

Mendelian randomization analysis of metabolic blood biomarkers and gastrointestinal cancer risk

Xiufeng Huang^{A,D,F}, Jianxin Chen^{A,D–F}, Feiteng Gu^{A,C,F}, Xiaodan Zheng^{A,C,F}

Second Department of Gastrointestinal Surgery, The Affiliated Hospital of Putian University, China

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online)

Adv Clin Exp Med. 2026;35(6):1037–1045

Address for correspondence

Jianxin Chen
E-mail: lhxlptxy@sina.com

Funding sources

None declared

Conflict of interest

None declared

Received on May 28, 2025

Reviewed on July 25, 2025

Accepted on August 27, 2025

Published online on June 25, 2026

Abstract

Background. Gastrointestinal (GI) cancers remain among the most lethal malignancies worldwide, highlighting the need for novel insights into modifiable risk factors. Blood-based metabolic biomarkers – routinely measured in clinical settings – may play a role in cancer etiology, but their causal impact remains unclear.

Objectives. This study aimed to explore the causal relationship between metabolic blood biomarkers and the risk of GI cancers using Mendelian randomization (MR).

Materials and methods. We conducted an MR analysis using large-scale genome-wide association study (GWAS) data to evaluate the causal effects of metabolic blood traits (e.g., low-density lipoprotein (LDL) cholesterol, creatinine, uric acid, total protein, and total cholesterol) on the risk of 4 major GI cancers: gastric, colorectal, pancreatic, and gallbladder cancer. Statistical robustness was evaluated using the MR-PRESSO test and Cochran's Q test.

Results. Mendelian randomization analysis revealed several significant associations. Low-density lipoprotein cholesterol was inversely associated with gastric cancer risk (odds ratio (OR) = 0.815, 95% confidence interval (95% CI): 0.703–0.946, $p < 0.01$), while total cholesterol also showed a protective effect (OR = 0.790, 95% CI: 0.693–0.900, $p < 0.01$). Serum creatinine levels were strongly associated with a reduced risk of gallbladder cancer (OR = 0.037, 95% CI: 0.005–0.287, $p < 0.01$). Higher serum total protein (OR = 0.855, 95% CI: 0.777–0.940, $p < 0.01$) and uric acid levels (OR = 0.855, 95% CI: 0.769–0.951, $p < 0.01$) were associated with a reduced risk of colorectal cancer (CRC). Serum uric acid levels were also associated with a reduced risk of gastric cancer (OR = 0.822, 95% CI: 0.719–0.941, $p < 0.01$), but with an increased risk of pancreatic cancer (OR = 1.246, 95% CI: 1.01–1.539, $p = 0.040$).

Conclusions. Our findings provide causal evidence linking common metabolic blood biomarkers to site-specific GI cancer risks. These results may inform biomarker-based risk stratification and preventive strategies in oncology and public health.

Key words: cancer risk, genetic variants, gastrointestinal cancer, Mendelian randomization, metabolic blood biomarkers

Cite as

Huang X, Chen J, Gu F, Zheng X. Mendelian randomization analysis of metabolic blood biomarkers and gastrointestinal cancer risk. *Adv Clin Exp Med.* 2026;35(6):1037–1045. doi:10.17219/acem/209956

DOI

10.17219/acem/209956

Copyright

Copyright by Author(s)

This is an article distributed under the terms of the Creative Commons Attribution 3.0 Unported (CC BY 3.0) (<https://creativecommons.org/licenses/by/3.0/>)

Highlights

- Low-density lipoprotein (LDL) and total cholesterol showed protective effects against gastric cancer (odds ratio (OR) = 0.815 and OR = 0.790, respectively; $p < 0.01$), suggesting a lipid-related mechanism in gastric carcinogenesis.
- Serum creatinine significantly reduced the risk of gallbladder cancer (OR = 0.037, $p < 0.01$), highlighting a potential novel metabolic biomarker for risk assessment.
- Higher serum total protein and uric acid levels were protective against colorectal cancer (CRC; OR = 0.855 for both, $p < 0.01$), underscoring the role of metabolic balance in CRC prevention.
- Uric acid displayed dual effects, being protective against gastric cancer but associated with increased pancreatic cancer risk (OR = 0.822 vs OR = 1.246), indicating tumor site-specific metabolic pathways.

Background

Gastrointestinal (GI) cancers, including gastric, colorectal, pancreatic, and gallbladder cancers, are among the leading causes of cancer-related mortality worldwide.^{1,2} According to recent global cancer statistics, gastric cancer ranks 5th in incidence and 4th in mortality, while colorectal cancer (CRC) ranks 3rd and 2nd, respectively.³ These cancers have complex etiologies involving genetic, environmental, and lifestyle factors.^{4,5} Gastric cancer, for instance, is influenced by *Helicobacter pylori* infection, dietary factors, and genetic predisposition.⁶ Colorectal cancer risk is associated with lifestyle factors such as diet, smoking, and physical activity, as well as genetic susceptibility.⁷ Pancreatic cancer, known for its poor prognosis, is influenced by smoking, chronic pancreatitis, and diabetes.⁸ Gallbladder cancer is associated with gallstones, chronic inflammation, and certain infections.⁹ The multifaceted nature of these cancers necessitates comprehensive studies to better understand their risk factors and potential preventive measures.¹⁰ Despite advances in early detection and treatment, the overall prognosis of these cancers remains poor. Identifying modifiable risk factors is essential for developing effective prevention strategies.

