Higher Educational Attainment Reduces the Risk of Acute Pancreatitis by Decreasing Triglycerides and the Occurrence of Cholelithiasis

Xuxu Liu
Ministry of Education, The First Affiliated Hospital of Harbin Medical University
Liyi Wang
Ministry of Education, The First Affiliated Hospital of Harbin Medical University
Heming Wang
Ministry of Education, The First Affiliated Hospital of Harbin Medical University
Qiang Wang
Qilu Hospital of Shandong university
Jingjing Yu
Ministry of Education, The First Affiliated Hospital of Harbin Medical University
Qingxu Jing
Ministry of Education, The First Affiliated Hospital of Harbin Medical University
Zhenyi Lv
Ministry of Education, The First Affiliated Hospital of Harbin Medical University
Zhiwei Du
Ministry of Education, The First Affiliated Hospital of Harbin Medical University
Yi Zheng
Ministry of Education, The First Affiliated Hospital of Harbin Medical University
Tianming Liu
Ministry of Education, The First Affiliated Hospital of Harbin Medical University
Chenjun Hao
Ministry of Education, The First Affiliated Hospital of Harbin Medical University
Dongbo Xue
Ministry of Education, The First Affiliated Hospital of Harbin Medical University
Yingmei Zhang (zhangyingmei@hrbmu.edu.cn)
Ministry of Education, The First Affiliated Hospital of Harbin Medical University

Research Article

Keywords: Acute pancreatitis, education attainment, Mendelian randomization, cholelithiasis, triglycerides

Posted Date: October 5th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3389099/v1

Additional Declarations: No competing interests reported.

Abstract

Background: Acute pancreatitis (AP) is a significant public health concern. Although a higher level of education attainment (EA) has been observed to be associated with a lower incidence of AP, the causal relationship and potential mediators remain unclear.

Method: In this study, we investigated the years of schooling as the primary indicator of EA, as well as cognitive performance and intelligence as secondary indicators. We used a large-scale database to obtain genome-wide association data on factors related to Years of schooling, cognitive performance, intelligence, cholelithiasis, triglycerides, alcohol consumption, and AP. Through two-sample Mendelian randomization (MR) analysis, including inverse variance weighted, weighted median, and MR-Egger methods, we explored the causal relationship between years of schooling, cognitive performance, intelligence, and AP. MR-Egger and MR-PRESSO were used for sensitivity analysis to address pleiotropy issues. Additionally, multivariable MR analysis helped identify independent protective factors and potential mediators.

Results: Longer years of schooling (OR=0.556, 95% CI: 0.456-0.677, P=6.01E-09), better cognitive performance (OR=0.796, 95% CI: 0.653-0.970, P=0.024), and higher intelligence (OR=0.789, 95% CI: 0.637-0.977, P=0.030) had a causal effect on reducing the incidence of AP. Furthermore, cholelithiasis and triglycerides mediated the causal relationship between years of schooling and AP risk. In this causal relationship, cholelithiasis and triglycerides together accounted for 19.6% of the mediation effect.

Conclusion: These research findings support the causal impact of education attainment on the occurrence of AP, with a substantial portion of the causal effect being mediated by modifiable risk factors. This suggests that strategies aimed at improving education levels are feasible for preventing AP, and interventions targeting cholelithiasis and triglyceride levels can reduce AP cases caused by imbalances in education attainment.

Background

Despite advances in medical knowledge and clinical interventions, acute pancreatitis (AP) remains a significant public health concern. Globally, there are 76.2 cases of AP per 100,000 population, with the highest age-standardized incidence rates observed in Central Europe (222.1), Eastern Europe (213.8), and Tropical Latin America (167.0) [1]. Conversely, the lowest rates are found in Sub-Saharan Africa - Southern (18.9), Sub-Saharan Africa - Eastern (18.7), and Sub-Saharan Africa - Central (18.6) [1]. In the United States, AP constitutes a major reason for hospital admissions, with around 300,000 patients requiring emergency treatment annually, amounting to $9.3 billion in healthcare expenditure [2, 3]. While early symptoms of AP involve sterile inflammation, a portion of patients progress to necrotizing pancreatitis, with 38% experiencing organ failure, a primary cause of death [4]. Common causes of AP include cholelithiasis, pancreatic duct obstruction, endoscopic retrograde cholangiopancreatography (ERCP), and hypertriglyceridemia [5–8]. However, many potential risk factors, such as educational attainment (EA), remain poorly understood.

Recent research indicates that lower EA is associated with increased risks of various diseases, including stroke, cardiovascular diseases, and lung cancer [9–11]. Similarly, lower EA has been linked to heightened AP risk, and Mendelian randomization (MR) studies have implicated lower EA as a cause of AP. However, the mediating factors remain unknown [12, 13]. Hence, the causal link between AP and EA requires further investigation.

