Current Science
CS 5 (1), 1042– 1060 (2025)
Received 16 Oct 2024 | **Revised 27 Nov.** 2024 | **Accepted 15 Dec**. 2024 | **Online Available 12 Jan** 2025
https://doi.org/10.52845/CS/2025-5-1-7

Current Science

Current Science

OPEN ACCESS

ISSN(O)2795-8639

ORIGINAL ARTICLE

The Causal Relationship between Circulating Metabolic Biomarkers and Gastric Cancer: A Mendelian Randomization Study

Minghao Tan[1], Duanyu Wang[3], Vicheth Virak[2], Nora Iv[2], Rattanaricky Ung[2], Gechhorng Lim[2], Vahid Say[2], Sokheng Phal[2], Sokhuon Cheat[2], Dinarong Phan[2], Chunshan Liu[4*], Pengkhun Nov[2*]

[1] Department of Gastrointestinal Surgery, Liuzhou Workers Hospital, Liuzhou, Guangxi Province 545005, China

[2] Oncology Center, Zhujiang Hospital of Southern Medical University, Guangzhou, Guangdong Province 510282, China

[3] Department of Oncology, Xiangya Hospital of Central South University, Changsha, Hunan Province 410119, China

[4]Department of Radiation Oncology, Guangzhou Institute of Cancer Research, the Affiliated Cancer Hospital, Guangzhou Medical University, Guangzhou, Guangdong Province 510095, China

***Corresponding Author: Dr. Pengkhun Nov and Dr. Chunshan Liu**

Abstract

Background: Gastric cancer (GC) is a major global health concern, and understanding its etiology is crucial for developing effective prevention strategies. Metabolites, as key intermediates in metabolic pathways, may play a significant role in cancer development. This study employs a Mendelian randomization approach to explore the causal relationship between circulating metabolic biomarkers and the risk of gastric cancer.

Methods: An extensive two-sample MR analysis was enrolled in this study. Briefly, the publicly available genetic data were utilized for investigation of the causal association between 233 metabolites and GC; the inverse variance weighted (IVW) model and weighted medians were employed for MR analyses; and sensitivity analyses were adopted for heterogeneity and pleiotropy assessments.

Results: Our analysis revealed a total of 49 circulating metabolic biomarkers associated with GC. Of them, Cholesteryl esters to total lipids ratio in large HDL [odds ratio (OR) = 1.850, 95% confidence interval (CI) = 1.264– 2.709, P adjusted (P_FDR) = 0.010], Free cholesterol to total lipids ratio in medium LDL (OR = 1.621, 95% CI=1.222–2.150, P_FDR = 0.008), Phospholipids to total lipids ratio in medium LDL (OR = 1.556, 95% CI= 1.193 – 2.030, P_FDR= 0.008), Total cholesterol levels in small HDL (OR = 0.472, 95% CI= 0.302 – 0.739, P_FDR= 0.008), Cholesterol esters in small HDL (OR = 0.574, 95% CI= 0.391 – 0.843, P_FDR= 0.024), and Phospholipids to total lipids ratio in large HDL (OR = 0.580, 95% CI= 0.416 – 0.809, P_FDR= 0.009) were strongly associated with GC. Notably, Cholesteryl esters to total lipids ratio in large HDL, Free cholesterol to total lipids ratio in medium LDL, and Phospholipids to total lipids ratio in medium LDL were linked to increased risk factors of GC, while Total cholesterol levels in small HDL, Phospholipids to total lipids ratio in large HDL, Cholesterol esters in small HDL, and Phospholipids to total lipids ratio in large HDL are the protective factor of GC.

Conclusion: This study provides evidence for a causal relationship between circulating metabolic biomarkers and gastric cancer, emphasizing the importance of metabolic factors in cancer etiology. Our findings contribute to the understanding of gastric cancer mechanisms and may inform future research on prevention and treatment strategies. Further studies are warranted to validate these associations and explore

the underlying biological mechanisms.

Keywords: Gastric cancer, circulating metabolic biomarkers, Mendelian randomization, UK Biobank, GWAS.

Introduction

Gastric cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide, with complex etiological factors contributing to its development. With over 1 million estimated new cases annually, gastric cancer is the fifth most diagnosed malignancy worldwide [1]. Among these factors, metabolites—small molecules involved in metabolic processes have garnered increasing attention for their potential role in cancer pathogenesis. Understanding the relationship between metabolites and gastric cancer can provide insights into the underlying mechanisms of the disease and identify potential biomarkers for early detection and intervention [2].

Recent advances in genetic research have enabled the application of Mendelian randomization (MR) as a powerful tool to investigate causal relationships between exposures (such as metabolites) and health outcomes (such as gastric cancer) [3, 4]. Unlike traditional observational studies, MR leverages genetic variants as instrumental variables, helping to mitigate confounding factors and reverse causation. This approach allows for a more robust assessment of whether metabolites truly influence the risk of developing gastric cancer [5].

In this study, we aim to elucidate the causal relationship between 233 circulating metabolic biomarkers and the risk of gastric cancer using a Mendelian randomization framework. By analyzing genetic data and metabolomic profiles from large population cohorts, we seek to clarify whether certain circulating metabolic biomarkers are causally linked to gastric cancer development. Our findings have the potential to contribute to the growing body of literature on the metabolic aspects of cancer and may pave the way for novel preventive strategies and therapeutic targets in the fight against gastric cancer.

2 Materials and methods

2.1 Study design

The cause-and-effect relationship between 233 types of circulating metabolic biomarkers and gastric cancer was assessed using two-sample MR analyses. MR leveraged genetic variations as proxies for risk factors. For ensuring reliable causal inference, instrumental variables (IVs) applied in MR must meet three key assumptions as follows: (1) There must be a direct association between the genetic variation and the exposure; (2) The genetic variant should not be linked to any potential confounders that existed between the exposure and the outcome; (3) The influence of the genetic variation on the outcome must occur exclusively through the exposure, avoiding alternative pathways (**Figure 1**).

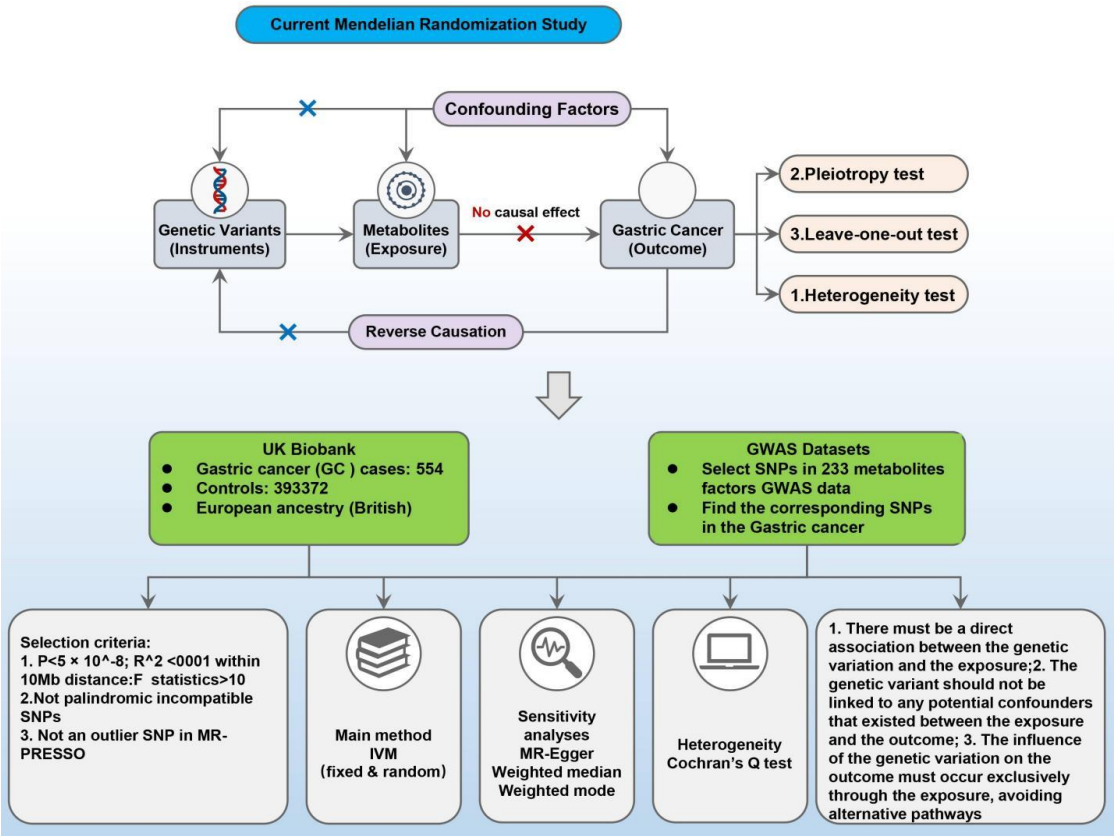

Figure 1. Study Design Flowchart. The initial assumption is that the instrument variables have a strong correlation with the exposure. The second assumption states that the instrument variables are not linked to any confounding factors. The third assumption asserts that the instrument variables affect the outcome exclusively through the exposure.