Circulating blood-based biomarkers have attracted increasing attention in cancer epidemiology because of their accessibility, routine clinical use, and potential mechanistic relevance. Among them, platelets – traditionally known for their role in hemostasis – have also been shown to actively promote tumor progression by releasing cytokines and growth factors that facilitate angiogenesis, immune evasion, and metastasis, particularly in GI cancers.¹¹ These findings highlight the biological importance of systemic blood components in cancer development. In addition to cellular elements such as platelets, metabolic blood biomarkers such as low-density lipoprotein (LDL) cholesterol and total cholesterol have been linked to membrane structure, cell signaling, and modulation of the tumor microenvironment (TME).^{12–14} Serum creatinine and total protein reflect renal function, muscle metabolism, and nutritional status – factors known to influence cancer progression and prognosis.^{15–17} Uric acid, while traditionally associated with gout and metabolic disorders, has demonstrated

both antioxidant and pro-inflammatory effects that may affect cancer risk in a tissue-specific manner.^{18,19} However, evidence from conventional observational studies remains inconclusive because of confounding and potential reverse causation.

In parallel, the causal role of these blood biomarkers in GI cancers has not been comprehensively investigated. Previous studies have often focused on individual biomarkers or single cancer types, limiting the generalizability and comparability of the results. The 4 cancers selected in this study – gastric, colorectal, pancreatic, and gallbladder cancer – are among the most common and lethal GI malignancies worldwide. They also represent distinct anatomical and biological subtypes, providing an opportunity to assess both shared and divergent metabolic risk factors. Furthermore, high-quality genome-wide association study (GWAS) data are available for these cancers, enabling robust Mendelian randomization (MR) analyses.

Mendelian randomization is a genetic epidemiological approach that uses genetic variants as instrumental variables (IVs) to estimate the causal effect of an exposure (e.g., biomarker levels) on disease outcomes.^{20,21} Previous MR studies have provided valuable insights into the relationships between various risk factors and diseases, thereby informing clinical practice and public health strategies. For instance, MR has been used to investigate the causal effects of lipid levels, inflammatory markers, and other metabolic factors on cardiovascular disease (CVD), diabetes, and different cancer types.^{22–24}

Objectives

The present study aims to evaluate the potential causal effects of 5 clinically relevant blood metabolic biomarkers – LDL cholesterol, total cholesterol, serum creatinine, serum total protein, and uric acid – on the risk of 4 major GI cancers using a 2-sample MR approach. By integrating genetic and epidemiological data, this study seeks to provide novel insights into the metabolic determinants of GI tumorigenesis and to inform future prevention and risk stratification strategies.

Materials and methods

Data source and study design

This study adopted a 2-sample MR design to assess the causal effects of metabolic blood biomarkers on GI cancer risk. Summary-level genetic association data for exposures (LDL cholesterol, total cholesterol, serum creatinine, serum total protein, and uric acid) and outcomes (gastric, colorectal, pancreatic, and gallbladder cancers) were obtained from large-scale GWASs available through the MRC IEU Open GWAS database (<https://gwas.mrcieu.ac.uk>).

All data were derived from previous studies that had received ethical approval and informed consent.

Selection of genetic instruments and quality control

For each biomarker, single nucleotide polymorphisms (SNPs) strongly associated with the exposure were selected as IVs at the genome-wide significance level ($p < 5 \times 10^{-8}$). To ensure instrument independence, we applied linkage disequilibrium (LD) clumping at $r^2 < 0.001$ using a 10,000-kb window. When fewer SNPs met the strict threshold, a relaxed p-value threshold of 5×10^{-6} was used while retaining LD filtering. Palindromic SNPs with intermediate allele frequencies were excluded. To ensure instrument strength, F-statistics were calculated for each SNP, and variants with $F < 10$ were excluded to avoid weak instrument bias. Additionally, we reported the median and range of F-statistics for each biomarker to characterize the distributional strength of the instruments. These metrics are provided in Supplementary Table 1.

Outcome GWAS inclusion criteria

Summary-level genetic association data for both exposures and outcomes were obtained from the MRC IEU Open GWAS platform. All datasets included in this study were derived exclusively from individuals of European ancestry to minimize population stratification bias. The outcome datasets included large-scale GWASs for gastric cancer ($n = 476,116$), CRC ($n = 470,002$), pancreatic cancer ($n = 476,245$), and gallbladder cancer ($n = 907$), each comprising more than 24 million SNPs, except for gallbladder cancer, which included approx. 419,000 SNPs.

The selected exposures – LDL cholesterol, total cholesterol, serum total protein, serum creatinine, and serum uric acid – were chosen based on biological plausibility and prior literature and were each associated with more than 19 million SNPs in cohorts exceeding 340,000 individuals. All GWAS datasets underwent rigorous quality control procedures, including imputation to the Haplotype Reference Consortium (HRC) panel and adjustment for population structure. Detailed dataset identifiers, sample sizes, and SNP coverage are provided in Table 1.