With the rapid emergence of genome-wide association studies (GWAS), MR has become a convenient tool for epidemiological research. By utilizing different genetic phenotypes as instrumental variables (IVs), MR examines causal relationships between exposures and outcomes. Random allocation of these genetic phenotypes during conception minimizes confounding and reverse causation bias, providing robust causal evidence akin to clinical randomized trials [14, 15].

In this study, we employ MR to investigate the potential causal relationship between EA and AP, as well as to elucidate mediating factors, offering novel insights for AP prevention and treatment strategies.

Methods

1. Study Design

The overall research design of the Mendelian Randomization (MR) study is depicted in Fig. 1. GWAS summary data for Years of Schooling, Cognitive performance, Intelligence, Alcohol consumption, Cholelithiasis, and Triglycerides were extracted from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/), while AP GWAS summary data were obtained from the Finngen database. Years of Schooling, Cognitive performance, and Intelligence were considered exposure factors, while Alcohol consumption, Cholelithiasis, and Triglycerides were defined as candidate mediator variables, and AP was treated as the outcome. Single nucleotide polymorphisms (SNPs) were employed as instrumental variables to investigate the impact of Years of Schooling on AP risk through the intermediary factors Alcohol consumption, Cholelithiasis, and Triglycerides. Single-variable and multivariable analyses were conducted using IVW regression to estimate causality and effect size. Mediation analysis was performed through a two-step MR approach. In brief, after identifying candidate mediator variables through single-variable MR, exposure and candidate mediator variables were jointly included in multivariable MR analysis, and the proportion of mediation effects was calculated. Concerning the interpretation of results from mediation MR analysis, the effect value of exposure on the outcome obtained from single-variable MR represents the total effect, whereas, after adjusting for mediator factors using multivariable MR, the effect value of exposure on the outcome indicates the direct effect. Indirect effect equals total effect minus direct effect; proportion of mediation effect equals indirect effect divided by total effect.

2. Data Sources

GWAS summary data, including AP, Years of Schooling, Cognitive performance, Intelligence, Alcohol consumption, Cholelithiasis, and Triglycerides, were sourced from European ethnic populations. Genetic data associated with Years of Schooling (standard deviation [SD]: 4.2 years) were from the SSGAC Consortium (GWAS ID: ieu-a-1239). Genetic data linked to Cognitive performance came from a GWAS study comprising 257,841 participants (GWAS ID: ebi-a-GCST006572). Intelligence-related GWAS data were obtained from a study involving 269,867 participants (GWAS ID: ebi-a-GCST006250). Alcohol consumption data were from the UK Biobank, including 112,117 participants (GWAS ID: ieu-a-1283). Triglycerides GWAS data were sourced from the GLGC Consortium, including 177,861 participants (GWAS ID: ieu-a-302). Cholelithiasis data were from the UK Biobank, encompassing 6,986 cases and 330,213 controls (GWAS ID: ukb-a-559). AP data were acquired from the Finngen Consortium (Round 8) GWAS analysis, covering 5,509 cases and 301,383 controls. Detailed data information is presented in Table 1.

Table 1
Genome-wide association studies and Consortium used in present study.

Exposure/Outcome	Population	Participants	Data Source	Download Link
Years of schooling	European	766345 participates	SSGAC Consortium	https://gwas.mrcieu.ac.uk/datasets/ieu-a−1239/
Cognitive performance	European	257841 participates	IEU Open GWAS	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006572/
Intelligence	European	269867 participates	IEU Open GWAS	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006250/
AP	European	5509 cases and 301383 controls	Finngen	https://storage.googleapis.com/finngen-public-data-r8/summary_stats/finngen_R8_K11_ACUTPANC.gz
Alcohol consumption	European	112117 participates	UK Biobank	https://gwas.mrcieu.ac.uk/datasets/ieu-a−1283/
Triglycerides	European	177861 participates	GLGC Consortium	https://gwas.mrcieu.ac.uk/datasets/ieu-a−302/
Cholelithiasis	European	6986 cases and 330213 controls	UK Biobank	https://gwas.mrcieu.ac.uk/datasets/ukb-a−559/

Table 2
The multivariable MR analysis results of the causal effects of each exposure on AP.