2.2 Data sources for exposure and outcome

The statistics summary of Genome-Wide Association Study (GWAS) data for each circulating metabolic biomarkers is publicly available from the European GWAS catalogue (https://www.ebi.ac.uk/gwas) (accession number: GCST90301941–GCST90302173) [6]. Cancer-specific keywords were applied to search relevant data for gastric cancer was downloaded from UK Biobank database (https://pheweb.org/UKB-SAIGE/). To be specific, ukb-saige-151 was selected for GC identification screening. Referring to the ID of each cancer, related data were downloaded from UK biobank (https://pheweb.org/UKB-SAIGE/) including 393926 European individuals (n = 554 case patients and 475,308 control participants) for GC, and 233 circulating metabolic biomarkers were downloaded from GWAS catalogue (https://www.ebi.ac.uk/gwas) including 136,016 European individuals. Finally, the relationship between circulating metabolic biomarkers and gastric cancer was analyzed.

2.3 Instrument selection

Considering the extensive number of single-nucleotide polymorphisms (SNPs) demonstrating genome-wide significance ($p < 5 \times 10^{-8}$) for circulating metabolic biomarkers traits, we implemented more stringent correlation thresholds ($p < 5 \times 10^{-9}$) for the selection of genetic IVs. These IVs were identified by grouping them according to the reference panel of the Linkage Disequilibrium (LD) from the 1000 Genomes Project, with a threshold of $R^2 < 0.001$ at a distance of 1,000 kilobases (kb). Owing to the relatively limited size of the GWAS data for circulating metabolic biomarkers, we employed a p-value cutoff of 5×10^{-8} and a less significant clustering threshold ($R2 < 0.001$ at a distance of 1000 kb) [7]. To ensure the reliability of our tools, IVs with F-statistics exceeding 10 were selected and identified as strong instruments for subsequent analyses. Then, these IVs were extracted from the summary statistics pertaining to gastric cancer outcome, excluding any that showed potential pleiotropic effects ($p < 10^{-5}$) on gastric cancer, in line with methodologies from

previous studies [8]. To maintain consistency in our analysis, the SNPs between the exposure and outcome datasets were synchronized to ensure uniform effect estimates for the same effect allele [7].

2.4 Statistical analysis

In our study, a range of genetic variants were employed as IVs, rather than relying solely on an allele score. This approach was chosen to thoroughly examine key assumptions, uncover potential pleiotropy, and facilitate more effective sensitivity and multivariable MR analyses [9]. Four distinct MR methodologies, including the inverse variance weighted (IVW; random-effects model), weighted median, MR-Egger, and MR-pleiotropy residual sum and outlier (PRESSO), were utilized to assess the consistency of our findings under different assumptions about heterogeneity and pleiotropy. The IVW method, employing a random-effects model, served as the primary analysis framework for all four sets of IVs. As for heterogeneity, it was quantified using Cochran's Q statistic.

Our study also included analyses with more stringent conditions. Under the assumption that all genetic variants were valid, the IVW method may be biased if a significant number of SNPs were affected by horizontal pleiotropy [10]. Conversely, the weighted median approach, effective when less than 50% of variants exhibited horizontal pleiotropy, presumed that most genetic variants were valid [11]. In cases where over 50% of variants were affected by horizontal pleiotropy, the strength of our genetic instruments was evaluated through F statistics, considering a mean F-statistic of less than 10 indicative of weak IVs [12].

Furthermore, the MR-Egger method was applied to assess potential directional pleiotropy. Here, a significant intercept would indicate a violation of IV assumptions, suggesting directional pleiotropy [13]. Also, the MR-PRESSO method was implement to minimize heterogeneity in causal effect estimates by excluding disproportionately influential SNPs (NbDistribution = 1,500) [14]. In addition, Steiger-filtering analyses were conducted to detect and eliminate genetic variants more strongly associated with the outcome than the exposure, indicating possible reverse causality [15]. All statistical analyses were performed using R version 4.3.1 (R Foundation) and specific R packages ("TwoSampleMR" and "MR") tailored for MR analysis [16, 17].

3 Results

To assess the causal impact of various circulating metabolic biomarkers on GC, the IVW method was employed for a two-sample MR analysis. The assessment results showed that 49 circulating metabolic biomarkers were association with GC (**Figure 2**), highlighting some of the strongest associations. Briefly, the GC risk was strongly associated with Cholesteryl esters to total lipids ratio in large HDL [odds ratio (OR) = 1.850, 95% confidence interval (CI) = 1.264– 2.709, *P*_FDR= 0.010], Free cholesterol to total lipids ratio in medium LDL (OR = 1.621, 95% CI=1.222–2.150, *P*_FDR = 0.008), Phospholipids to total lipids ratio in medium LDL (OR = 1.556, 95% CI= 1.193 – 2.030, *P*_FDR= 0.008), Total cholesterol levels in small HDL (OR = 0.472, 95% CI= 0.302 – 0.739, *P*_FDR= 0.008), Cholesterol esters in small HDL (OR = 0.574, 95% CI= 0.391 – 0.843, *P*_FDR= 0.024), and Phospholipids to total lipids ratio in large HDL (OR = 0.580, 95% CI= 0.416 – 0.809, *P*_FDR= 0.009) (**Figure 3**). Furthermore, a sensitivity analysis was performed. No heterogeneity was observed, with significant results from Cochran's Q test (P >0.05), the causal estimates remained robust when analyzed using the random-effects inverse variance weighting (IVW) model (**Table SI**). The P-values for the MR-Egger intercept were above 0.05, indicating no significant pleiotropic effects (**Table SII**). Additionally, we further evaluated the data using scatter plots (**Fig. 4A-F**), funnel plots (**Fig. 5A-F**), and leave-one-out plots (**Fig. 6A-F**), which helped to eliminate the potential influence of outliers and horizontal pleiotropy on the identified circulating metabolic biomarkers.

Exposure	Method	No.of SNP	OR(95% CI)	P_FDR	P
Cholesteryl esters to total lipids ratio in large HDL	IVW	46	1.850 (1.264 to 2.709)	0.010	0.002
Free cholesterol to total lipids ratio in medium LDL	IVW	76	1.621 (1.222 to 2.150)	0.008	0.001
Phospholipids to total lipids ratio in medium LDL	IVW	74	1.556 (1.193 to 2.030)	0.008	0.001
Total cholesterol levels in small HDL	IVW	36	0.472 (0.302 to 0.739)	0.008	0.001
Cholesterol esters in small HDL	IVW	43	0.574 (0.391 to 0.843)	0.024	0.005
Apolipoprotein B levels	IVW	85	0.677 (0.517 to 0.887)	0.024	0.005
Esterified cholesterol levels	IVW	84	0.643 (0.494 to 0.838)	0.008	0.001
Total Cholesterol in IDL	IVW	86	0.655 (0.505 to 0.848)	0.009	0.001
Cholesterol esters in IDL	IVW	84	0.641 (0.495 to 0.830)	0.008	0.001
Free cholesterol in IDL	IVW	92	0.664 (0.516 to 0.854)	0.010	0.001
Total lipids in IDL	IVW	83	0.692 (0.539 to 0.888)	0.021	0.004
Concentration of IDL particles	IVW	80	0.671 (0.522 to 0.863)	0.011	0.002
Phospholipids in IDL	IVW	83	0.632 (0.492 to 0.813)	0.008	0.000
Total cholesterol levels in LDL	IVW	83	0.650 (0.507 to 0.832)	0.008	0.001
Phospholipids to total lipids ratio in large HDL	IVW	47	0.580 (0.416 to 0.809)	0.009	0.001
Total cholesterol in large LDL	IVW	83	0.625 (0.488 to 0.802)	0.008	0.000
Total cholesterol to total lipids ratio in large LDL	IVW	69	0.684 (0.512 to 0.913)	0.046	0.010
Cholesterol esters in large LDL	IVW	83	0.655 (0.510 to 0.841)	0.008	0.001
Cholesteryl esters to total lipids ratio in large LDL	IVW	63	0.602 (0.463 to 0.783)	0.008	0.000
Free cholesterol in large LDL	IVW	82	0.640 (0.499 to 0.820)	0.008	0.000
Total lipids in large LDL	IVW	85	0.617 (0.481 to 0.793)	0.008	0.000
Concentration of large LDL particles	IVW	82	0.614 (0.477 to 0.791)	0.008	0.000
Phospholipids in large LDL	IVW	83	0.636 (0.492 to 0.821)	0.008	0.001
Phospholipids to total lipids ratio in large LDL	IVW	82	1.515 (1.181 to 1.945)	0.008	0.001
Total cholesterol in medium LDL	IVW	76	0.646 (0.502 to 0.830)	0.008	0.001
Total cholesterol to total lipids ratio in medium LDL	IVW	63	0.678 (0.509 to 0.905)	0.039	0.008
Cholesterol esters in medium LDL	IVW	75	0.653 (0.508 to 0.839)	0.008	0.001
Cholesteryl esters to total lipids ratio in medium LDL	IVW	61	0.626 (0.477 to 0.822)	0.008	0.001
Free cholesterol in medium LDL	IVW	80	0.621 (0.480 to 0.803)	0.008	0.000
Total lipid levels in medium LDL	IVW	82	0.631 (0.489 to 0.812)	0.008	0.000
Concentration of medium LDL particles	IVW	81	0.626 (0.484 to 0.808)	0.008	0.000
Phospholipids in medium LDL	IVW	78	0.632 (0.484 to 0.824)	0.008	0.001
Remnant cholesterol (non−HDL, non−LDL −cholesterol)	IVW	80	0.657 (0.493 to 0.874)	0.021	0.004
Serum total cholesterol levels	IVW	81	0.674 (0.520 to 0.874)	0.017	0.003
Total Cholesterol in small LDL	IVW	82	0.629 (0.490 to 0.807)	0.008	0.000
Total cholesterol to total lipids ratio in small LDL	IVW	68	0.695 (0.529 to 0.915)	0.044	0.009
Cholesterol esters in small LDL	IVW	76	0.644 (0.502 to 0.826)	0.008	0.001
Cholesteryl esters to total lipids ratio in small LDL	IVW	67	0.626 (0.481 to 0.814)	0.008	0.000
Free cholesterol in small LDL	IVW	78	0.625 (0.478 to 0.818)	0.008	0.001
Free cholesterol to total lipids ratio in small LDL	IVW	77	1.618 (1.230 to 2.128)	0.008	0.001
Total lipids in small LDL	IVW	82	0.635 (0.492 to 0.820)	0.008	0.000
Concentration of small LDL particles	IVW	83	0.631 (0.488 to 0.817)	0.008	0.000
Phospholipids in small LDL	IVW	81	0.632 (0.482 to 0.829)	0.008	0.001
Phospholipids to total lipids ratio in small LDL	IVW	75	1.593 (1.228 to 2.066)	0.008	0.000
Cholesterol esters in small VLDL	IVW	75	0.626 (0.448 to 0.875)	0.030	0.006
Total cholesterol in very small VLDL	IVW	72	0.618 (0.464 to 0.825)	0.008	0.001
Cholesterol esters in very small VLDL	IVW	67	0.622 (0.460 to 0.840)	0.011	0.002
Total lipids in very small VLDL	IVW	81	0.673 (0.507 to 0.893)	0.030	0.006
Phospholipids in very small VLDL	IVW	87	0.664 (0.515 to 0.857)	0.010	0.002