Statistical analyses and pleiotropy testing

The estimation of causal effects between blood cell traits and GI tumors was performed using multiple MR methodologies, including inverse variance weighted (IVW), MR-Egger, weighted median, and simple mode methods. The MR-PRESSO (Mendelian Randomization Pleiotropy RESidual Sum and Outlier) test was employed to detect and adjust for horizontal pleiotropy by identifying and excluding statistical outliers from the analysis. Heterogeneity among the selected genetic instruments was evaluated using Cochran's Q test,

Table 1. Summary of genome-wide association study (GWAS) datasets for exposure and outcome variables

GWAS ID	Exposure	Sample size	Number of SNPs	Population
ebi-a-GCST90018849	gastric cancer	476,116	24,188,662	European
ebi-a-GCST90018808	colorectal cancer	470,002	24,182,361	European
ebi-a-GCST90018893	pancreatic cancer	476,245	24,195,229	European
ebi-a-GCST001404	gallbladder cancer	907	419,385	European
ebi-a-GCST90018961	LDL cholesterol	343,621	19,037,976	European
ebi-a-GCST90018956	HDL cholesterol	315,133	19,051,633	European
ebi-a-GCST90018974	total cholesterol	344,278	19,043,498	European
ebi-a-GCST90025991	serum urea	437,580	4,231,983	European
ebi-a-GCST90025992	serum albumin	400,938	4,219,040	European
ebi-a-GCST90025995	serum total protein	400,482	4,218,824	European
ebi-a-GCST90025948	serum phosphate	400,159	4,218,812	European
ebi-a-GCST90018942	serum alkaline phosphatase	344,292	19,052,566	European
ebi-a-GCST90018979	serum creatinine	344,104	19,034,241	European
ebi-a-GCST90018977	serum uric acid	343,836	19,041,286	European
ebi-a-GCST90092992	total triglycerides	115,082	11,590,399	European

HDL – high-density lipoprotein; LDL – low-density lipoprotein; SNP – single-nucleotide polymorphism.

with $p < 0.05$ indicating the absence of significant heterogeneity.²⁵ The presence of pleiotropy was assessed using the MR-Egger intercept test, wherein a nonsignificant p -value suggested no substantial pleiotropy among the IVs. The robustness and reliability of the causal estimates were evaluated using the leave-one-out approach, which entails sequential exclusion of each IV to determine its influence on the overall results. All analyses were performed in R v. 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) using the TwoSampleMR and MR-PRESSO packages.

Results

A summary of the key causal estimates is presented in Table 2.

Gastric cancer

Mendelian randomization analysis (Fig. 1) revealed that genetically predicted LDL cholesterol levels were significantly associated with a decreased risk of gastric cancer (IVW odds ratio (OR) = 0.815, 95% confidence interval

(95% CI): 0.703–0.946, $p < 0.01$). Similarly, total cholesterol also exhibited a protective effect (IVW OR = 0.790, 95% CI: 0.693–0.900, $p < 0.01$). Serum uric acid was inversely associated with gastric cancer risk (OR = 0.822, 95% CI: 0.719–0.941, $p < 0.01$). These associations were consistent across the MR-Egger and weighted median methods, although the MR-Egger estimates had wider CIs.

Colorectal cancer

Higher serum total protein levels were associated with a reduced risk of CRC (IVW OR = 0.855, 95% CI: 0.777–0.940, $p < 0.01$). Serum uric acid also showed a protective effect (OR = 0.855, 95% CI: 0.769–0.951, $p < 0.01$) (Fig. 1). The robustness of these findings was supported by MR-Egger, weighted median, and MR-PRESSO sensitivity analyses.

Pancreatic cancer

Serum uric acid levels were positively associated with pancreatic cancer risk (IVW OR = 1.246, 95% CI: 1.010–1.539, $p = 0.040$), contrasting with their protective role

Table 2. Summary of the main Mendelian randomization (MR) findings for biomarkers and gastrointestinal (GI) cancers

Exposure	Cancer outcome	IVW OR (95% CI)	p-value	Effect
LDL cholesterol	gastric cancer	0.815 (0.703–0.946)	<0.01	protective
Total cholesterol	gastric cancer	0.790 (0.693–0.900)	<0.01	protective
Serum creatinine	gallbladder cancer	0.037 (0.005–0.287)	<0.01	strong protective effect
Total protein	colorectal cancer	0.855 (0.777–0.940)	<0.01	protective
Uric acid	colorectal cancer	0.855 (0.769–0.951)	<0.01	protective
Uric acid	gastric cancer	0.822 (0.719–0.941)	<0.01	protective
Uric acid	pancreatic cancer	1.246 (1.010–1.539)	0.040	risk factor

HDL – high-density lipoprotein; LDL – low-density lipoprotein; OR – odds ratio; 95% CI – 95% confidence interval; IVW – inverse variance weighted.