Exposure	Outcome	SNPs(n)	OR	P-Value
Years of schooling	AP	229	0.665(0.512−0.866)	2.39E-03
Triglycerides	AP	229	1.172(1.021−1.345)	0.024
Cholelithiasis	AP	229	14025(542−364258)	8.88E-09

3. Instrumental Variable Selection

SNPs were selected based on a threshold of $P < 5 \times 10$. Subsequently, the threshold was set to $r^2 < 0.001$ and Kb > 10,000 to address linkage disequilibrium. Palindromic SNPs were excluded from instrumental variable selection. To estimate the overall strength of the selected SNPs in explaining phenotypic variation, the F-statistic was calculated as $F = \beta^2/SE^2$. An F-value > 10 indicated significant reduction in potential bias by the selected SNP, while F-value ≤ 10 indicated a weak instrumental variable. Phenoscanner V2 was used to query and eliminate SNPs associated with confounding factors related to the outcome. Confounding factors for AP as an outcome included alcohol, cholelithiasis, and triglycerides.

4. Statistical Analysis

Five MR methods were utilized for single-variable MR analysis to examine the causal impact of exposure on the outcome, with Inverse Variance Weighting (IVW) being the primary MR strategy. MR Egger, Weighted Median, Weighted Mode, and Simple Mode were used as supplementary methods. The diversity of effects was assessed using MR Egger, MR Pleiotropy RESidualSum and Outlier (MR-PRESSO) tests, with P > 0.05 indicating effect diversity. Cochrane Q statistics were employed for heterogeneity analysis using mr_egger and IVW, with P > 0.05 indicating no heterogeneity. To enhance the robustness of instrumental variables, during heterogeneity analysis, we used the IVW_radial (alpha = 0.05, weights = 1, tol = 0.0001) function to compute the corrected Q statistic and removed outlier SNPs with P < 0.05 as the threshold. Additionally, "Leave-one-out" sensitivity analysis was performed to demonstrate that individual SNPs did not affect the

causal effect of exposure on the outcome. All statistical analyses were conducted using R packages "devtools," "TwoSampleMR," "LDlinkR," and "MRPRESSO." We conducted six single-variable MR analyses, and according to multiple testing correction, $P < 0.0083$ (0.05/6) was considered significant causality, while $0.0083 < P < 0.05$ was considered potential causality.

Results

1. Causal Relationships Between Years of Schooling, Cognitive Performance, Intelligence, and AP

Years of Schooling initially yielded 310 SNPs, and after harmonizing with AP GWAS data, 269 SNPs remained following the removal of 13 palindromic SNPs and 28 potential pleiotropic SNPs (F statistic: 13205.19; Supplementary Table 1). Cognitive performance initially yielded 147 SNPs, and after harmonizing with AP GWAS data, 117 SNPs remained following the removal of 7 palindromic SNPs and 23 potential pleiotropic SNPs (F statistic: 4741.14; Supplementary Table 1). Intelligence initially yielded 163 SNPs, and after harmonizing with AP GWAS data, 120 SNPs remained following the removal of 19 palindromic SNPs and 24 potential pleiotropic SNPs (F statistic: 4935.60; Supplementary Table 1). IVW results indicated a significant negative causal relationship between Years of Schooling (OR = 0.556, 95% CI: 0.456–0.677, P = 6.01E-09) and AP risk. Additionally, Cognitive performance (OR = 0.796, 95% CI: 0.653–0.970, P = 0.024) and Intelligence (OR = 0.789, 95% CI: 0.637–0.977, P = 0.030) demonstrated potential negative causal relationships with AP risk (Fig. 2). Detailed MR results are provided in Supplementary Table 2. Sensitivity analysis indicated no significant heterogeneity or pleiotropy in our MR analysis (Supplementary Table 3).

2. Mediation MR Analysis

Subsequently, we explored whether the causal effect of Years of Schooling on AP was mediated through established risk factors, including Alcohol consumption, Cholelithiasis, and Triglycerides. We assessed whether Years of Schooling was causally related to Alcohol consumption, Cholelithiasis, and Triglycerides. Years of Schooling initially yielded 310 SNPs, and after harmonizing with Alcohol consumption GWAS data, 240 SNPs remained following the removal of 10 palindromic SNPs and 60 potential pleiotropic SNPs (F statistic: 11485.62; Supplementary Table 1). After harmonizing with Cholelithiasis GWAS data, 299 SNPs remained following the removal of 10 palindromic SNPs and 1 potential pleiotropic SNP (F statistic: 14707.95; Supplementary Table 1). After harmonizing with Triglycerides GWAS data, 126 SNPs remained following the removal of 21 palindromic SNPs and 163 potential pleiotropic SNPs (F statistic: 6105.74; Supplementary Table 1). IVW results indicated a significant positive causal relationship between Years of Schooling and Alcohol consumption (OR = 1.117, 95% CI: 1.087–1.147, P = 7.54E-16), as well as significant negative causal relationships with Cholelithiasis (OR = 0.989, 95% CI: 0.985–0.992, P = 4.08E-11) and Triglycerides (OR = 0.868, 95% CI: 0.808–0.932, P = 9.64E-05) (Supplementary Table 2). Detailed MR results are provided in Supplementary Table 2. Sensitivity analysis indicated no significant heterogeneity or pleiotropy in our MR analysis (Supplementary Table 3). Consequently, we identified Cholelithiasis and Triglycerides as candidate mediator variables for the causal effect of Years of Schooling on AP.