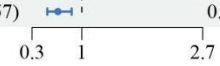

Figure 2. The causal association between all circulating metabolic biomarkers and Gastric cancer (GC). We selected Inverse variance weighted (IVW) as a primary method p<0.05 showed statistically significant; OR value >1 indicated a risk factor, while OR value <1 indicated a protective factor.

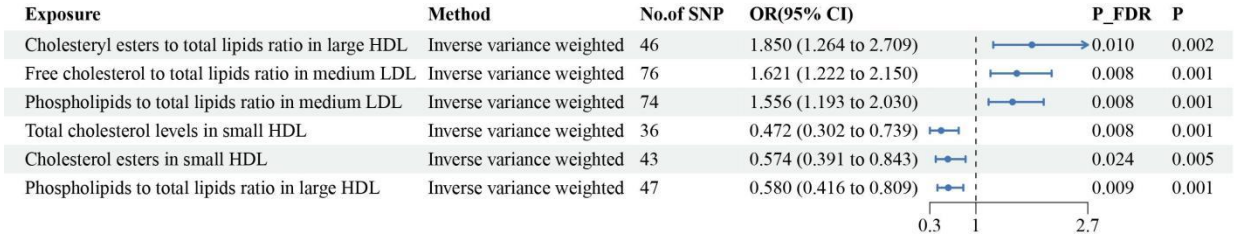

Figure 3. The causal association between six circulating metabolic biomarkers and Gastric cancer (GC). We selected Inverse variance weighted (IVW) as a primary method p<0.05 showed statistically significant; OR value >1 indicated a risk factor, while OR value <1 indicated a protective factor.

Table SI The heterogeneity of causal association between all circulating metabolic biomarkers and Gastric cancer (GC). The p-values for the Cochran's Q yielded were above 0.05, suggesting that no significant heterogeneity effects were found.

exposure	method	Q	Q_df	Q_pval
Cholesteryl esters to total lipids ratio in large HDL	MR Egger	42.44977805	44	0.538193253
Cholesteryl esters to total lipids ratio in large HDL	Inverse variance weighted	42.92384447	45	0.560282718
Free cholesterol to total lipids ratio in medium LDL	MR Egger	76.80454528	74	0.388838761
Free cholesterol to total lipids ratio in medium LDL	Inverse variance weighted	76.91652255	75	0.417020003
Phospholipids to total lipids ratio in medium LDL	MR Egger	62.11619353	72	0.790576952
Phospholipids to total lipids ratio in medium LDL	Inverse variance weighted	62.9916265	73	0.792073131
Total cholesterol levels in small HDL	MR Egger	33.00483538	34	0.516242533
Total cholesterol levels in small HDL	Inverse variance weighted	33.09897774	35	0.56013513
Cholesterol esters in small HDL	MR Egger	35.78725584	41	0.701083886
Cholesterol esters in small HDL	Inverse variance weighted	35.99090877	42	0.731082823
Apolipoprotein B levels	MR Egger	89.52869696	83	0.292718627
Apolipoprotein B levels	Inverse variance weighted	89.55562033	84	0.318923568
Esterified cholesterol levels	MR Egger	74.91894175	82	0.697503972
Esterified cholesterol levels	Inverse variance weighted	74.93156255	83	0.724263611
Total Cholesterol in IDL	MR Egger	89.13161559	84	0.330209971
Total Cholesterol in IDL	Inverse variance weighted	89.23536511	85	0.355488218
Cholesterol esters in IDL	MR Egger	84.6586	82	0.39845345

		4268		9
Cholesterol esters in IDL	Inverse variance weighted	84.6598 4394	83	0.42870678 6
Free cholesterol in IDL	MR Egger	95.4877 4092	90	0.32618518 3
Free cholesterol in IDL	Inverse variance weighted	95.5012 2559	91	0.35288335 5
Total lipids in IDL	MR Egger	72.7561 5322	81	0.73178122
Total lipids in IDL	Inverse variance weighted	72.7733 215	82	0.75704798 5
Concentration of IDL particles	MR Egger	62.8979 1614	78	0.89307594 4
Concentration of IDL particles	Inverse variance weighted	62.9041 0012	79	0.90750226
Phospholipids in IDL	MR Egger	75.1652 37	81	0.66172911 9
Phospholipids in IDL	Inverse variance weighted	75.2274 6723	82	0.68853247 9
Total cholesterol levels in LDL	MR Egger	68.5209 8135	81	0.83713580 5
Total cholesterol levels in LDL	Inverse variance weighted	68.5935 2473	82	0.85479803 7
Phospholipids to total lipids ratio in large HDL	MR Egger	42.4790 8362	45	0.57933012 9
Phospholipids to total lipids ratio in large HDL	Inverse variance weighted	42.8027 7804	46	0.60695820 5
Total cholesterol in large LDL	MR Egger	74.3313 1529	81	0.68661416 7
Total cholesterol in large LDL	Inverse variance weighted	74.7020 6495	82	0.70375486 2
Total cholesterol to total lipids ratio in large LDL	MR Egger	81.8635 7647	67	0.10449134 2
Total cholesterol to total lipids ratio in large LDL	Inverse variance weighted	83.3151 9299	68	0.09990418
Cholesterol esters in large LDL	MR Egger	71.9952 0301	81	0.75258092 2
Cholesterol esters in large LDL	Inverse variance weighted	72.0737 0631	82	0.77522650 4
Cholesteryl esters to total lipids ratio in large LDL	MR Egger	53.5918 2159	61	0.73856315 8
Cholesteryl esters to total lipids ratio in large LDL	Inverse variance weighted	53.6367 2986	62	0.76642810 7
Free cholesterol in large LDL	MR Egger	82.6369 1431	80	0.39789013 2
Free cholesterol in large LDL	Inverse variance weighted	82.6824 0117	81	0.42716484 4