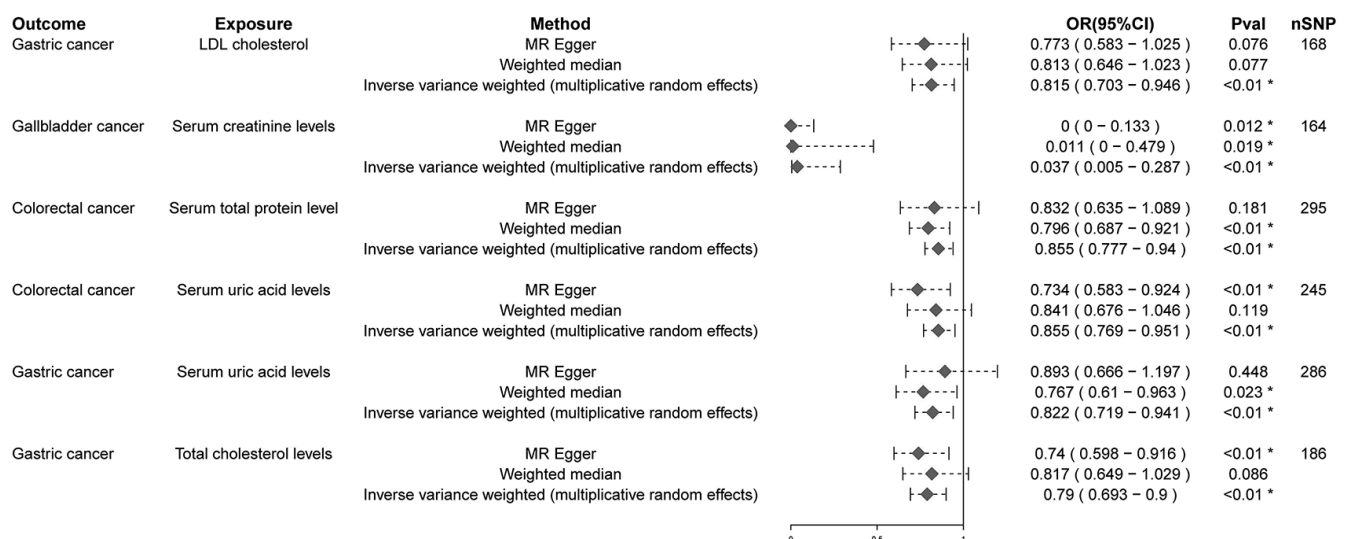


Fig. 1. Association between blood cell traits and GI tumors

GI – gastrointestinal; MR-Egger – Mendelian randomization–Egger; OR – odds ratio; 95% CI – 95% confidence interval; SNP – single nucleotide polymorphism; *indicates statistical significance; LDL – low-density lipoprotein.

in gastric and colorectal cancer (Supplementary Fig. 1). MR-Egger and weighted median estimates demonstrated consistent directionality, although statistical significance was attenuated (weighted median $p = 0.061$).

Gallbladder cancer

Serum creatinine was strongly associated with a decreased risk of gallbladder cancer (IVW OR = 0.037, 95% CI: 0.005–0.287, $p < 0.01$), with consistent results across the MR-Egger and weighted median methods (Fig. 1).

Scatter plot visualization

The MR scatter plots presented in Fig. 2 visually support the causal estimates derived from statistical modeling. In Fig. 2A,B, clear negative slopes are observed between LDL cholesterol and gastric cancer, and between serum creatinine and gallbladder cancer, respectively, indicating protective effects. Figure 2C,D shows similar inverse relationships for serum total protein and uric acid with CRC risk. In contrast, Fig. 2F shows a positive slope between uric acid and pancreatic cancer, consistent with its observed risk-enhancing effect. The alignment of most SNPs along the IVW regression lines, with minimal outliers, suggests that the instrumental variables exert consistent directional effects with limited horizontal pleiotropy. These visual findings reinforce the robustness of the causal estimates obtained through MR methods.

Sensitivity and robustness

These estimates were consistent across the MR-Egger and weighted median methods, with no indication of directional pleiotropy (MR-Egger intercept $p > 0.05$ for all pairs). Heterogeneity testing using Cochran's Q test showed no significant heterogeneity in most models (Q p -value > 0.05) (Table 3). MR-PRESSO analysis did not identify influential outlier SNPs, and leave-one-out analyses further supported the robustness of the results.

The F-statistics of the included instrumental variables were all above the conventional threshold ($F > 10$), confirming strong instrument strength. For example, in the HDL cholesterol–CRC model, 287 independent SNPs yielded F-statistics with a median of 33.86 (interquartile range (IQR): 26.72–61.65) and a range from 19.74 to 701.81 (Supplementary Table 1).

Discussion

Gastrointestinal cancers, including gastric, colorectal, pancreatic, and gallbladder cancers, are among the leading causes of cancer-related mortality worldwide.¹ The etiology of these cancers is multifactorial, involving genetic predisposition, lifestyle factors, and environmental exposures.⁴

Despite advancements in cancer treatment, the prognosis of many GI cancers remains poor, underscoring the importance of identifying modifiable risk factors.²⁶ This study employed MR to explore the causal relationships between blood cell traits and GI cancer risk, providing insights that could inform clinical practice and public health strategies.

The results of this study show that the protective effect of LDL cholesterol against gastric cancer, as indicated by the IVW method, may be attributed to its role in cellular processes. Low-density lipoprotein cholesterol is known to influence membrane fluidity and signaling pathways that may affect cell proliferation and apoptosis.¹² Furthermore, it is involved in modulation of immune responses, which may contribute to tumor suppression.¹³ This finding is consistent with previous studies suggesting that certain lipid profiles may exert protective effects against specific cancers.^{14,27}

Serum creatinine levels showed a protective effect against gallbladder cancer. Creatinine, a breakdown product of creatine phosphate derived from muscle metabolism, has been linked to kidney function and overall metabolic health.¹⁵ Its protective role may be related to better metabolic control and lower levels of metabolic waste, thereby reducing chronic inflammation that could contribute to cancer development.²⁸ This interpretation is supported by studies indicating that improved metabolic health may reduce cancer risk.²⁹ Given the relatively small sample size of the gallbladder cancer cohort ($n = 907$), the statistical power to detect modest associations may be limited. Therefore, although the observed protective effect of serum creatinine is biologically plausible, further validation in larger datasets is warranted.