Incorporating Years of Schooling, Cholelithiasis, and Triglycerides into a multivariable MR analysis revealed that the causal effect of Years of Schooling on AP was attenuated after adjusting for Cholelithiasis and Triglycerides (OR = 0.665, 95% CI: 0.512–0.866, P = 0.0024, Fig. 3). The calculated proportion of mediation effect for Cholelithiasis and Triglycerides as candidate mediator variables for the causal effect of Years of Schooling on AP was 19.6%.

Discussion

Despite a significant decline in the mortality rate of AP over the past decade, its incidence continues to rise [16, 17]. While studies have demonstrated a relationship between higher levels of EA and a reduced risk of AP [13], the specific mediators between the two have not been elucidated. Observational studies struggle to establish strong causal relationships between EA and AP due to confounding factors. Fortunately, MR offers a new avenue to explore causal links between EA and AP. Consistent with prior research, our study also confirmed a causal relationship between higher EA and a lower risk of AP, specifically manifesting as a reduced incidence of cholelithiasis in individuals with longer education.

Higher EA can regulate the risk of AP through multiple pathways. Several intermediate phenotypes may mediate the causal relationship between EA and AP. Common risk factors for AP include cholelithiasis, pancreatic duct obstruction, and hypertriglyceridemia [5, 6, 8]. Education could be an important strategy to modulate these factors for AP prevention. Our findings highlight cholelithiasis and hypertriglyceridemia as key drivers for AP occurrence. Importantly, we demonstrate that higher levels of EA may lead to a reduction in AP incidence by lowering the occurrence rates of cholelithiasis and hypertriglyceridemia.

Cholelithiasis has been established as an inducer of AP [18]. It is the most common cause of AP in high-income countries, with some experts even suggesting early gallbladder removal as a preventive measure against AP [19]. Research indicates that gallstone obstruction of the pancreatic duct activates the Piezo1 receptor, causing intracellular calcium overload, leading to cell necrosis [20]. Additionally, bile acids can impair pancreatic duct cell mitochondrial function and induce duct cell necrosis [21]. The elevated intraductal pressure caused by gallstone obstruction can trigger inflammation and activate the STAT3 signaling pathway, causing cell damage [22]. Furthermore, pancreatic duct obstruction can result in the release of cathepsin B within pancreatic acinar cells, leading to autodigestion and necrotic apoptosis [3, 23–25]. Hypertriglyceridemia may trigger AP through excessive triglycerides generating free fatty acids (FFAs) within the pancreas. These FFAs trigger inflammation and necrotic apoptosis within the ducts [26]. Microcirculatory disturbances within the pancreas also play a crucial role in HTG-related AP by causing excessive constriction of pancreatic capillaries, worsening pancreatic microcirculation [27]. Alcohol is another significant risk factor for AP [28], significantly lowering the function and bicarbonate secretion of the cystic fibrosis transmembrane conductance regulator (CFTR) in the pancreatic duct, leading to an acidic intraductal environment and enzyme activation, ultimately triggering AP [29].

Higher EA may impact cholelithiasis and hypertriglyceridemia in several ways. Firstly, individuals with higher EA tend to adopt healthier lifestyles. Studies have shown that as the overall EA of society increases, healthier lifestyles become more common [30]. People with higher EA consume less red meat, sugary beverages, and engage in less sedentary behavior [31]. They are more likely to quit smoking, adopt healthier diets, purchase health insurance, and seek medical care promptly when ill [32]. Additionally, parents with higher EA are more likely to instill healthy habits in their children, such as consuming adequate fruits and vegetables, limiting sugary beverage intake, and managing screen time [33]. Therefore, individuals with higher EA may reduce the risk of cholelithiasis and hypertriglyceridemia through their lifestyle choices. Secondly, higher EA is associated with a reduced risk of certain diseases. People with higher EA are more aware of obesity and are more likely to employ specific weight loss strategies, such as exercise, reducing caloric intake, and lowering fat consumption [34]. As a result, they are more likely to succeed in weight loss, thus reducing the risk of obesity [35]. Conversely, a study by Afroz et al. indicated that individuals with lower educational levels lack awareness of diabetes, leading to poor blood glucose control. Additionally, the socioeconomic status of most individuals with lower education levels may prevent them from affording medical care until diabetes complications arise [36]. As obesity and diabetes are significant risk factors for cholelithiasis and HTG [37, 38], higher EA might reduce the risk of cholelithiasis and HTG by lowering the incidence of obesity and diabetes, subsequently preventing AP. Lastly, individuals with higher EA often have higher social status and income, enabling them to afford better healthcare, control their health status more effectively, and access medical services promptly [36].