Total lipids in large LDL	MR Egger	77.41252552	83	0.652373288
Total lipids in large LDL	Inverse variance weighted	77.82765995	84	0.668803691
Concentration of large LDL particles	MR Egger	76.10737256	80	0.602539114
Concentration of large LDL particles	Inverse variance weighted	76.49961796	81	0.620843714
Phospholipids in large LDL	MR Egger	70.41351132	81	0.793329449
Phospholipids in large LDL	Inverse variance weighted	70.43833473	82	0.81497831
Phospholipids to total lipids ratio in large LDL	MR Egger	74.94924705	80	0.638707414
Phospholipids to total lipids ratio in large LDL	Inverse variance weighted	76.5147274	81	0.620374696
Total cholesterol in medium LDL	MR Egger	64.72922211	74	0.770652604
Total cholesterol in medium LDL	Inverse variance weighted	64.83151336	75	0.792734694
Total cholesterol to total lipids ratio in medium LDL	MR Egger	68.41769825	61	0.240111644
Total cholesterol to total lipids ratio in medium LDL	Inverse variance weighted	70.03773372	62	0.226002316
Cholesterol esters in medium LDL	MR Egger	61.20515404	73	0.83604234
Cholesterol esters in medium LDL	Inverse variance weighted	61.26060196	74	0.855078536
Cholesteryl esters to total lipids ratio in medium LDL	MR Egger	53.86249046	59	0.664778128
Cholesteryl esters to total lipids ratio in medium LDL	Inverse variance weighted	53.94003977	60	0.695523277
Free cholesterol in medium LDL	MR Egger	73.11797131	78	0.635197006
Free cholesterol in medium LDL	Inverse variance weighted	74.46113361	79	0.623589847
Total lipid levels in medium LDL	MR Egger	68.30196849	80	0.821413466
Total lipid levels in medium LDL	Inverse variance weighted	68.54633771	81	0.836586992
Concentration of medium LDL particles	MR Egger	66.31572603	79	0.844947472
Concentration of medium LDL particles	Inverse variance weighted	66.39319944	80	0.862154373
Phospholipids in medium LDL	MR Egger	64.34525189	76	0.827328391
Phospholipids in medium LDL	Inverse variance	64.7866	77	0.83821153

	weighted	4521		9
Remnant cholesterol (non-HDL, non-LDL -cholesterol)	MR Egger	86.4708 7818	78	0.23945688 4
Remnant cholesterol (non-HDL, non-LDL -cholesterol)	Inverse variance weighted	86.4832 3978	79	0.26428998 1
Serum total cholesterol levels	MR Egger	72.7776 5361	79	0.67552698 6
Serum total cholesterol levels	Inverse variance weighted	72.7811 9403	80	0.70391154 1
|| id:ebi-cfb233-GCST90302091	MR Egger	64.5406 1437	80	0.89571961 9
Total Cholesterol in small LDL	Inverse variance weighted	65.6364 2013	81	0.89248509 3
Total cholesterol to total lipids ratio in small LDL	MR Egger	72.5423 9956	66	0.27117963 3
Total cholesterol to total lipids ratio in small LDL	Inverse variance weighted	73.3462 0741	67	0.27792767 8
Cholesterol esters in small LDL	MR Egger	60.5344 1275	74	0.87001501 9
Cholesterol esters in small LDL	Inverse variance weighted	60.8073 343	75	0.88216035 5
Cholesteryl esters to total lipids ratio in small LDL	MR Egger	60.3672 265	65	0.63965231 7
Cholesteryl esters to total lipids ratio in small LDL	Inverse variance weighted	60.5604 7837	66	0.66590905 9
Free cholesterol in small LDL	MR Egger	75.0737 8374	76	0.50848519 6
Free cholesterol in small LDL	Inverse variance weighted	75.2417 2368	77	0.53542790 3
Free cholesterol to total lipids ratio in small LDL	MR Egger	69.5782 7875	75	0.65506092 1
Free cholesterol to total lipids ratio in small LDL	Inverse variance weighted	70.7844 0022	76	0.64754557 4
Total lipids in small LDL	MR Egger	69.6536 7027	80	0.78895767 4
Total lipids in small LDL	Inverse variance weighted	69.9395 0919	81	0.80483030 7
Concentration of small LDL particles	MR Egger	70.8929 4693	81	0.78135377 5
Concentration of small LDL particles	Inverse variance weighted	70.8938 7906	82	0.80430894 5
Phospholipids in small LDL	MR Egger	69.7592 6326	79	0.76187400 4
Phospholipids in small LDL	Inverse variance weighted	70.0390 3376	80	0.77919123 7
Phospholipids to total lipids ratio in small LDL	MR Egger	58.1918 2376	73	0.89682039 6

Phospholipids to total lipids ratio in small LDL	Inverse variance weighted	58.95881144	74	0.899007594
Cholesterol esters in small VLDL	MR Egger	88.71091594	73	0.10178395
Cholesterol esters in small VLDL	Inverse variance weighted	88.91745014	74	0.113852655
Total cholesterol in very small VLDL	MR Egger	68.36587262	70	0.5329576
Total cholesterol in very small VLDL	Inverse variance weighted	68.40874656	71	0.565135199
Cholesterol esters in very small VLDL	MR Egger	65.63553453	65	0.454608866
Cholesterol esters in very small VLDL	Inverse variance weighted	65.63652264	66	0.489469433
Total lipids in very small VLDL	MR Egger	89.93215258	79	0.188068081
Total lipids in very small VLDL	Inverse variance weighted	90.01783484	80	0.208008198
Phospholipids in very small VLDL	MR Egger	70.17441897	85	0.876751947
Phospholipids in very small VLDL	Inverse variance weighted	70.56332268	86	0.88575073

Table SII The pleiotropy of causal association between all metabolites and Gastric cancer (GC). The p-values for the MR-Egger intercept were above 0.05, suggesting that no significant pleiotropy effects were found.

exposure	egger_intercept	se	pval
Cholesteryl esters to total lipids ratio in large HDL	-0.012524063	0.018189705	0.494736844
Free cholesterol to total lipids ratio in medium LDL	0.004594276	0.013987168	0.743488785
Phospholipids to total lipids ratio in medium LDL	0.012192473	0.013031079	0.352583258
Total cholesterol levels in small HDL	0.006224478	0.020286655	0.760846948
Cholesterol esters in small HDL	0.00782642	0.017342745	0.654166329
Apolipoprotein B levels	0.002081163	0.013172966	0.874850419
Esterified cholesterol levels	0.001434179	0.012766153	0.910826554
Total Cholesterol in IDL	0.003948071	0.012626068	0.755289641
Cholesterol esters in IDL	0.000438586	0.012857728	0.972871796
Free cholesterol in IDL	0.001377397	0.012217752	0.910489889
Total lipids in IDL	-0.001628814	0.012431057	0.89607823
Concentration of IDL particles	0.00101797	0.012944967	0.937521747
Phospholipids in IDL	-0.003082423	0.012356389	0.803636599
Total cholesterol levels in LDL	-0.003268732	0.012136137	0.78835391
Phospholipids to total lipids ratio in large HDL	-0.009738335	0.017116584	0.572224701
Total cholesterol in large LDL	-0.007507384	0.012329579	0.544299865
Total cholesterol to total lipids ratio in large LDL	0.015922169	0.01460778	0.279627268
Cholesterol esters in large LDL	0.003448235	0.012307018	0.78005035
Cholesteryl esters to total lipids ratio in large LDL	-0.003049406	0.014389713	0.832879275

Free cholesterol in large LDL	-0.00259587	0.012370352	0.834321276
Total lipids in large LDL	-0.007853429	0.012188913	0.521151574
Concentration of large LDL particles	-0.007743603	0.012364146	0.53290447
Phospholipids in large LDL	0.001944683	0.012342922	0.875199964
Phospholipids to total lipids ratio in large LDL	0.016150842	0.012908369	0.214511174
Total cholesterol in medium LDL	-0.004101862	0.012825129	0.749998418
Total cholesterol to total lipids ratio in medium LDL	0.01742318	0.014497211	0.234074598
Cholesterol esters in medium LDL	-0.003045577	0.012933826	0.814500335
Cholesteryl esters to total lipids ratio in medium LDL	0.003998034	0.014356796	0.781620085
Free cholesterol in medium LDL	-0.01445959	0.01247647	0.250012887
Total lipid levels in medium LDL	-0.006232562	0.012607917	0.622422826
Concentration of medium LDL particles	-0.003503637	0.012587596	0.78147826
Phospholipids in medium LDL	0.008746417	0.013164892	0.508461496
Remnant cholesterol (non-HDL, non-LDL - cholesterol)	0.001600828	0.015159852	0.916173554
Serum total cholesterol levels	0.000781469	0.013133613	0.952702976
Total Cholesterol in small LDL	-0.013036399	0.012453483	0.298340917
Total cholesterol to total lipids ratio in small LDL	0.011675254	0.013652564	0.395551186
Cholesterol esters in small LDL	-0.006669143	0.012765891	0.602939185
Cholesteryl esters to total lipids ratio in small LDL	-0.005994685	0.013636549	0.661681929
Free cholesterol in small LDL	-0.005339637	0.013029709	0.683102008
Free cholesterol to total lipids ratio in small LDL	0.014480837	0.013185547	0.275614853
Total lipids in small LDL	-0.006876018	0.012861047	0.594382302
Concentration of small LDL particles	0.000380897	0.012475827	0.975718822
Phospholipids in small LDL	0.006897335	0.013040083	0.598334716
Phospholipids to total lipids ratio in small LDL	0.011362656	0.012974352	0.384023199
Cholesterol esters in small VLDL	0.006721372	0.016303808	0.681358624
Total cholesterol in very small VLDL	0.003063268	0.01479409	0.836563975
Cholesterol esters in very small VLDL	0.000480099	0.015347618	0.975140751
Total lipids in very small VLDL	-0.004000345	0.014581289	0.784533467
Phospholipids in very small VLDL	0.007821334	0.012541797	0.534546179

