effect of education on AP were 18.5% (95% CI 8.53–28.6%) and 28.8% (95% CI 2.26–55.3%), respectively. College completion has a protective effect against AP, partly through its influence on smoking and cholelithiasis. These findings highlight education as a potential upstream determinant of AP risk and emphasize the role of lifestyle and metabolic factors in shaping preventive strategies.

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Introduction

Acute pancreatitis (AP), characterized by the abnormal activation of trypsinogen, is a significant global health concern with an incidence of ~34 cases per 100,000 individuals. It is one of the most prevalent conditions leading to emergency room visits and hospital admissions (Peery et al., 2022; Xiao et al., 2016). Approximately 20% of AP cases manifest as moderate to severe, marked by pancreatic or peripancreatic tissue necrosis and organ dysfunction, with a mortality rate ranging from 20 to 40% (Boxhoorn et al., 2020; Schepers et al., 2019). Additionally, ~17% of patients with AP experience recurrent episodes, and ~8% progress to chronic pancreatitis within 5 years (Liu et al., 2019). Chronic pancreatitis, characterized by exocrine fibroinflammation of the pancreas, presents with recurring abdominal pain and escalates the risk of diabetes and cancer, significantly affecting the quality of life of the patients (Beyer et al., 2020; Vege & Chari, 2022). Given the substantial global public health and economic burden of AP, identifying and mitigating its risk factors is paramount.

Education serves as a robust predictor of socioeconomic status, exerting a profound influence on individual lifestyles, behaviors, and access to healthcare resources (Rosengren et al., 2019). Socioeconomic status and educational disparities are linked to increased cardiovascular morbidity and mortality rates (Lu et al., 2023; Schultz et al., 2018). Furthermore, completion of college education has been associated with

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a reduced incidence of alcoholic fatty liver disease (Vilar-Gomez et al., 2022). However, the causal relationship between education and AP remains poorly understood. In particular, it is unclear whether education reduces AP risk directly or indirectly through pathways, such as smoking, alcohol use, triglyceride metabolism, diabetes, or gallstone disease. This represents a critical knowledge gap, as clarifying these pathways could provide new targets for prevention.

Mendelian randomization (MR) is a cutting-edge approach to causal inference that uses genetic variation as an instrumental variable, avoiding confounding and reverse causation inherent in traditional observational studies (Davies et al., 2018; Skrivankova et al., 2021). The application of MR extends to inferring the mediating causal effects, offering insights into mechanisms underlying exposure–outcome associations (Carter et al., 2021). In this study, we applied MR to examine the causal association between college completion and AP, and further evaluated whether smoking, alcohol consumption, triglyceride levels, type 2 diabetes, and cholelithiasis mediate this relationship.

Methods

Research design

This study employed a two-sample MR approach to estimate the impact of college completion on AP. In addition, the mediating effects of smoking, alcohol consumption, triglyceride levels, type 2 diabetes, and cholelithiasis on AP after college completion were investigated. Mediating MR analysis revealed that smoking and cholelithiasis played mediating roles in the percentage of AP cases associated with college completion. Figure 1 shows a detailed illustration of the mediating MR study design.

GWAS data

The genome-wide association study (GWAS) data utilized in this study were sourced from the 'MRC-IEU OpenGWAS project' (https://gwas.mrcieu.ac.uk/) database (summarized in Table 1). These datasets were derived from large-scale, population-based cohorts of European ancestry, ensuring broad