Our study boasts several strengths. Firstly, the causal relationships uncovered through MR are less susceptible to confounding factors, providing a significant advantage over traditional observational studies. Secondly, we have a large

sample size in our study; for instance, Years of Schooling includes 766,345 participants, AP includes 5,509 cases and 301,383 controls, Triglycerides include 177,861 participants, and Cholelithiasis includes 6,986 cases and 330,213 controls. Such substantial sample sizes lend credibility to potential causal relationships. Moreover, all our samples are of European descent, reducing heterogeneity. Lastly, we used instrumental variables from different databases for exposure and outcome, minimizing potential sample overlap between exposure and outcome.

However, our study does have limitations. Firstly, our GWAS data exclusively originates from European populations, and our findings might not generalize to other populations. For instance, a study by Mangemba et al. found a higher likelihood of obesity and HTG in individuals with higher education in the Zimbabwean population, which contradicts our conclusions [39]. Secondly, the data we used doesn't account for factors like gender, age, and disease severity, which could potentially influence our results.

Conclusion

This study demonstrates that higher levels of EA are associated with a reduced risk of AP, achieved through lowered risks of hypertriglyceridemia and cholelithiasis. Establishing causal relationships between these factors enhances our understanding of AP's etiology and offers insights for AP prevention strategies and identifying high-risk populations.

Declarations

Ethics approval and consent to participate:

The data used in this study are sourced from public databases, therefore further ethical review is not required.

Consent for publication:

Not applicable.

Availability of data and materials:

The data sources used in this study are specified in the methodology section and download links are provided in Table 1.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Funding: This work was supported by National Natural Science Foundation of China (Grant numbers [82370650]), and Key Research and Development Program of Heilongjiang Province (Grant numbers [2022ZX06C06]).

Authors' contributions:

XL designed the study and analyzed the data. LW and HW wrote the manuscript. QW, JY, QJ, ZL, ZD, YZ, TL and CH prepared the images and tables. YZ and DX supervised the research. All authors read and approved the final manuscript.

Acknowledgements:

Not applicable.

References

1. Ouyang G, Pan G, Liu Q, et al. The global, regional, and national burden of pancreatitis in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017[J]. BMC medicine, 2020, 18: 1–13.

2. Mederos M A, Reber H A, Girgis M D. Acute pancreatitis: a review[J]. Jama, 2021, 325(4): 382–390.
3. Lee P J, Papachristou G I. New insights into acute pancreatitis[J]. Nature reviews Gastroenterology & hepatology, 2019, 16(8): 479–496.
4. Schepers N J, Bakker O J, Besselink M G, et al. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis[J]. Gut, 2019, 68(6): 1044–1051.
5. Littlefield A, Lenahan C. Cholelithiasis: Presentation and management[J]. Journal of midwifery & women's health, 2019, 64(3): 289–297.
6. Yao W, Wang G, Wang Q, et al. Stenting of the pancreatic duct in the early phase of acute pancreatitis: a retrospective study[J]. BMC gastroenterology, 2022, 22(1): 414.
7. Pekgöz M. Post-endoscopic retrograde cholangiopancreatography pancreatitis: A systematic review for prevention and treatment[J]. World journal of gastroenterology, 2019, 25(29): 4019.
8. Tan H L E, McDonald G, Payne A, et al. Incidence and management of hypertriglyceridemia-associated acute pancreatitis: a prospective case series in a single Australian Tertiary Centre[J]. Journal of clinical medicine, 2020, 9(12): 3954.
9. Xiuyun W, Qian W, Minjun X, et al. Education and stroke: evidence from epidemiology and Mendelian randomization study[J]. Scientific Reports, 2020, 10(1): 21208.
10. van Oort S, Beulens J W J, van Ballegooijen A J, et al. Association of cardiovascular risk factors and lifestyle behaviors with hypertension: a mendelian randomization study[J]. Hypertension, 2020, 76(6): 1971–1979.
11. Pettit R W, Byun J, Han Y, et al. The shared genetic architecture between epidemiological and behavioral traits with lung cancer[J]. Scientific reports, 2021, 11(1): 17559.
12. Morton C, Klatsky A L, Udaltsova N. Smoking, coffee, and pancreatitis[J]. Official journal of the American College of Gastroenterology| ACG, 2004, 99(4): 731–738.
13. Mao X, Mao S, Sun H, et al. Causal associations between modifiable risk factors and pancreatitis: A comprehensive Mendelian randomization study[J]. Frontiers in Immunology, 2023, 14: 1091780.
14. Chen G, Xie J, Liang T, et al. Exploring the causality between educational attainment and gastroesophageal reflux disease: A Mendelian randomization study[J]. Digestive and Liver Disease, 2023.
15. Wang Q, Wang R, Chen C, et al. Educational attainment and endometrial cancer: A Mendelian randomization study[J]. Frontiers in Genetics, 2022, 13: 993731.
16. Krishna S G, Kamboj A K, Hart P A, et al. The changing epidemiology of acute pancreatitis hospitalizations: a decade of trends and the impact of chronic pancreatitis[J]. Pancreas, 2017, 46(4): 482.
17. Iannuzzi J P, King J A, Leong J H, et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis[J]. Gastroenterology, 2022, 162(1): 122–134.
18. Yuan S, Giovannucci E L, Larsson S C. Gallstone disease, diabetes, calcium, triglycerides, smoking and alcohol consumption and pancreatitis risk: Mendelian randomization study[J]. NPJ genomic medicine, 2021, 6(1): 27.
19. Moody N, Adiamah A, Yanni F, et al. Meta-analysis of randomized clinical trials of early versus delayed cholecystectomy for mild gallstone pancreatitis[J]. Journal of British Surgery, 2019, 106(11): 1442–1451.
20. Romac J M J, Shahid R A, Swain S M, et al. Piezo1 is a mechanically activated ion channel and mediates pressure induced pancreatitis[J]. Nature communications, 2018, 9(1): 1715.
21. Hegyi P, Petersen O H. The exocrine pancreas: the acinar-ductal tango in physiology and pathophysiology[J]. Reviews of Physiology, Biochemistry and Pharmacology, Vol. 165, 2013: 1–30.
22. Wen L, Javed T A, Yimlamai D, et al. Transient high pressure in pancreatic ducts promotes inflammation and alters tight junctions via calcineurin signaling in mice[J]. Gastroenterology, 2018, 155(4): 1250–1263. e5.