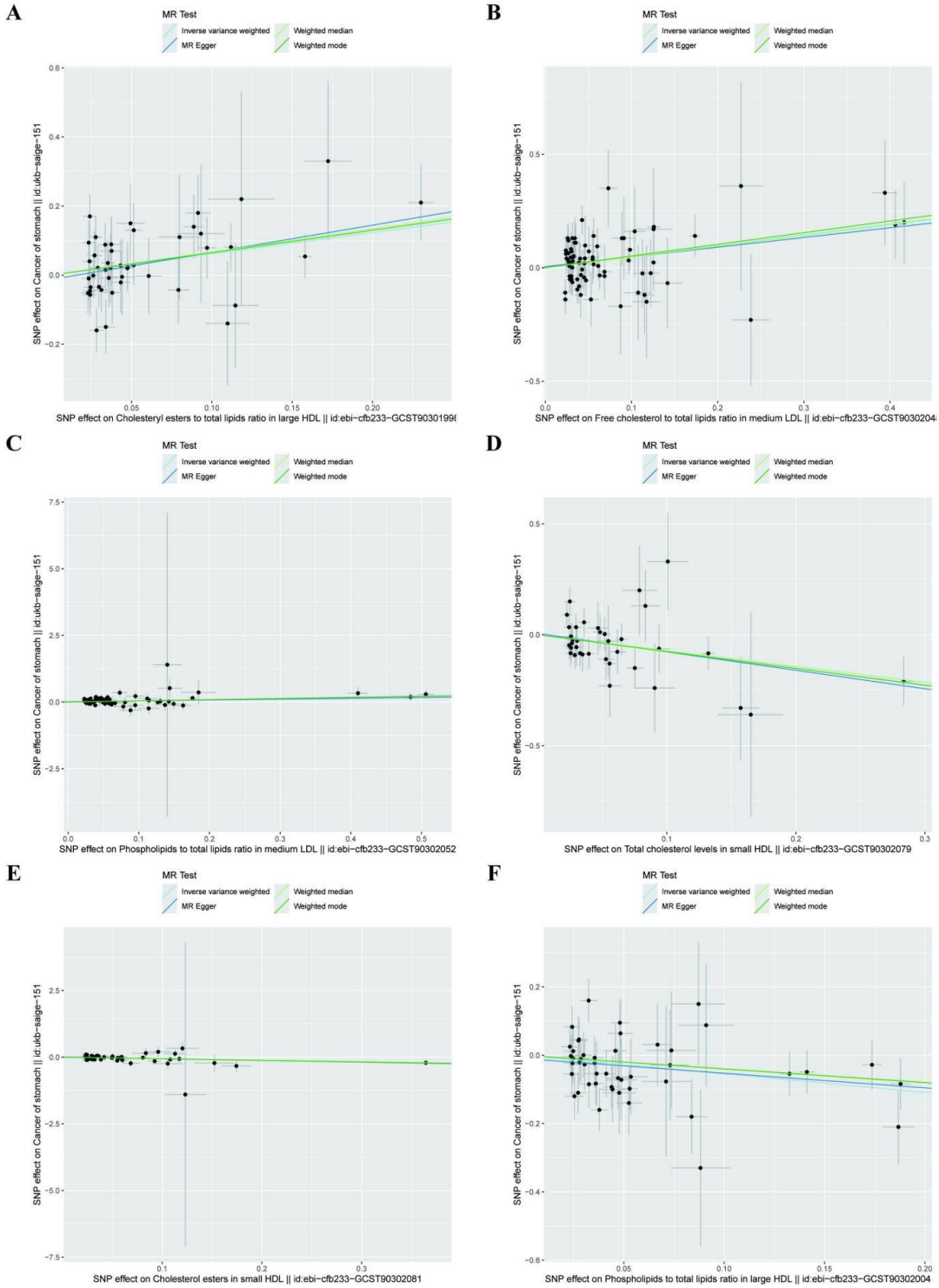

Figure 4. Scatter plot showing the relationship of six circulating metabolic biomarkers with the risk of Gastric cancer (GC). (A) Cholesteryl esters to total lipids ratio in large HDL in GC. (B) Free cholesterol to total lipids ratio in medium LDL in GC. (C) Phospholipids to total lipids ratio in medium LDL in GC. (D) Total cholesterol levels in small HDL in GC. (E) Cholesterol esters in small HDL in GC. (F) Phospholipids to total lipids ratio in large HDL in GC.

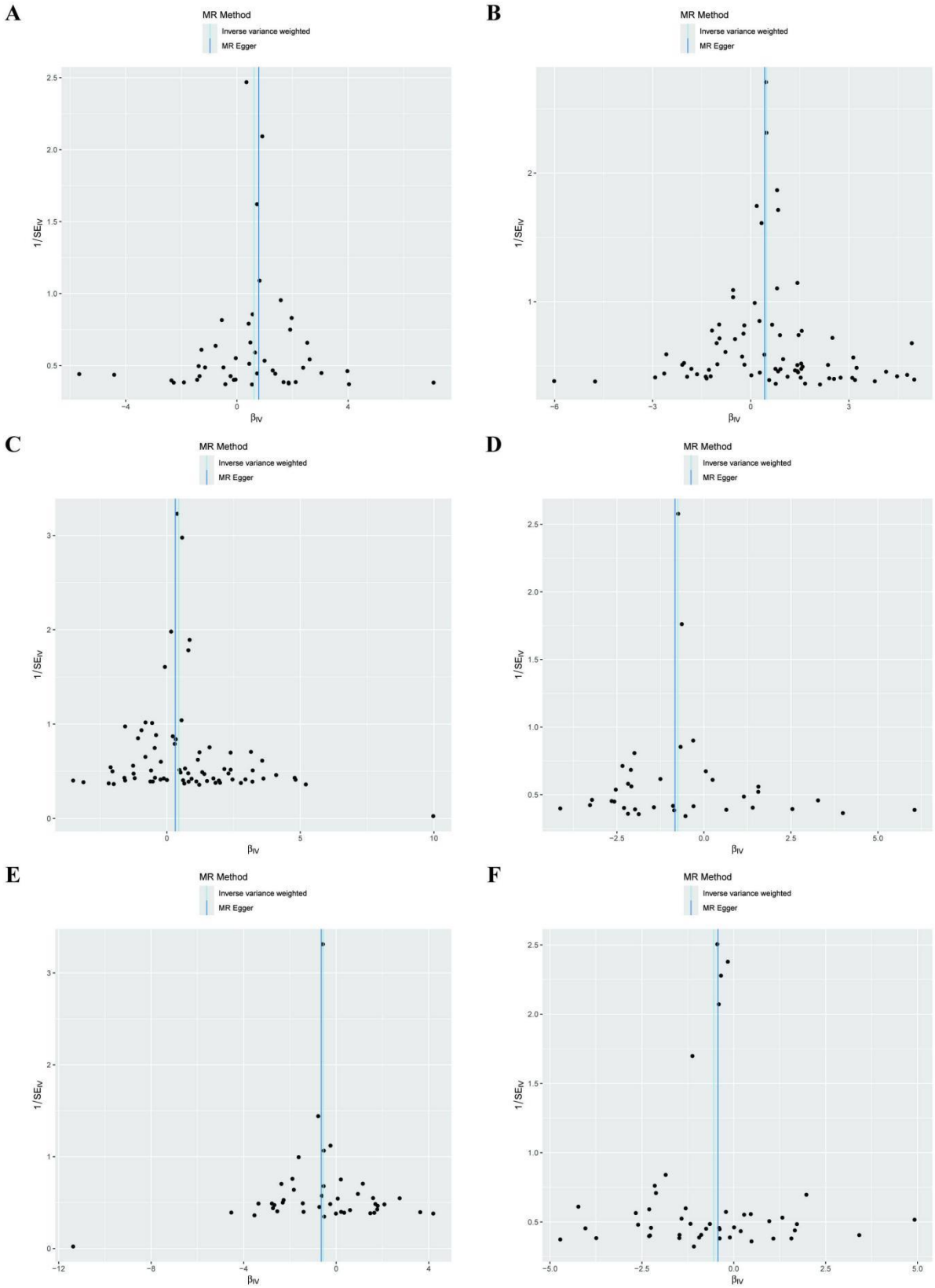

Figure 5. Funnel plot showing instrumental variables for each significant causal association between six circulating metabolic biomarkers and GC. ((A) Cholesteryl esters to total lipids ratio in large HDL in GC. (B) Free cholesterol to total lipids ratio in medium LDL in GC. (C) Phospholipids to total lipids ratio in medium LDL in GC. (D) Total cholesterol levels in small HDL in GC. (E) Cholesterol esters in small HDL in GC. (F) Phospholipids to total lipids ratio in large HDL in GC.