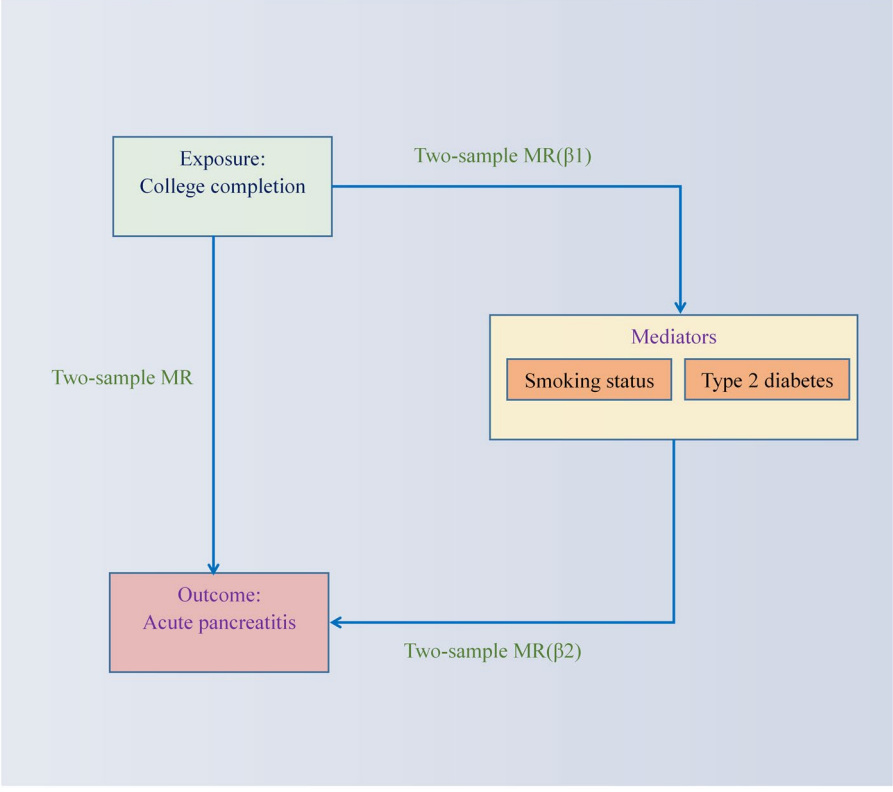

Figure 1. Mediational Mendelian randomisation (MR) analysis study design.

Table 1. Summary of GWAS datasets used in the Mendelian randomization analysis.

Phenotype	GWAS ID	Year	Population	Sample size	PMID
College completion	ebi-a-GCST90029012	2018	European	470,941	29892013
Acute pancreatitis	ebi-a-GCST90018789	2021	European	479,902	34594039
Smoking status	ebi-a-GCST90029014	2018	European	468,170	29892013
Alcohol consumption	ieu-a-1283	2017	European	112,117	28937693
Total triglycerides levels	ebi-a-GCST90092992	2022	European	115,082	35213538
Type 2 diabetes	ebi-a-GCST90018926	2021	European	490,089	34594039
Cholelithiasis	ebi-a-GCST90018819	2021	European	487,553	34594039

representativeness of the target population. Only summary-level data from individuals of European descent were included, and GWAS datasets with a total sample size <100,000 or without adequate quality control were excluded. Specifically, as the GWAS data are part of a public database, no additional ethical approval was required for their use in this study, and all original studies had obtained appropriate ethical approval and informed consent.

Instrumental variable filtering

In the present study, single nucleotide polymorphisms (SNPs) served as instrumental variables representing each exposure of interest. The instrumental variables underwent rigorous screening as outlined below: Genome-wide significance: SNPs with a significance level of $p < 5 \times 10^{-8}$ were retained. Linkage disequilibrium: SNPs with no significant linkage disequilibrium, where the linkage disequilibrium region distance (kb) was >10,000 and the linkage disequilibrium parameter r^2 was <0.001, were included. Strength of instrumental variables: Weak instrumental variables were eliminated based on an *F*-test value of >10, indicating a strong correlation with exposure. Conversely, instrumental variables with an *F*-test value of <10 were removed. Reconciliation of datasets: Exposure and outcome GWAS datasets were reconciled, and palindromic SNPs were excluded from further analysis.

MR analysis method

Mendelian randomization was applied to reduce confounding bias and provide more reliable causal inference between college completion and acute pancreatitis. The two-sample Mendelian randomization (MR) analysis primarily employed the inverse variance weighting (IVW) method. This method was utilized to combine the causal estimates of each single nucleotide polymorphism (SNP), generating a collective causal effect of exposure on the outcome variable. To evaluate heterogeneity within the exposure-outcome dataset, Cochran's *Q* statistical test was employed, with a significance level set at $p < 0.05$ to indicate significant heterogeneity.

Additionally, supplementary methods were utilized, including MR-Egger regression, weighted median, simple models, and weighted models. Horizontal pleiotropy was assessed using the MR-Egger intercept, where a significance level of $p < 0.05$ suggested the presence of horizontal pleiotropy. IVW estimates were deemed causal when they aligned with the direction of the effect from the supplementary methods and demonstrated statistical significance without evidence of pleiotropy. Effect sizes were reported as odds ratios (OR), beta coefficients, or proportions with corresponding 95% confidence intervals (CI).