23. Xie Z, Zhao M, Yan C, et al. Cathepsin B in programmed cell death machinery: mechanisms of execution and regulatory pathways[J]. Cell Death & Disease, 2023, 14(4): 255.
24. Peng C, Tu G, Wang J, et al. MLKL signaling regulates macrophage polarization in acute pancreatitis through CXCL10[J]. Cell Death & Disease, 2023, 14(2): 155.
25. Wang G, Qu F Z, Li L, et al. Necroptosis: a potential, promising target and switch in acute pancreatitis[J]. Apoptosis, 2016, 21: 121–129.
26. Hong Y, Yu J, Su Y, et al. High-fat diet aggravates acute pancreatitis via TLR4-mediated necroptosis and inflammation in rats[J]. Oxidative medicine and cellular longevity, 2020, 2020.
27. Yang A L, McNabb-Baltar J. Hypertriglyceridemia and acute pancreatitis[J]. Pancreatology, 2020, 20(5): 795–800.
28. Singh V K, Yadav D, Garg P K. Diagnosis and management of chronic pancreatitis: a review[J]. Jama, 2019, 322(24): 2422–2434.
29. Maléth J, Balázs A, Pallagi P, et al. Alcohol disrupts levels and function of the cystic fibrosis transmembrane conductance regulator to promote development of pancreatitis[J]. Gastroenterology, 2015, 148(2): 427–439. e16.
30. Nguyen B, Smith J, Clare P, et al. Sixteen-year trends in multiple lifestyle risk behaviours by socioeconomic status from 2004 to 2019 in New South Wales, Australia[J]. PLOS Global Public Health, 2023, 3(2): e0001606.
31. Lawrence E M. Why do college graduates behave more healthfully than those who are less educated?[J]. Journal of health and social behavior, 2017, 58(3): 291–306.
32. Maalouf E, Hallit S, Salameh P, et al. Eating behaviors, lifestyle, and ischemic stroke: a Lebanese case-control study[J]. International Journal of Environmental Research and Public Health, 2023, 20(2): 1487.
33. World Health Organization. WHO European regional obesity report 2022[M]. World Health Organization. Regional Office for Europe, 2022.
34. Song P, Li X, Bu Y, et al. Temporal trends in normal weight central obesity and its associations with cardiometabolic risk among Chinese adults[J]. Scientific reports, 2019, 9(1): 5411.
35. Guendelman S, Ritterman Weintraub M, Kaufer-Horwitz M. Weight loss success among overweight and obese women of mexican-origin living in Mexico and the United States: a comparison of two national surveys[J]. Journal of immigrant and minority health, 2017, 19: 41–49.
36. Afroz A, Ali L, Karim M N, et al. Glycaemic control for people with type 2 diabetes mellitus in Bangladesh-an urgent need for optimization of management plan[J]. Scientific reports, 2019, 9(1): 10248.
37. Zhang J, Chen L, Shen K, et al. Association between metabolically healthy overweight/obesity and cholelithiasis in Chinese adults[J]. Nutrition & Metabolism, 2023, 20(1): 1–9.
38. Cortés V A, Barrera F, Nervi F. Pathophysiological connections between gallstone disease, insulin resistance, and obesity[J]. Obesity Reviews, 2020, 21(4): e12983.
39. Mangemba N T, San Sebastian M. Societal risk factors for overweight and obesity in women in Zimbabwe: a cross-sectional study[J]. BMC public health, 2020, 20(1): 1–8.