The association between serum total protein levels and a reduced risk of CRC may reflect the overall nutritional status and immune competence of individuals. Higher protein levels may enhance the body's ability to repair DNA damage and maintain immune surveillance, which are crucial in preventing carcinogenesis.¹⁶ Similar mechanisms have been proposed in other studies linking nutritional status to cancer risk.¹⁷

Serum uric acid levels showed a dual role in cancer risk, acting as a protective factor in colorectal and gastric cancer, but as a risk factor in pancreatic cancer. This duality may stem from uric acid's complex involvement in redox balance and inflammation. At moderate levels, uric acid may act as an antioxidant, whereas at elevated concentrations, it can promote oxidative stress and *NLRP3* inflammasome activation – particularly in pancreatic tissues.^{18,19,30,31} These microenvironmental mechanisms may help explain its divergent effects across different cancer types. Furthermore, the association between uric acid and pancreatic cancer might be partially mediated by obesity-related inflammatory pathways,³² which warrants further evaluation through multivariable MR (MVMR).

Total cholesterol levels showed a significant protective effect against gastric cancer. Cholesterol plays a role in cellular membrane integrity and signaling pathways, and its

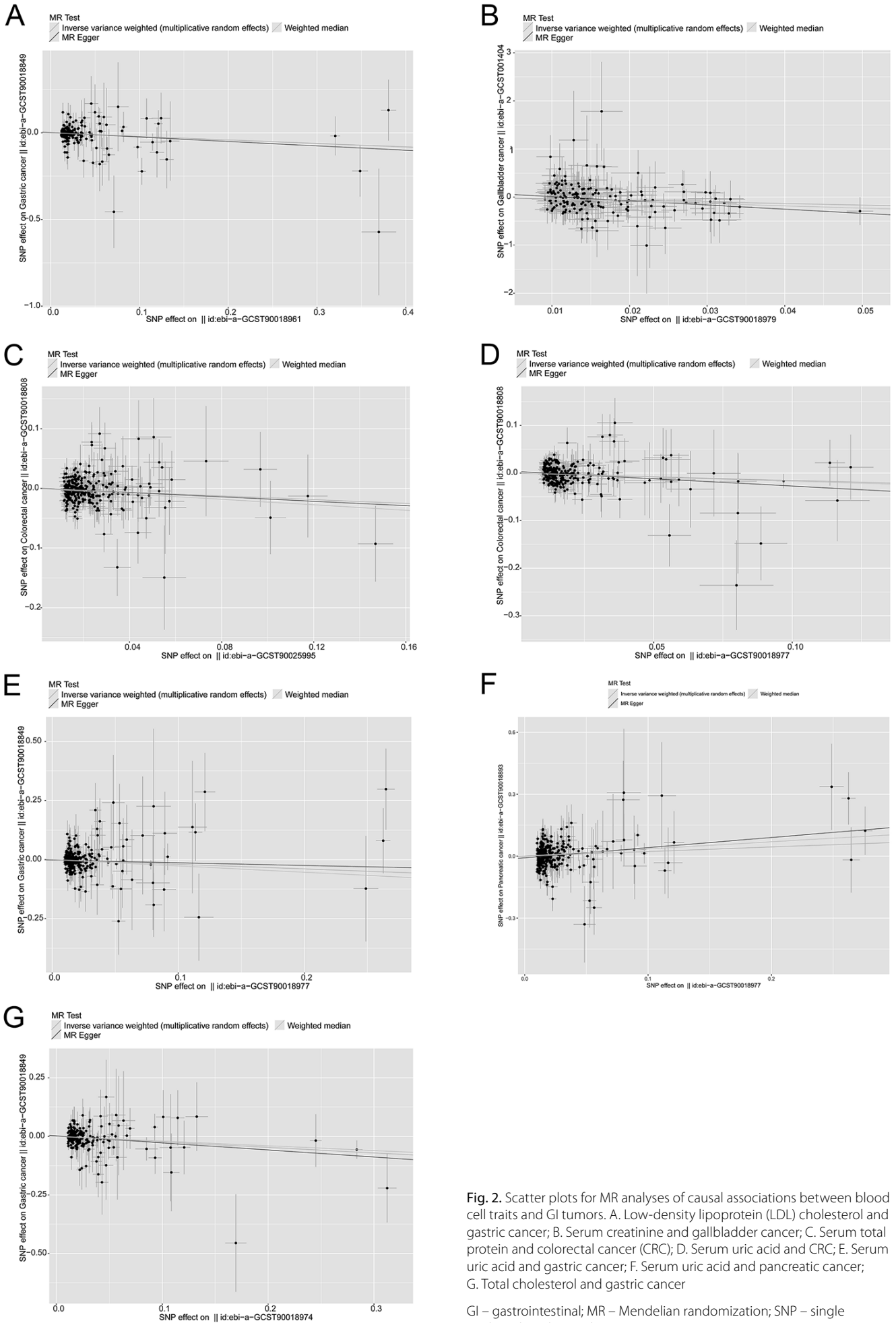


Fig. 2. Scatter plots for MR analyses of causal associations between blood cell traits and GI tumors. A. Low-density lipoprotein (LDL) cholesterol and gastric cancer; B. Serum creatinine and gallbladder cancer; C. Serum total protein and colorectal cancer (CRC); D. Serum uric acid and CRC; E. Serum uric acid and gastric cancer; F. Serum uric acid and pancreatic cancer; G. Total cholesterol and gastric cancer

GI – gastrointestinal; MR – Mendelian randomization; SNP – single nucleotide polymorphism.