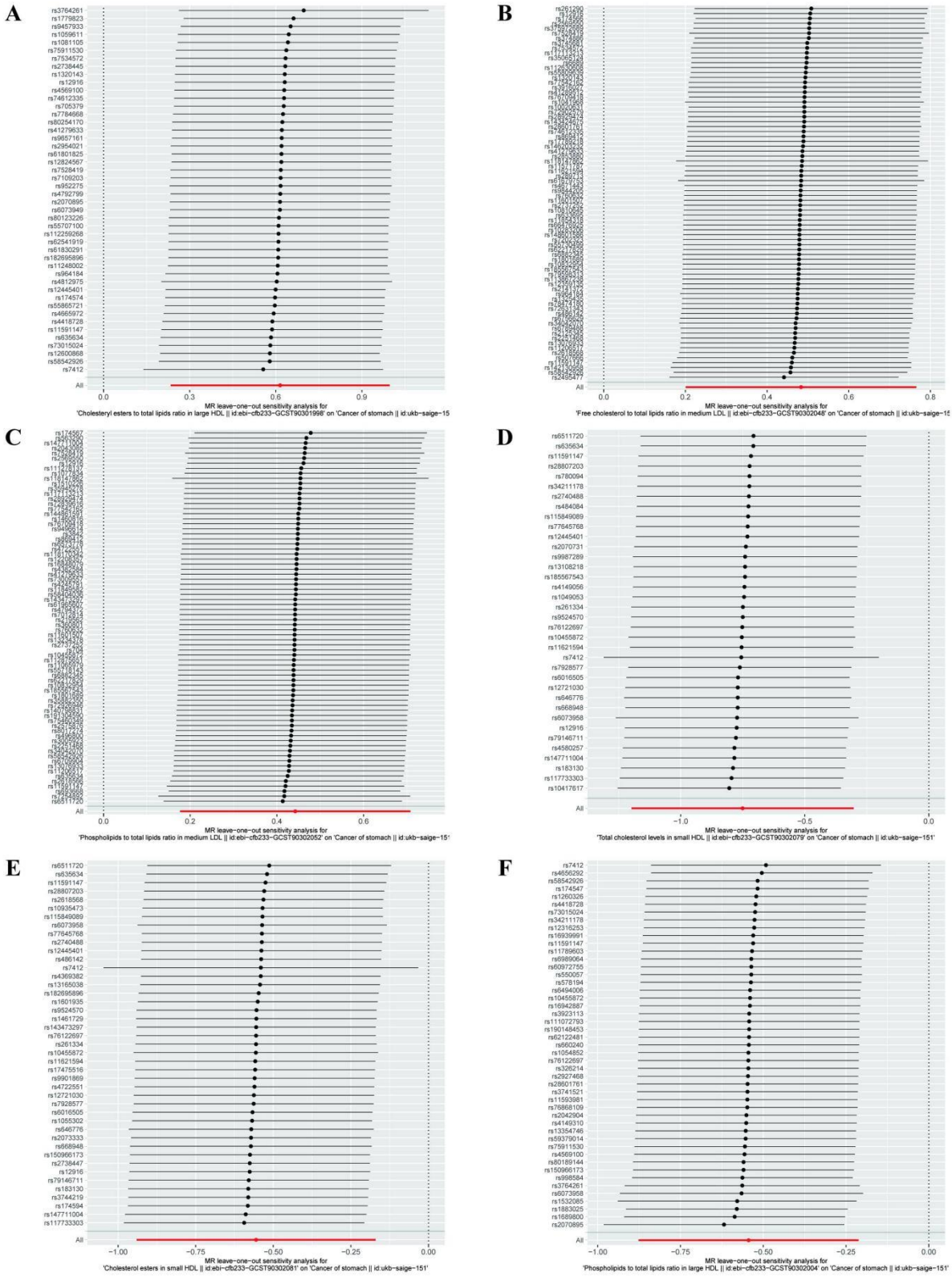

Figure 6. Leave-one-out plot showing the genetic associations of six circulating metabolic biomarkers with the risk of GC. (A) Cholesteryl esters to total lipids ratio in large HDL in GC. (B) Free cholesterol to total lipids ratio in medium LDL in GC. (C) Phospholipids to total lipids ratio in medium LDL in GC. (D) Total cholesterol levels in small HDL in GC. (E) Cholesterol esters in small HDL in GC. (F) Phospholipids to total lipids ratio in large HDL in GC.

Discussion

Current recommendations for the prevention and treatment of gastric cancer by intervening on risk factors still need to be refined. Meanwhile, the impact of available early biomarkers on gastric cancer treatment strategies is understudied. Therefore, matching modifiable risk factors with potential biomarkers and verifying the causal relationship between them and the disease are crucial for the prevention and treatment of gastric cancer. In this study, we conducted a comprehensive MR study to elucidate the causal relationship between 233 circulating metabolic biomarkers and gastric cancer. We found that Cholesteryl esters to total lipids ratio in large HDL, Free cholesterol to total lipids ratio in medium LDL, and Phospholipids to total lipids ratio in medium LDL were significantly associated with a higher risk of gastric cancer. While Total cholesterol levels in small HDL and Cholesterol esters in small HDL were associated with lower risk of gastric cancer. Gastric cancer (GC), a primary epithelial malignant tumour originating from the stomach, is a complex and heterogeneous disease with multiple risk factors. Risk factors associated with gastric carcinogenesis include Helicobacter pylori infection, obesity, unhealthy dietary habits and lifestyle, smoking and alcohol consumption, and chemical, radiation, or viral exposure [18]. Poor dietary habits such as processed foods, processed meats, red meat, alcohol, foods high in dietary fat and dietary cholesterol grow the risk of gastric cancer [19]. In obese patients, peritoneal-derived adipocytes induce robust lipid droplet (LD) accumulation and fatty acid oxidation in GC cells by up-regulating diacylglycerol acyltransferase 2 (DGAT2) in a C/EBPα-dependent manner, and, importantly, overexpression of DGAT2 has been identified as an independent predictor of low survival, which promotes lung and peritoneal metastasis of GC and correlates with poor prognosis of gastric cancer [20]. It is evident that the correlation between obese patients and gastric cancer is of significant clinical value.

High-density lipoprotein (HDL) particles are heterogeneous plasma lipoproteins, varying in size and composition, that mediate the reverse cholesterol transport (ReCT) from peripheral cells to the liver [21]. In cancer, HDL promotes cholesterol clearance from cancer cells, thereby altering their homeostasis. HDL-associated apolipoproteins and enzymes also exert antioxidant, anti-inflammatory, anti-angiogenic, anti-apoptotic, and immunomodulatory activities, resulting in an overall anti-tumourigenic effect [22], which is negatively correlated with cancer risk. Low-density lipoprotein (LDL) is a lipoprotein primarily responsible for the distribution of cholesterol in extrahepatic tissues and body cells [23], and in breast cancer, LDL promotes tumourigenesis by a mechanism that may be attributed to the activation of HER2 by LDL, which grows oncogenic signalling pathways, Akt and extracellular signal-regulated kinase (ERK) [24], and activation of these pathways by LDL can mediate tumour cell proliferation, and LDL is also positively correlated with tumour size and lymph node metastasis. In colorectal cancer, elevated LDL levels are associated with increased risk of colorectal cancer development and poor prognosis, and can promote migration of colorectal cancer cells and upregulate the expression of tumour stem cells. In addition, LDL mediates increased p38 protein expression thereby promoting MAPK signalling pathway gene expression, and LDL also grows stemness genes such as Sox2, Oct4, Nanog and Bmi1 in CRC cells [25].

Several previous case-control studies have observed that increased intake of cholesterol increases the risk of gastric cancer, and that blood cholesterol levels are positively associated with the development of gastric cancer [26-28]. Our study observed that in large HDL, the proportion of cholesteryl esters grows to promote cancer progression, whereas in medium LDL the ratio of free cholesterol to phospholipids grows similarly positively associated with cancer risk. Our findings are similar to those of previous studies. Rapidly proliferating tumour cells usually require large amounts of cholesterol for the synthesis of membrane organelles and fatty acids, as fatty acid oxidation generates a large number of intermediates, including NADPH, for energy supply and ROS detoxification, which promotes cancer progression [20, 29]. It has also been reported that increased cholesterol is associated with elevated inflammatory activity, which may play a role in cancer development. Hypercholesterolaemia leads to cholesterol accumulation in macrophages and other immune

cells, which contributes to inflammatory responses, including enhanced Toll-like receptor (TLR) signalling, activation of inflammatory vesicles, and, at the cellular level, activation of TLR signalling, which leads to reduced cholesterol efflux, thus contributing to further cholesterol accumulation and amplification of inflammatory responses [30]. While Keisuke Oguma et al. demonstrated through mouse experiments that activated macrophages in H. pylori infected and inflamed gastric mucosa express TNF-α, which stimulates the surrounding epithelial cells to activate the Wnt signalling pathway, and the over-activated Wnt signalling pathway promotes the development of gastric cancer [31]. In addition to this, hypercholesterolaemia is a risk factor for the development of gastric dysplasia, which is considered to be the penultimate stage of gastric carcinogenesis [32]. It has also been reported that cholesterol metabolism may play an important role in the eradication of H. pylori, which may be related to the mechanism of cholesterol glucosylation in H. pylori, mediated by cholesterol-α-glucosyltransferase, encoded by the gene cgt. Cholesterol glucosylation has several functions, including promotion of immune evasion and enhancement of antibiotic resistance, which promotes H. pylori growth [33]. For cholesteryl esters, lecithin cholesterol acyltransferase (LCAT) located on the surface of HDL particles converts free cholesterol to cholesteryl esters, a conversion that allows for more cholesterol molecules to be stored in individual lipoproteins than in free cholesterol [23], and thus may lead to higher cholesterol levels in the body, which may be more tumour promoting. According to the findings we have described above, it is evident that the relationship between cholesteryl esters, free cholesterol and phospholipids as a percentage of total lipids in large HDL and medium LDL is the most important in relation to cancer.