Figures

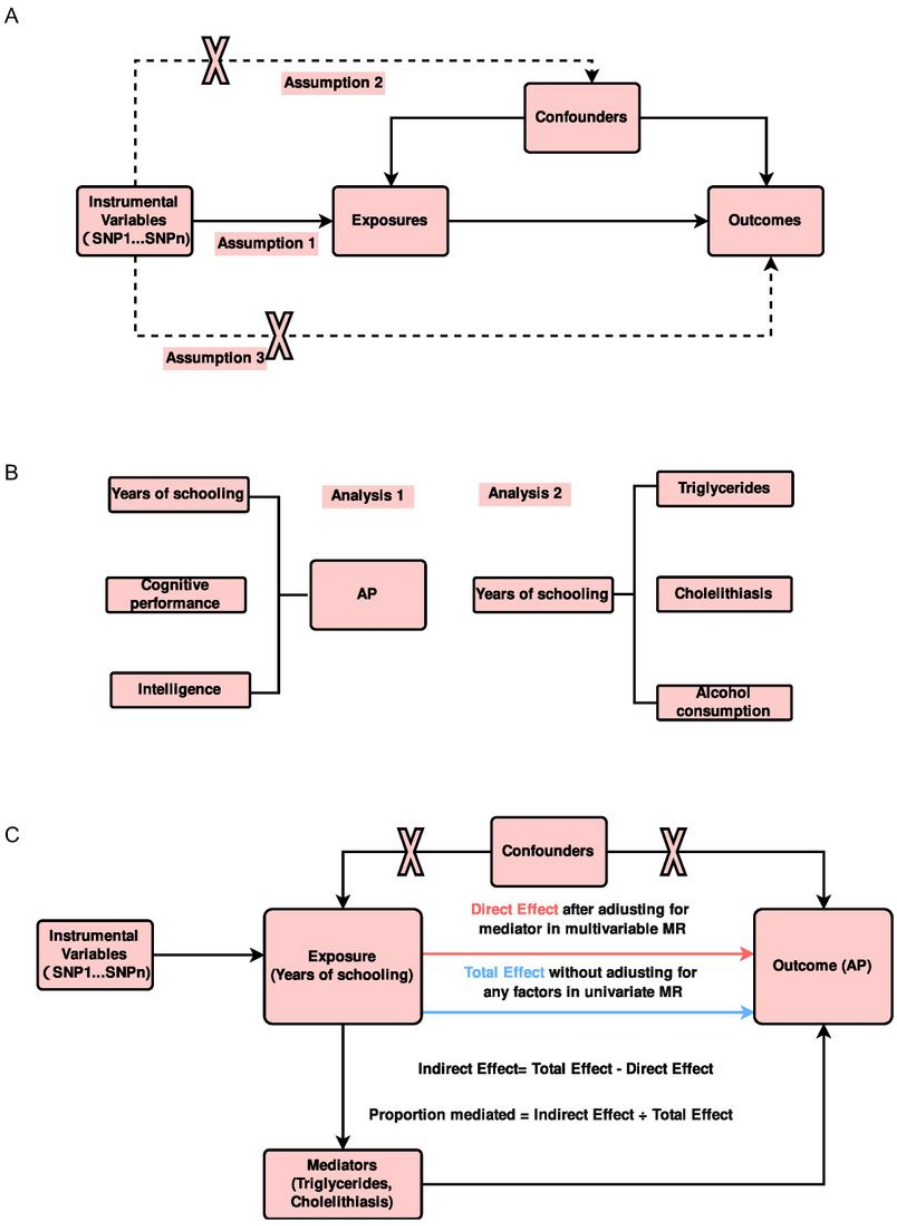

Figure 1

Flowchart of the study. A. Three hypotheses of MR analysis. B. Analysis process of univariable MR. C. Schematic diagram of mediation MR.