Table 3. Assessment of pleiotropy and heterogeneity in Mendelian randomization (MR) models across biomarkers and cancer outcomes

Outcome	Exposure	Heterogeneity		Pleiotropy
		Q	Q p-value	p-value
Colorectal cancer	HDL cholesterol	316.383	0.097	0.197
Gallbladder cancer	HDL cholesterol	135.428	0.144	0.464
Pancreatic cancer	HDL cholesterol	328.424	0.171	0.960
Colorectal cancer	LDL cholesterol	150.300	0.301	0.744
Gallbladder cancer	LDL cholesterol	68.786	0.157	0.948
Gastric cancer	LDL cholesterol	185.351	0.145	0.662
Pancreatic cancer	LDL cholesterol	180.006	0.322	0.443
Colorectal cancer	serum albumin	269.259	0.087	0.087
Gallbladder cancer	serum albumin	98.235	0.918	0.624
Gastric cancer	serum albumin	244.249	0.359	0.921
Pancreatic cancer	serum albumin	278.128	0.107	0.081
Colorectal cancer	serum alkaline phosphatase	326.321	0.333	0.505
Gallbladder cancer	serum alkaline phosphatase	94.128	0.961	0.666
Gastric cancer	serum alkaline phosphatase	394.954	0.093	0.310
Pancreatic cancer	serum alkaline phosphatase	311.963	0.675	0.371
Colorectal cancer	serum creatinine	422.894	0.197	0.404
Gallbladder cancer	serum creatinine	102.047	1.000	0.089
Gastric cancer	serum creatinine	455.188	0.150	0.646
Pancreatic cancer	serum creatinine	436.112	0.583	0.624
Colorectal cancer	serum phosphate	200.221	0.169	0.513
Gallbladder cancer	serum phosphate	108.639	0.088	0.950
Gastric cancer	serum phosphate	190.015	0.327	0.919
Pancreatic cancer	serum phosphate	215.832	0.125	0.407
Colorectal cancer	serum total protein	290.537	0.530	0.830
Gallbladder cancer	serum total protein	177.126	0.080	0.872
Pancreatic cancer	serum total protein	330.559	0.497	0.381
Colorectal cancer	serum urea	218.545	0.076	0.217
Gallbladder cancer	serum urea	83.991	0.804	0.619
Gastric cancer	serum urea	231.534	0.083	0.372
Pancreatic cancer	serum urea	228.816	0.112	0.541
Colorectal cancer	serum uric acid	223.663	0.808	0.140
Gallbladder cancer	serum uric acid	109.855	0.618	0.723
Gastric cancer	serum uric acid	286.208	0.452	0.538
Pancreatic cancer	serum uric acid	283.044	0.666	0.054
Colorectal cancer	total cholesterol	197.675	0.096	0.582
Gallbladder cancer	total cholesterol	80.917	0.246	0.444
Gastric cancer	total cholesterol	202.338	0.168	0.451
Pancreatic cancer	total cholesterol	229.433	0.090	0.736
Colorectal cancer	total triglycerides	82.093	0.075	0.066
Gallbladder cancer	total triglycerides	8.269	0.974	0.079
Gastric cancer	total triglycerides	72.943	0.208	0.390
Pancreatic cancer	total triglycerides	68.491	0.529	0.253

HDL – high-density lipoprotein; LDL – low-density lipoprotein.

modulation may affect cancer cell behavior.³³ The protective effect observed in this study aligns with previous findings suggesting that maintaining balanced cholesterol levels may contribute to cancer prevention.³⁴

The observed associations between blood cell traits and GI cancers have significant implications for clinical practice. For instance, monitoring and potentially modifying lipid profiles, creatinine, total protein, and uric acid levels in patients could represent a strategy to mitigate cancer risk.³⁵ The findings suggest that clinicians should consider the impact of these blood cell traits on cancer risk, especially in patients with a high predisposition to GI cancers.³⁶ Among these associations, the strong inverse association observed between serum creatinine and gallbladder cancer highlights potential biological relevance. However, its clinical utility is limited by the low incidence of the disease and the lack of established screening strategies. Further studies are needed to confirm this association and explore its feasibility for individualized risk prediction.

Limitations of the study

Several limitations should be acknowledged. First, the scope of blood biomarkers analyzed was limited. Other potentially relevant variables such as inflammatory markers (e.g., C-reactive protein (CRP)), micronutrients (e.g., vitamin D), or liver enzymes (e.g., alanine transaminase (ALT) and aspartate transaminase (AST)) were not included because of data availability or the lack of strong genetic instruments. Second, we did not perform MVMR, which may help disentangle collinearity between closely related exposures such as LDL and total cholesterol. This should be prioritized in future studies. Third, our GWAS data were derived exclusively from individuals of European ancestry, which may limit generalizability to other ethnic groups. This is particularly relevant for cancers such as gastric and gallbladder cancer, which have higher incidence rates in Asian and South American populations. Trans-ethnic validation will be essential to establish broader applicability.

Additionally, we did not examine sex- or age-specific effects, nor did we stratify by cancer subtype (e.g., colon compared with rectal cancer), which may obscure biologically meaningful heterogeneity. Future work could incorporate stratified MR analyses to explore population-specific and tumor-specific metabolic pathways. Finally, functional validation using experimental models is needed to confirm the mechanistic pathways suggested by our findings.