Sensitivity analysis

Sensitivity analysis involved a leave-one-out test in which single SNPs were systematically removed individually to assess changes in the effect of exposure on outcomes. Significant changes indicated potential SNPs with disproportionate effects on outcomes, suggesting that the MR results may not be robust. This study adhered to the recommendations outlined in the reporting guidelines for enhanced epidemiological observational studies using Mendelian randomization, ensuring methodological rigor and transparency of analysis (Burgess et al., 2017; Skrivankova et al., 2021).

Intermediate MR analysis

In this study, we performed an intermediate Mendelian randomization (MR) analysis using a two-sample MR approach to assess the causal relationship between college completion and several mediators. Subsequently, we examined the causal effect of these mediators on the risk of acute pancreatitis (AP). The MR analysis employed the coefficient multiplication method, multiplying the effects of college completion on each mediator (β1) with the causal effects of the mediators on AP risk (β2). This approach allowed us to derive an indirect effect, which was then compared with the total effect, providing insight into the proportion of each mediator's effect on the overall association between education and AP risk.

Statistical analysis

Our statistical analysis utilized R software (version 4.42) with the 'TwoSampleMR', 'ggplot2', and 'VariantAnnotation' packages. Instrumental variable selection and MR analyses followed established methodological guidelines (Skrivankova et al., 2021), ensuring robustness and reproducibility.

Results

Effect of college completion on AP and mediating factors

After screening, the instrumental variables for college completion are presented in Table 2. Heterogeneity was observed in the effects of college completion on pancreatitis, smoking status, total triglyceride levels, type 2 diabetes, and cholelithiasis (see Table 3). Heterogeneity tests are statistical analyses of instrumental variable compatibility, and positive results allow the interpretation of heterogeneity (see Table 4). The results indicate that completing college education was associated with a 71% decrease in pancreatitis risk (OR = 0.29, 95% CI 0.10–0.80). Additionally, smoking status was linked to a 22% risk reduction (OR = 0.78, 95% CI 0.69–0.89), total triglyceride levels reduced the risk by 32% (OR = 0.67, 95% CI 0.53–0.85), and cholelithiasis lowered the risk by 45% (OR = 0.46, 95% CI 0.32–0.66). The MR-Egger regression method, weighted median method, simple model, and weighted model all exhibited consistent effect directions with the IVW method, as depicted in Figure 2. The MR intercept test ($p > 0.05$) indicated no evidence of horizontal pleiotropy, please refer to Supplementary Table 3. Sensitivity analysis confirmed the robustness of the results, as removal of any single SNP did not materially alter the estimated effects (see Figure 3). For type 2 diabetes and alcohol consumption, the MR-Egger regression method yielded effect directions inconsistent with the IVW method, indicating that there is no evidence that college completion causally affects these exposures (see Supplementary Table 5).

Table 2. Instrumental variable strength for each exposure trait.

Exposure	Number of SNPs	Mean *F*	Median *F*	Min *F*	Max *F*
College completion	52	15.29	12.5	10.48	40.08
Cholelithiasis	48	1872.22	938.75	499.56	30,640.33
Smoking status	127	19.07	16.55	12.92	84.51
Alcohol consumption	3	31.93	38.88	13.75	43.17
Total triglycerides levels	73	128.71	54.01	27.81	1284.84
Type 2 diabetes	186	888.89	512.85	215.73	14,664.29

F: *F*-statistics.

Table 3. Heterogeneity statistics across MR methods.

Exposure	Outcome	Method	*Q*	*df*	*p*
College completion	Acute pancreatitis	MR Egger	78.19	45	0.0016
College completion	Smoking status	MR Egger	360.35	48	<0.001
College completion	Total triglycerides levels	MR Egger	138.38	48	<0.001
College completion	Cholelithiasis	MR Egger	63.99	45	0.033
Smoking status	Acute pancreatitis	MR Egger	139.14	115	0.06
Alcohol consumption	Acute pancreatitis	MR Egger	0.043	1	0.84
Cholelithiasis	Acute pancreatitis	MR Egger	44.88	45	0.48
Type 2 diabetes	Acute pancreatitis	MR Egger	212.74	177	0.034

df: degrees of freedom.