Interestingly, our study observed a significant reduction in cancer risk with increasing total cholesterol levels and cholesteryl esters in small HDL. This suggests that in HDL of different sizes, elevated levels of cholesterol and cholesteryl esters and cancer risk may be inconsistent, and the exact mechanism is not clear. One study measured circulating HDL of six different sizes and found that the metabolic structure of apolipoprotein A4 (APOA4) on HDL of different sizes was different, with APOA4 appearing delayed on circulating large HDL (1-2 hours post-infusion), while APOA4 on small HDL appeared rapidly, and once in the circulation, APOA4 on small HDL appeared rapidly, and once in the circulation, APOA4 on small HDL appeared rapidly. The catabolic rate of APOA4 on small HDL is almost three times that of APOA4 on large HDL.These different metabolic structures of APOA4 on large and small HDL suggest that HDL particles of different sizes may have unique origins and functions [34]. APOA4 activates celiac lipolysis, cholesterol efflux [35], cholesterol esterification [36], cholesterol chemotaxis [36] , promote reverse cholesterol transport and protect LDL from oxidation [37].Because of its rapid appearance on small HDL, it can rapidly promote cholesterol efflux, promote reverse cholesterol transport and reduce cholesterol levels in the body, thus exerting an inhibitory effect on cancer, but the specific mechanism needs to be further confirmed.

In addition, our study also found that an increased ratio of phospholipids to total lipids in intermediate LDL was a risk factor for gastric cancer, and an increased ratio of phospholipids to total lipids in large HDL was a protective factor for gastric cancer. Phospholipids are key components of cell membranes. Phosphatidylcholine (PC) and phosphatidylethanolamine (PE) are two phospholipids that make up the majority of cell membranes, and are involved in cellular processes such as chemical energy storage, cellular signalling, and intercellular interactions in cell membranes and tissues, which are closely associated with cancer progression and metastasis. A growing body of research evidence suggests that phospholipids have the potential to be cancer biomarkers and anticancer targets [38, 39]. Long Zou et al. found that serum levels of phospholipids were higher in patients with early gastric cancer than in healthy controls as identified by mass spectrometry in serum from 199 subjects [40]. Significantly elevated phospholipid metabolism can also be observed in breast and colorectal cancers, which may be attributed to the increased phosphate metabolism of cancer cells due to the large amount of phospholipids needed to synthesise cell membranes in rapidly proliferating cancer cells

[39]. Whereas Kai-Bo Chen and his team found that gastric cancer tumour-derived exosomes may be involved in the pathological process of peritoneal dissemination by mediating crosstalk between cancer cells and mesothelial cells, which leads to the induction of enhanced tumour growth, migration, adhesion and invasive ability, whereas exosomes are macromolecular phospholipid bilayer vesicles, and the elevation of phospholipids in gastric cancer patients may contribute to the progression of tumours by increasing the level of exosomes in the blood [41]. In addition, remodelling of membrane phospholipids is another important mechanism for tumour progression and metastasis [42, 43]. In our study, similar results were obtained that an increase in the ratio of phospholipids to total lipids in medium LDL was increasing the risk of gastric carcinogenesis. However, in large HDL, an increase in the ratio of phospholipids to total lipids was associated with a decreased risk of gastric cancer, thus suggesting that the role of phospholipids may be different in different lipoproteins. Unfortunately, we have not found evidence that phospholipids can inhibit the growth of cancer cells, which may be related to the cancer inhibitory effect of HDL itself, which requires more studies to further explore the specific mechanisms involved.

In summary, the occurrence and development of gastric cancer are closely related to metabolites, especially blood metabolites associated with the above mechanisms. Therefore, it is of great significance to study the causal relationship between haematological metabolites and gastric cancer, and to clarify the specific effects of particular haematological metabolite species on the risk of gastric cancer for the clinical control and management of gastric cancer.

Strength and Limitations

Our two-sample MR analysis was designed to analyze the causality between metabolites and GC using large-sample GWAS and UK Biobank data. This design reduced the limitations of traditional observational studies by eliminating the influence of confounding factors and reverse causality. In addition, MR mitigated the representativeness and feasibility issues inherent to RCTs. However, this study is subject to several limitations. Firstly, non-fasting plasma samples were utilized for metabolomics profiling in this paper. Despite adjustments made for the time elapsed since the last meal or beverage, there might still exist unaccounted residual variability. Secondly, the study's focus was on gene-metabolite pairs deemed most likely based on current expression data and biological understanding, specifically those with effector genes. However, the potential relevance of other metabolites or ratios with high heritability to the disease under study can not be negated. Future research, enriched with additional expression data and metabolic insights, is required to identify effector genes for these other metabolites and ratios. Thirdly, the MR analyses in this study were constrained by the fact that most metabolites and metabolite ratios were associated with only a single IV. This limitation hindered the application of common MR sensitivity tests, like MR-Egger, which necessitate multiple IVs. Despite this, our approach mitigated the risk of horizontal pleiotropy by using IVs closely linked to effector genes that influenced metabolite levels. Additionally, we conducted manual assessments of metabolic pleiotropy, discarding IVs linked to multiple metabolites not involved in the same metabolic pathways. While these steps helped reduce potential biases, we acknowledged that bias might not be fully eliminated due to the limitations in metabolome profiling and gaps in metabolite-protein interaction databases. Further research with a more comprehensive assessment for the metabolome is essential for a more accurate understanding of the genetic influence on metabolites. Finally, this study primarily involved elderly individuals of European descent. Investigating the effects of the identified genetic variations on metabolites and their ratios in diverse demographic groups represents a promising direction for future research.

Conclusions

In summary, this Mendelian randomization study elucidates a significant causal relationship between circulating metabolic biomarkers and the risk of gastric cancer. Our findings indicate that specific metabolic alterations may contribute to the pathogenesis of gastric cancer, highlighting the importance of metabolic profiling in understanding cancer risk. These results underscore the potential for incorporating metabolic biomarkers into risk assessment frameworks, which could enhance early detection

and inform targeted prevention strategies. Future studies are essential to further elucidate the biological mechanisms underlying these associations and to validate the clinical applicability of these biomarkers in the context of gastric cancer management. Overall, our research contributes to the growing body of evidence linking metabolism and cancer, paving the way for innovative approaches to mitigate gastric cancer risk.

Author Contribution Pengkhun Nov acquisition of data, analyzing,

interpretation of data, Minghao Tan drafting the article; Minghao Tan, Duanyu Wang and Pengkhun Nov designing, revising, and guiding the study. The authors read and approved.

Data Availability All the data for this article can be found on GWAS and UK biobank database.

Declarations

Ethics approval Not applicable because this study extracted data from database.

Consent for publication All the authors of the article agreed to be published

in the journal.

Competing interests The authors declare no competing interests.

Funding: None (self-support for APC)

Reference

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A: **Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries**. *CA: a cancer journal for clinicians* 2024, **74**(3):229-263.
2. Huang S, Guo Y, Li Z, Zhang Y, Zhou T, You W, Pan K, Li W: **A systematic review of metabolomic profiling of gastric cancer and esophageal cancer**. *Cancer biology & medicine* 2020, **17**(1):181-198.
3. Nov P, Zheng C, Wang D, Sou S, Touch S, Kouy S, Ni P, Kou Q, Li Y, Prasai A *et al*: **Causal association between metabolites and upper gastrointestinal tumors: A Mendelian randomization study**. *Molecular medicine reports* 2024, **30**(6).
4. Nov P, Wang D, Zheng C, Sou S, Touch S, Kouy S, Vicheth V, Li L, Zhang Y, Liu X *et al*: **Phosphate-to-alanine ratio and bilirubin-to-androsterone glucuronide ratio are the hub metabolites in upper gastrointestinal cancers: a Mendelian randomisation (MR) study**. *Ecancermedicalscience* 2024, **18**:1731.
5. Davey Smith G, Hemani G: **Mendelian randomization: genetic anchors for causal inference in epidemiological studies**. *Human molecular genetics* 2014, **23**(R1):R89-98.
6. Karjalainen MK, Karthikeyan S, Oliver-Williams C, Sliz E, Allara E, Fung WT, Surendran P, Zhang W, Jousilahti P, Kristiansson K *et al*: **Genome-wide characterization of circulating metabolic biomarkers**. *Nature* 2024, **628**(8006):130-138.
7. Sidore C, Busonero F, Maschio A, Porcu E, Naitza S, Zoledziewska M, Mulas A, Pistis G, Steri M, Danjou F *et al*: **Genome sequencing elucidates Sardinian genetic architecture and augments association analyses for lipid and blood inflammatory markers**. *Nature genetics* 2015, **47**(11):1272-1281.
8. Sun Y, Zhou J, Ye K: **White Blood Cells and Severe COVID-19: A Mendelian Randomization Study**. *Journal of personalized medicine* 2021, **11**(3).
9. Davies NM, Holmes MV, Davey Smith G: **Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians**. *BMJ (Clinical research ed)* 2018, **362**:k601.
10. Hartwig FP, Davey Smith G, Bowden J: **Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption**. *International journal of epidemiology* 2017, **46**(6):1985-1998.
11. Bowden J, Davey Smith G, Haycock PC, Burgess S: **Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator**. *Genetic epidemiology* 2016, **40**(4):304-314.
12. Allen RJ, Porte J, Braybrooke R, Flores C, Fingerlin TE, Oldham JM, Guillen-Guio B, Ma SF, Okamoto T, John AE *et al*: **Genetic variants associated with susceptibility to idiopathic pulmonary fibrosis in people of European ancestry: a genome-wide association study**. *The Lancet Respiratory*