While our findings suggest that certain metabolic blood biomarkers, such as LDL cholesterol and serum uric acid, may play protective roles in specific GI cancers, these biomarkers are also known risk factors for CVD, gout, and kidney dysfunction. Thus, it is essential to interpret our findings within a broader clinical context. We do not advocate artificial elevation of these biomarkers as a preventive

strategy. Instead, the observed associations may reflect complex metabolic or immunological mechanisms that warrant further mechanistic investigation. Clinical interventions should always consider the balance between cancer risk and other disease burdens.

Conclusions

This study provides genetic evidence supporting causal links between selected blood metabolic traits and GI cancer risk. These results highlight new avenues for biomarker-guided screening and underscore the need for further mechanistic and translational research to translate these associations into actionable clinical tools.

Supplementary data

The supplementary materials are available at <https://doi.org/10.5281/zenodo.15621795>. The package contains the following files:

Supplementary Table 1. Instrumental variables for biomarkers in GI cancers.

Supplementary Fig. 1. The detailed results from the MR analysis for all identified markers and their associations with GI cancers.

Data Availability Statement

Data sharing does not apply to this article, as no new data were generated during the current study.

Consent of publication


Not applicable.


Use of AI and AI-assisted technologies


Not applicable.

ORCID iDs

Xiufeng Huang  <https://orcid.org/0009-0009-7979-925X>

Jianxin Chen  <https://orcid.org/0000-0003-2467-3333>

Feiteng Gu  <https://orcid.org/0000-0002-2789-074X>

Xiaodan Zheng  <https://orcid.org/0009-0003-2731-1888>

References

1. Dizdar Ö, Kılıçkap S. Global epidemiology of gastrointestinal cancers. In: Yalçın Ş, Philip PA, eds. *Textbook of Gastrointestinal Oncology*. Cham, Switzerland: Springer; 2019:1–12. ISBN:978-3-030-18888-7.
2. Wang S, Zheng R, Li J, et al. Global, regional, and national lifetime risks of developing and dying from gastrointestinal cancers in 185 countries: A population-based systematic analysis of GLOBOCAN. *Lancet Gastroenterol Hepatol*. 2024;9(3):229–237. doi:10.1016/S2468-1253(23)00366-7
3. Huang M, Feng L, Ren H, et al. Knowledge, attitudes, and practices regarding whole-course management among patients with gastrointestinal cancers: A cross-sectional study. *World J Surg Oncol*. 2025;23(1):45. doi:10.1186/s12957-025-03668-7