Table 4. MR-Egger intercept test for horizontal pleiotropy.

Exposure	Outcome	Egger intercept	*SE*	*p*
College completion	Acute pancreatitis	−0.0026	0.023	0.91
College completion	Smoking status	−0.0012	0.0030	0.70
College completion	Total triglycerides levels	−0.0034	0.0054	0.53
College completion	Cholelithiasis	−0.0049	0.0082	0.55
Smoking status	Acute pancreatitis	−0.00021	0.010	0.98
Alcohol consumption	Acute pancreatitis	−0.025	0.091	0.83
Cholelithiasis	Acute pancreatitis	0.0030	0.0058	0.60
Type 2 diabetes	Acute pancreatitis	0.000824	0.0045	0.86

SE: standard error.

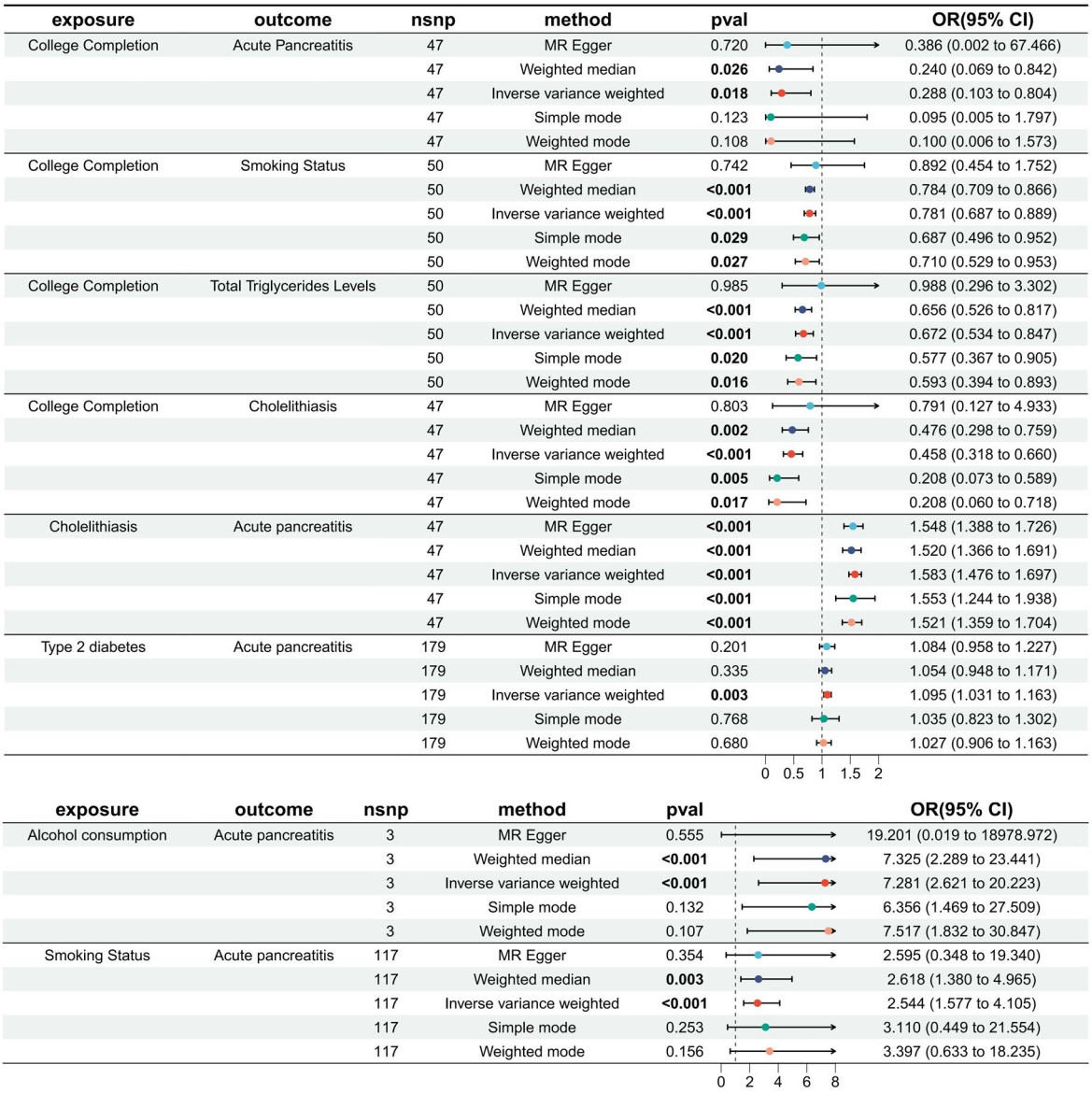

Figure 2. Forest plot of Mendelian randomization estimates.
Note: MR Egger; Weighted median; Inverse variance weighted; Simple mode; Weighted mode.