medicine 2017, **5**(11):869-880.
13. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG: **Sensitivity Analyses for Robust Causal Inference from Mendelian Randomization Analyses with Multiple Genetic Variants**. *Epidemiology (Cambridge, Mass)* 2017, **28**(1):30-42.
14. Verbanck M, Chen CY, Neale B, Do R: **Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases**. *Nature genetics* 2018, **50**(5):693-698.
15. Hemani G, Tilling K, Davey Smith G: **Orienting the causal relationship between imprecisely measured traits using GWAS summary data**. *PLoS genetics* 2017, **13** (1 1):e1007081.
16. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R *et al*: **The MR-Base platform supports systematic causal inference across the human phenome**. *eLife* 2018, **7**.
17. Yavorska OO, Burgess S: **MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data**. *Interna tional journal of epidemiology* 2017, **46**(6): 1734-1739.
18. Yang WJ, Zhao HP, Yu Y, Wang JH, Guo L, Liu JY, Pu J, Lv J: **Updates on global epidemiology, risk and prognostic factors of gastric cancer**. *World journal of gastroenterology* 2023, **29**(16):2452-2468.
19. Maddineni G, Xie JJ, Brahmbhatt B, Mutha P: **Diet and carcinogenesis of gastric cancer**. *Current opinion in gastroenterology* 2022, **38**(6):588-591.
20. Li S, Wu T, Lu YX, Wang JX, Yu FH, Yang MZ, Huang YJ, Li ZJ, Wang SL, Huang L *et al*: **Obesity promotes gastric cancer metastasis via diacylglycerol acyl transferase 2-dependent lipid droplets accumulation and redox homeostasis**. *Redox biology* 2020, **36**:101596.
21. Gomaraschi M: **Role of Lipoproteins in the Microenvironment of Hormone-Dependent Cancers**. *Trends in endocrinology and metabolism: TEM* 2020, **31**(3):256-268.
22. Ganjali S, Ricciuti B, Pirro M, Butler AE, Atkin SL, Banach M, Sahebkar A: **High-Density Lipoprotein Components and Functionality in Cancer: State-of-the-Art**. *Trends in endocrinology and metabolism: TEM* 2019, **30**(1):12-24.
23. Patel KK, Kashfi K: **Lipoproteins and cancer: The role of HDL-C, LDL-C, and cholesterol-lowering drugs**. *Biochemical pharmacology* 2022, **196**:114654.
24. dos Santos CR, Domingues G, Matias I, Matos J, Fonseca I, de Almeida JM, Dias S: **LDL-cholesterol signaling induces breast cancer proliferation and invasion**. *Lipids in health and disease* 2014, **13**:16.
25. Wang C, Li P, Xuan J, Zhu C, Liu J, Shan L, Du Q, Ren Y, Ye J: **Cholesterol Enhances Colorectal Cancer Progression via ROS Elevation and MAPK Signaling Pathway Activation**. *Cellular physiology and biochemistry : international journal of experimental cellular physiology, bioche mistry, and pharmacology* 2017,**42**(2):729-74 2.
26. Allehdan S, Bassil M, Alatrash RM, Al-Jaberi T, Hushki A, Rayyan Y, Dahoud M, Abu EK, Tayyem RF: **Macronutrients Intake and Risk of Stomach Cancer: Findings from Case-Control Study**. *Nutrients* 2022, **14**(12).
27. Hu J, La Vecchia C, Negri E, de Groh M, Morrison H, Mery L: **Macronutrient intake and stomach cancer**. *Cancer causes & control : CCC* 2015, **26**(6):839-847.
28. Zhu YH, Jeong S, Wu M, Jin ZY, Zhou JY, Han RQ, Yang J, Zhang XF, Wang XS, Liu AM *et al*: **Dietary Intake of Fatty Acids, Total Cholesterol, and Stomach Cancer in a Chinese Population**. *Nutrients* 2019, **11**(8).
29. Carracedo A, Cantley LC, Pandolfi PP: **Cancer metabolism: fatty acid oxidation in the limelight**. *Nature reviews Cancer* 2013, **13**(4):227-232.
30. Tall AR, Yvan-Charvet L: **Cholesterol, inflammation and innate immunity**. *Nature reviews Immunology* 2015, **15**(2):104-116.
31. Oguma K, Oshima H, Oshima M: **Inflammation, tumor necrosis factor and Wnt promotion in gastric cancer develop ment**. *Future oncology (London, England)* 2010, **6**(4):515-526.
32. Jung MK, Jeon SW, Cho CM, Tak WY, Kweon YO, Kim SK, Choi YH, Bae HI, Lee JY, Chung JM: **Hyperglycaemia, hyper cholesterolaemia and the risk for**

developing gastric dysplasia. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver* 2008, **40**(5):361-365.
33. Qaria MA, Qumar S, Sepe LP, Ahmed N: **Cholesterol glucosylation-based survival strategy in Helicobacter pylori**. *Helicobacter* 2021, **26**(2):e12777.
34. Andraski AB, Singh SA, Higashi H, Lee LH, Aikawa M, Sacks FM: **The distinct metabolism between large and small HDL indicates unique origins of human apolipoprotein A4**. *JCI insight* 2023, **8**(8).
35. Stein O, Stein Y, Lefevre M, Roheim PS: **The role of apolipoprotein A-IV in reverse cholesterol transport studied with cultured cells and liposomes derived from an ether analog of phosphatidylcholine**. *Biochimica et biophysica acta* 1986, **878**(1):7-13.
36. Emmanuel F, Steinmetz A, Rosseneu M, Brasseur R, Gosselet N, Attenot F, Cuiné S, Séguret S, Latta M, Fruchart JC *et al*: **Identification of specific amphipathic alpha-helical sequence of human apolipoprotein A-IV involved in lecithin: cholesterol acyltransferase activation**. *The Journal of biological chemistry* 1994, **269**(47): 29883-29890.
37. Qin X, Swertfeger DK, Zheng S, Hui DY, Tso P: **Apolipoprotein AIV: a potent endogenous inhibitor of lipid oxidation**. *The American journal of physiology* 1998, **274**(5):H1836-1840.
38. Bandu R, Mok HJ, Kim KP: **Phospholipids as cancer biomarkers: Mass spectrometry-based analysis**. *Mass spectrometry reviews* 20 18, **37**(2):107-138.
39. Stoica C, Ferreira AK, Hannan K, Bakovic M: **Bilayer Forming Phospholipids as Targets for Cancer Therapy**. *International journal of molecular sciences* 2022, **23**(9).
40. Zou L, Guo L, Zhu C, Lai Z, Li Z, Yang A: **Serum phospholipids are potential biomarkers for the early diagnosis of gastric cancer**. *Clinica chimica acta; international journal of clinical chemistry* 2021, **519**:276-284.
41. Chen KB, Chen J, Jin XL, Huang Y, Su QM, Chen L: **Exosome-mediated peritoneal dissemination in gastric cancer and its clinical applications**. *Biomedical reports* 20 18, **8**(6):503-509.
42. Li Z, Hu Y, Zheng H, Li M, Liu Y, Feng R, Li X, Zhang S, Tang M, Yang M *et al*: **LPCAT1-mediated membrane phospholipid remodelling promotes ferroptosis evasion and tumour growth**. *Nature cell biology* 20 24, **26**(5):811-824.
43. Qiu Y, Wang X, Sun Y, Jin T, Tang R, Zhou X, Xu M, Gan Y, Wang R, Luo H *et al*: **ACSL4-Mediated Membrane Phospholipid Remodeling Induces Integrin β1 Activation to Facilitate Triple-Negative Breast Cancer Metastasis**. *Cancer research* 2024, **84**(11):18 56-1871.