4. Ashktorab H, Kupfer SS, Brim H, Carethers JM. Racial disparity in gastrointestinal cancer risk. *Gastroenterology*. 2017;153(4):910–923. doi:10.1053/j.gastro.2017.08.018
5. Barone E, Corrado A, Gemignani F, Landi S. Environmental risk factors for pancreatic cancer: An update. *Arch Toxicol*. 2016;90(11):2617–2642. doi:10.1007/s00204-016-1821-9
6. Yang L, Ying X, Liu S, et al. Gastric cancer: Epidemiology, risk factors and prevention strategies. *Chin J Cancer Res*. 2020;32(6):695–704. doi:10.21147/j.issn.1000-9604.2020.06.03
7. Lewandowska A, Rudzki G, Lewandowski T, Strykowska-Góra A, Rudzki S. Risk factors for the diagnosis of colorectal cancer. *Cancer Control*. 2022;29:10732748211056692. doi:10.1177/10732748211056692
8. Hu JX, Zhao CF, Chen WB, et al. Pancreatic cancer: A review of epidemiology, trend, and risk factors. *World J Gastroenterol*. 2021;27(27):4298–4321. doi:10.3748/wjg.v27.i27.4298
9. Pérez-Moreno P, Riquelme I, García P, Brebi P, Roa JC. Environmental and lifestyle risk factors in the carcinogenesis of gallbladder cancer. *J Pers Med*. 2022;12(2):234. doi:10.3390/jpm12020234
10. Drewes AM, Olesen AE, Farmer AD, Szigethy E, Rebours V, Olesen SS. Gastrointestinal pain. *Nat Rev Dis Primers*. 2020;6(1):1. doi:10.1038/s41572-019-0135-7
11. Bianchi S, Torge D, Rinaldi F, Piattelli M, Bernardi S, Varvara G. Platelets' role in dentistry: From oral pathology to regenerative potential. *Biomedicines*. 2022;10(2):218. doi:10.3390/biomedicines10020218
12. Codini M, Garcia-Gil M, Albi E. Cholesterol and sphingolipid enriched lipid rafts as therapeutic targets in cancer. *Int J Mol Sci*. 2021;22(2):726. doi:10.3390/ijms22020726
13. Huang B, Song BL, Xu C. Cholesterol metabolism in cancer: Mechanisms and therapeutic opportunities. *Nat Metab*. 2020;2(2):132–141. doi:10.1038/s42255-020-0174-0
14. Saini RK, Rengasamy KRR, Mahomoodally FM, Keum YS. Protective effects of lycopene in cancer, cardiovascular, and neurodegenerative diseases: An update on epidemiological and mechanistic perspectives. *Pharmacol Res*. 2020;155:104730. doi:10.1016/j.phrs.2020.104730
15. De Rosa S, Greco M, Rausedo M, Annetta MG. The good, the bad, and the serum creatinine: Exploring the effect of muscle mass and nutrition. *Blood Purif*. 2023;52(9–10):775–785. doi:10.1159/000533173
16. Molinaro C, Martoriati A, Cailliau K. Proteins from the DNA damage response: Regulation, dysfunction, and anticancer strategies. *Cancers (Basel)*. 2021;13(15):3819. doi:10.3390/cancers13153819
17. Bose S, Allen AE, Locasale JW. The molecular link from diet to cancer cell metabolism. *Mol Cell*. 2020;80(3):554. doi:10.1016/j.molcel.2020.10.006
18. Gherghina ME, Peride I, Tiglis M, Neagu TP, Niculae A, Checherita IA. Uric acid and oxidative stress: Relationship with cardiovascular, metabolic, and renal impairment. *Int J Mol Sci*. 2022;23(6):3188. doi:10.3390/ijms23063188
19. Mi S, Gong L, Sui Z. Friend or foe? An unrecognized role of uric acid in cancer development and the potential anticancer effects of uric acid-lowering drugs. *J Cancer*. 2020;11(17):5236–5244. doi:10.7150/jca.46200
20. Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. *Nat Rev Methods Primers*. 2022;2(1):6. doi:10.1038/s43586-021-00092-5
21. Richmond RC, Davey Smith G. Mendelian randomization: Concepts and scope. *Cold Spring Harb Perspect Med*. 2022;12(1):a040501. doi:10.1101/cshperspect.a040501
22. Yuan S, Carter P, Bruzelius M, et al. Effects of tumour necrosis factor on cardiovascular disease and cancer: A two-sample Mendelian randomization study. *eBioMedicine*. 2020;59:102956. doi:10.1016/j.ebiom.2020.102956
23. Chen K, Li J, Ouyang Y, et al. Blood lipid metabolic profiles and causal links to site-specific cancer risks: A Mendelian randomization study. *Nutr Cancer*. 2024;76(2):175–186. doi:10.1080/01635581.2023.2294521
24. Wang Z, Chen J, Zhu L, Jiao S, Chen Y, Sun Y. Metabolic disorders and risk of cardiovascular diseases: A two-sample mendelian randomization study. *BMC Cardiovasc Disord*. 2023;23(1):529. doi:10.1186/s12872-023-03567-3
25. Levin MG, Burgess S. Mendelian randomization as a tool for cardiovascular research: A review. *JAMA Cardiol*. 2024;9(1):79. doi:10.1001/jamacardio.2023.4115
26. Jardim SR, De Souza LMP, De Souza HSP. The rise of gastrointestinal cancers as a global phenomenon: Unhealthy behavior or progress? *Int J Environ Res Public Health*. 2023;20(4):3640. doi:10.3390/ijerph20043640
27. Martín-Pérez M, Urdiroz-Urricelqui U, Bigas C, Benitah SA. The role of lipids in cancer progression and metastasis. *Cell Metab*. 2022;34(11):1675–1699. doi:10.1016/j.cmet.2022.09.023
28. Peris-Fernández M, Roca-Marugán M, Amengual JL, et al. Uremic toxins and inflammation: Metabolic pathways affected in non-dialysis-dependent stage 5 chronic kidney disease. *Biomedicines*. 2024;12(3):607. doi:10.3390/biomedicines12030607
29. Clemente-Suárez VJ, Martín-Rodríguez A, Redondo-Flórez L, et al. Metabolic health, mitochondrial fitness, physical activity, and cancer. *Cancers (Basel)*. 2023;15(3):814. doi:10.3390/cancers15030814
30. Liu Y, Liu Y, Wang Q, et al. MIF inhibitor ISO-1 alleviates severe acute pancreatitis-associated acute kidney injury by suppressing the NLRP3 inflammasome signaling pathway. *Int Immunopharmacol*. 2021;96:107555. doi:10.1016/j.intimp.2021.107555
31. Braga TT, Forni MF, Correa-Costa M, et al. Soluble uric acid activates the NLRP3 inflammasome. *Sci Rep*. 2017;7(1):39884. doi:10.1038/srep39884
32. Park SK, Oh C, Kim M, Ha E, Choi Y, Ryoo J. Metabolic syndrome, metabolic components, and their relation to the risk of pancreatic cancer. *Cancer*. 2020;126(9):1979–1986. doi:10.1002/cncr.32737
33. Maja M, Tyteca D. Alteration of cholesterol distribution at the plasma membrane of cancer cells: From evidence to pathophysiological implication and promising therapy strategy. *Front Physiol*. 2022;13:999883. doi:10.3389/fphys.2022.999883
34. Xu H, Zhou S, Tang Q, Xia H, Bi F. Cholesterol metabolism: New functions and therapeutic approaches in cancer. *Biochim Biophys Acta Rev Cancer*. 2020;1874(1):188394. doi:10.1016/j.bbcan.2020.188394
35. Dent SF, Kikuchi R, Kondapalli L, et al. Optimizing cardiovascular health in patients with cancer: A practical review of risk assessment, monitoring, and prevention of cancer treatment-related cardiovascular toxicity. *Am Soc Clin Oncol Educ Book*. 2020;(40):501–515. doi:10.1200/EDBK_286019
36. Zametkin E, Guyer D, Tarshish Y, Bash K, Almhanna K. Total parenteral nutrition for patients with gastrointestinal cancers: A clinical practice review. *Ann Palliat Med*. 2023;12(5):1072–1080. doi:10.21037/apm-22-1380