Effect of mediating factors on AP

After screening, the instrumental variables for the mediating factors are presented in Table 2. Smoking status (OR = 2.54, 95% CI 1.58–4.10), alcohol consumption (OR = 7.3, 95% CI 2.62–20.22), type 2 diabetes

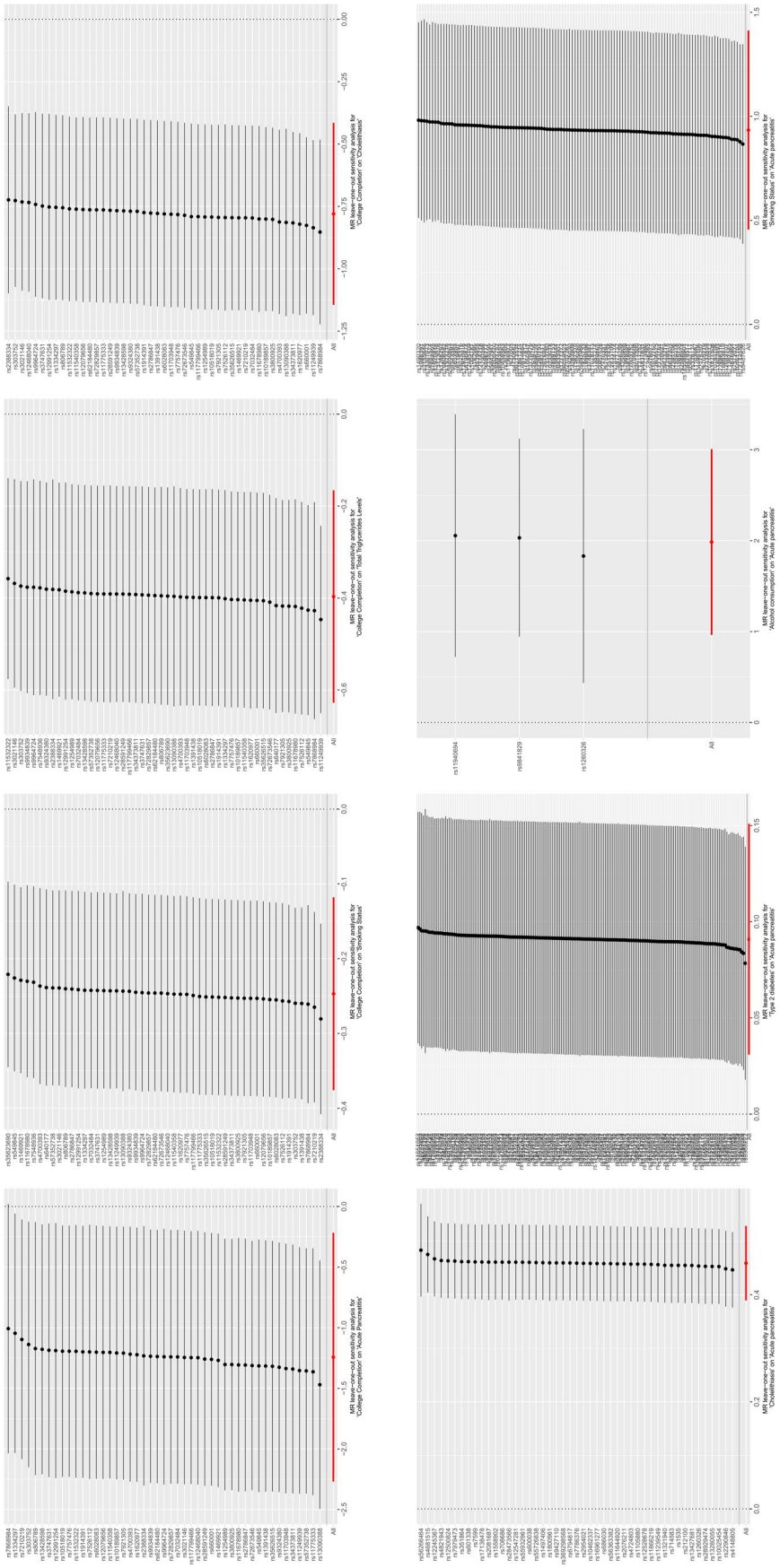

Figure 3. Leave-one-out sensitivity analysis for Mendelian randomization estimates.