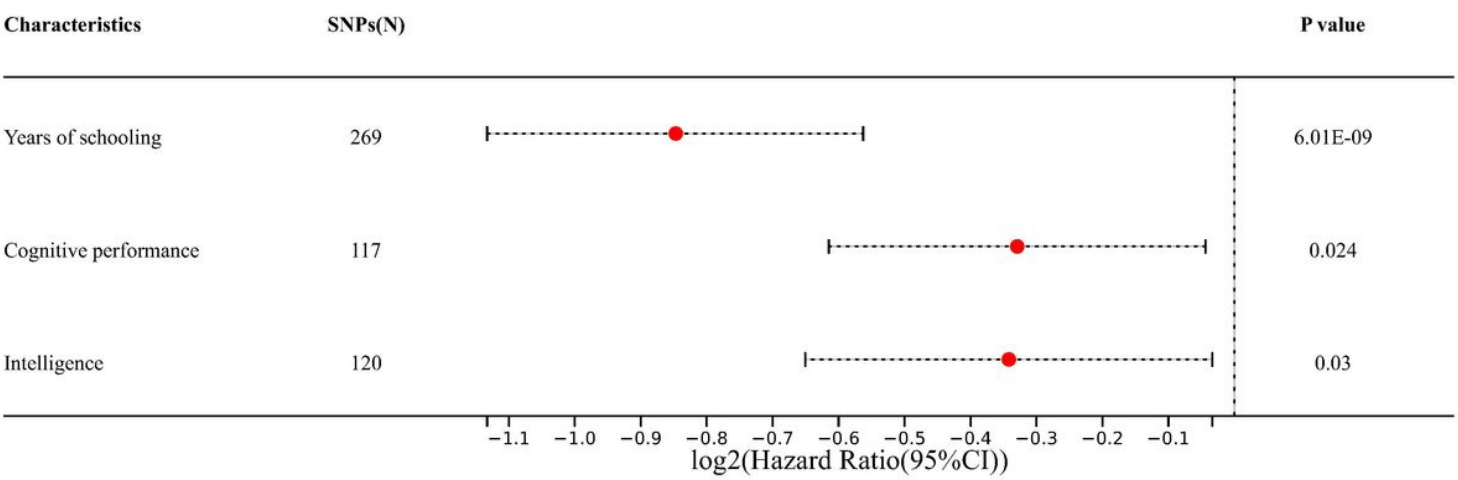

Figure 2

Univariable MR analysis results of school time, cognitive performance, and intelligence on the AP effect.

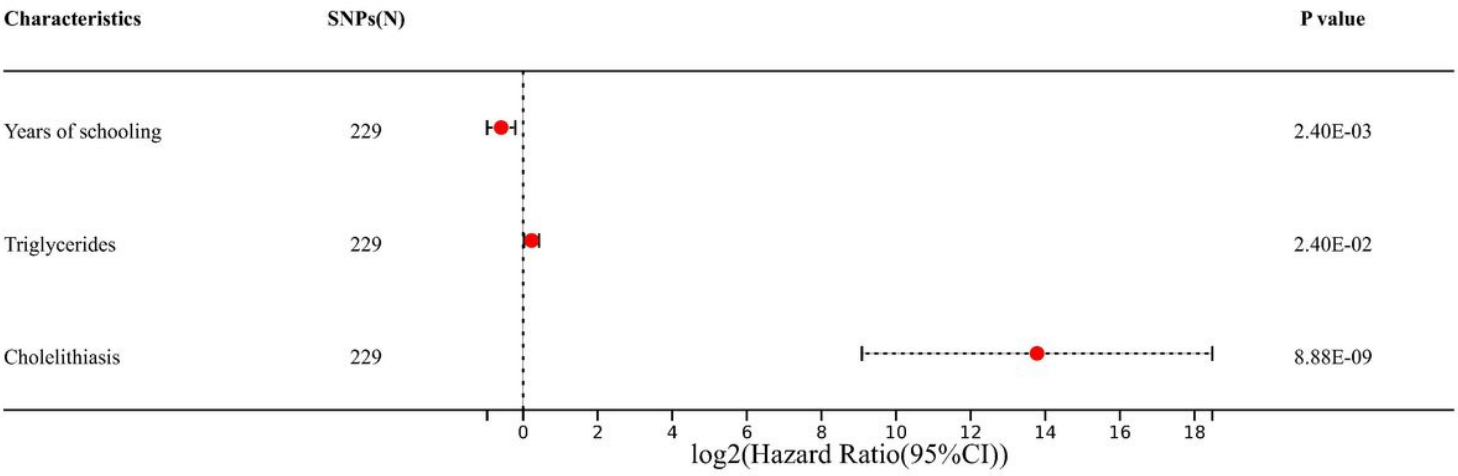

Figure 3

Multivariable MR analysis results of school time, triglycerides, and cholelithiasis on the AP effect after mutual correction.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx
- SupplementaryTable2.docx
- SupplementaryTable3.docx