(OR = 1.10; 95% CI, 1.03–1.16), and cholelithiasis (OR = 1.58, 95% CI 1.48–1.70) were found to increase the risk on AP. No evidence of heterogeneity (see Table 3) or pleiotropy (see Table 4) was observed and the effect directions observed across the five analytical methods were consistent (see Figure 2). Leave-one-out analyses further confirmed the robustness of results Figure 3. Notably, the total triglyceride levels did not show a significant causal effect on AP (see Supplementary Table 5).

Mediating factor proportion

Smoking status and cholelithiasis collectively mediated the effect of education on AP by 18.5% (95% CI 8.53–28.6%) and 28.8% (95% CI 2.26–55.3%), respectively (see Supplementary Table 6).

Discussion

Summary of key findings

This study utilized GWAS datasets from the MRC-IEU OpenGWAS project database, with college completion as the exposure factor and AP as the outcome factor for two-sample MR analysis. IVW analysis revealed a 71% reduction in the risk of acute pancreatitis following the completion of college education (OR = 0.29, 95% CI 0.10–0.80). The directional effects of the supplementary methods are aligned with the IVW direction. The MR intercept test ($p > 0.05$) indicated no evidence of horizontal pleiotropy, thus confirming the robustness of the analysis. Sensitivity analysis further supported the reliability of MR findings. Our study findings indicate that tackling educational inequality could prove to be a highly effective preventive measure against acute pancreatitis and its associated disease burdens.

Our MR study further demonstrated that college completion is associated with a reduction in smoking risk (OR = 0.78, 95% CI 0.69–0.79), decreased total triglyceride levels (OR = 0.68, 95% CI 0.60–0.76), and a reduced risk of cholelithiasis (OR = 0.55, 95% CI 0.43–0.72). However, we did not find robust causal evidence linking college completion to type 2 diabetes or alcohol consumption, which is consistent with findings from other MR studies (Na-Ek et al., 2022; Rosoff et al., 2021; Viinikainen et al., 2022), possibly due to heterogeneity across MR methods.

Alcohol consumption and smoking are well-established lifestyle risk factors associated with pancreatitis (Mederos et al., 2021; Park et al., 2025; Peery et al., 2022; Petrov & Yadav, 2019). Excessive alcohol consumption not only poses a risk for recurrent AP following an initial episode but also increases the likelihood of progression to chronic pancreatitis (Lee et al., 2023). In cohort studies conducted on the Korean population, current smokers exhibited a significantly elevated risk of AP compared to never smokers, with smoking cessation demonstrating a mitigating effect on acute pancreatitis incidence, irrespective of age or sex (European Association for the Study of the Liver, 2016). Cholelithiasis accounts for 45% of all cases and is the most prevalent cause of AP (Peery et al., 2022). Although ~75% of individuals with gallstones remain asymptomatic, ~8% eventually develop AP (Aune et al., 2020). Extensive cohort studies have consistently reported a heightened risk of acute pancreatitis among individuals with type 2 diabetes, particularly in Western populations, compared with individuals without diabetes (Lai et al., 2011; Noel et al., 2009). This trend has also been observed in Asian populations, with patients with diabetes exhibiting twice the incidence of AP compared with individuals without diabetes (Pang et al., 2018; Park et al., 2018).

MR analysis showed that alcohol consumption (OR = 7.3, 95% CI 2.62–20.22), smoking (OR = 2.54, 95% CI 1.58–4.10), cholelithiasis (OR = 1.58, 95% CI 1.48–1.70), and type 2 diabetes (OR = 1.10, 95% CI 1.03–1.16) are significant causal risk factors for AP. These findings provide strong genetic evidence complementing observational studies and emphasize the multifactorial nature of AP etiology.

Clinical and public-health implications

Educational attainment represents a distinctive facet of socioeconomic status and serves as a potent determinant of healthy behaviors, thereby impacting physical health and mortality rates (Kivimäki et al., 2020; Stringhini et al., 2017). Notably, lower education levels are often associated with higher smoking prevalence and an increased risk of diabetes (Bjerregaard et al., 2020; Özmen, 2023), whereas higher

education shows inverse associations with body mass index (BMI) and triglyceride levels (Hu et al., 2024). Smoking, BMI, and type 2 diabetes are the established risk factors for cholelithiasis (Chen et al., 2022; Yuan et al., 2022). These patterns reinforce the role of education as a powerful upstream determinant of metabolic and lifestyle factors.

From a policy perspective, our findings suggest that enhancing educational opportunities may indirectly reduce AP incidence by influencing downstream risk factors, such as smoking and gallstones. The proportions of smoking status and cholelithiasis in the effect of education on AP were estimated at 18.5% (95% CI 8.53–28.6%) and 28.8% (95% CI 2.26–55.3%). Public health programs combining smoking cessation, diabetes management, reduced binge drinking, and gallstone prevention with educational support may yield synergistic benefits. Importantly, these insights align with broader evidence showing that interventions on social determinants of health, such as education, can reduce the burden of gastrointestinal diseases and improve population-level outcomes.

Study limitations

Several limitations should be acknowledged. First, although no evidence of horizontal pleiotropy was observed in the MR intercept test, residual pleiotropy cannot be entirely excluded, and heterogeneity across MR methods suggests potential instrument instability for certain traits. Second, the study population was predominantly of European ancestry, which restricts the generalizability of our findings to non-European groups and to low- and middle-income countries; differences in genetic architecture, healthcare access, and lifestyle practices may influence how mediating pathways, such as smoking, gallstone disease, or metabolic disorders operate. Third, while triglyceride levels were evaluated, our data primarily reflected individuals with moderate triglyceride concentrations, which may not capture the causal impact of extreme hypertriglyceridemia (>1000 mg/dL) (Petrov & Yadav, 2019; Scherer et al., 2014), a well-established risk factor for AP. Fourth, GWAS-derived exposures may not fully reflect complex behavioral patterns, such as alcohol drinking styles, dietary components, or physical activity, which could interact with education and contribute to AP risk. Finally, although we examined smoking, triglycerides, diabetes, and gallstones as mediators, other unmeasured pathways may also underlie the protective effect of education, which warrants further investigation.

Future research directions

Future studies should extend MR analyses to non-European populations to assess whether the protective effects of education on AP are consistent across global contexts. In addition, deeper phenotyping of behavioral mediators—such as specific alcohol drinking patterns, dietary intake, and physical activity—is required to clarify the mechanisms underlying the education–AP relationship. Multi-omics integration, including proteomics and metabolomics, may also help identify biological pathways linking education with pancreatic health. Experimental validation using prospective cohorts or intervention studies targeting smoking cessation, triglyceride control, and gallstone prevention in relation to education could provide further mechanistic insights. Finally, embedding MR findings into health policy evaluations will be important for translating genetic evidence into actionable strategies that reduce educational disparities and lower the burden of AP worldwide.

Conclusion

In summary, by leveraging MR analysis, our study concluded that college completion exhibits a protective influence against AP risk, partly mediated by smoking, triglyceride levels, and cholelithiasis. These findings highlight the importance of addressing educational disparities and prioritizing actionable pathways—such as smoking cessation, triglyceride control, and gallstone management—in AP prevention strategies. Continued integration of genetic evidence with public health strategies may accelerate efforts to reduce the global burden of AP.

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Ethical approval

This study utilized publicly available GWAS data that had been summarized from previously published studies with ethical approval and participant consent, thus obviating the need for additional ethical approval.

Consent for publication

Not applicable.

Author contributions

All authors contributed to the study's conception and design. WZ: designing, data acquisition, drafting of the original draft, and revising. MF: methodology, conceptualization, and analysis. EZ: data acquisition and analysis. YP: conceptualization and analysis. XL and ZT: conceptualization. XH: conception and designing, revising, and the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

All data generated or analysed during this study are included in this published article, there are no additional unpublished data. You may contact [corresponding author/xiaotonghan1@163.com] with data requests, and the data will be provided upon reasonable request.

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