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Causal relationship between serum metabolites and Crohns disease: A bidirectional two-sample Mendelian randomization study

Shuanghu Zhang[1], Shengli Huang[1], Liu Ye[2], Guanghua Yang[1], Changyou Wang[1,*]

[1]Department of Gastrointestinal Oncology, Affiliated Hospital of North China University of Science and Technology, Tangshan, Hebei, 063000, China
[2]Breast Disease Treatment Center, Affiliated Hospital of North China University of Science and Technology, Tangshan, Hebei, 063000, China
**Corresponding author*

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Abstract: A two-way two-sample Mendelian randomization (MR) approach was used to explore the causal relationship between serum metabolites and Crohn's disease. The summary data from Genome-Wide Association Studies (GWAS) were analyzed using single nucleotide polymorphisms (SNPs) loci closely related to Crohns disease as instrumental variables (IVs). The causal relationship between serum metabolites and Crohns disease was comprehensively evaluated using methods such as Inverse-Variance Weighted (IVW), MR-Egger regression, Weighted Median Estimation (WME), Simple Mode (SM), and Weighted Mode (WM). The evaluation primarily focused on the P-value of IVW, odds ratio (OR), and 95% confidence intervals (CI). Respectively, the Cochran Q test for heterogeneity was performed using the IVW and MR-Egger methods, the pleiotropy test was conducted using the MR-Egger intercept method, and the MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) method was used to identify outliers. Leave-one-out sensitivity analysis was conducted. Additionally, the reverse causality between Crohns disease and serum metabolites was analyzed using these five methods. The IVW results show that four known metabolites and one unknown metabolite are closely related to Crohns disease. Among them, homocitrulline { OR (95% CI): 0. 845 (0. 761 to 0. 939), P = 0. 002}, X-17325 { OR (95% CI): 0. 825 (0. 733 to 0. 928), P = 0. 001}, 1-palmitoyl-2-arachidonoyl-gpc { OR (95% CI): 0. 842 (0. 783 to 0. 906), P < 0. 001} were protective factors for Crohns disease; plasma lactate { OR (95% CI): 1. 308 (1. 112 to 1. 537),P = 0. 001}, the ratio of Oleoyl-linoleoyl-glycerol /linoleoyl-arachidonoyl-glycerol { OR (95% CI): 1. 206 (1. 115 to 1. 304), P < 0. 001} were risk factors for Crohns disease. The results of the reverse MR analysis showed that there is no reverse causal relationship between Crohns disease and homocitrulline, X-17325, 1-palmitoyl-2-arachidonoyl-gpc, plasma lactate, and the ratio of Oleoyl-linoleoyl-glycerol/linoleoyl-arachidonoyl-glycerol(P > 0. 05). Five serum metabolites have been identified to have a causal association with the risk of Crohns disease, providing new theoretical basis and practical guidance for the design of treatment regimens for Crohns diseas.

1. Introduction

Crohns disease (CD) is an example of inflammatory bowel disease (inflammatory bowel disease, IBD), which can affect any part of the digestive tract and occur at the end of the ileum and cecum, with increasing incidence worldwide [1]. Typical clinical manifestations are abdominal pain, diarrhea, fever, weight loss, and parenteral manifestations include large arthritis, iris itis, uveitis, pleuritis, pyoderma, etc[2]. The etiology of Crohns disease is complex and unclear, and may be the result of the interaction between environmental factors, genetic factors, immune system dysfunction and other factors[3]. At present, CD cannot be cured, and the active and remission periods alternate repeatedly. Most patients need to take drugs for a long time, which is easy to produce serious adverse reactions[4], Early intervention of the disease plays an important role in promoting the recovery of the disease and relieving the pain of patients[5].

Serum metabolites are the general term for the intermediates or end-products of metabolic reactions, which are not only closely related to the occurrence and development of diseases, but also provide targets for intervention and treatment[6]. A growing number of studies have shown that CD may have complex links with metabolic disorders. For example, the concentrations of multiple amino acids and microbial metabolites in the serum of CD patients are significantly different from those of healthy people[7]. In addition, studies have demonstrated the imbalance of short-chain fatty acids and bile acid metabolites[8], Disdisorder of the intestinal flora[9]Is closely related to the occurrence and progression of CD. Therefore, it is crucial to further clarify the relationship between metabolites and CD, which is important guiding for the development of effective preventive and therapeutic measures.

Mendelian randomization (Mendelian randomization, MR) is a powerful tool for studying epidemiology, using genetic variants, with SNPs as instrumental variables (instrumental variables, IVs), to assess the causal relationships between exposure factors and disease[10], The advantage of MR is that it can avoid the interference of confounding factors, reverse causation and various deviations, enhancing the causal inference between the two[11]. There is no systematic study of the potential causal relationship between serum metabolites and CD, so this study, using 1400 serum metabolites and CD, selected metabolites associated with CD, which provides new ideas for the diagnosis, prevention and treatment strategies of CD.

2. Materials and Methods

2.1 Research design

This study used a two-sample MR approach to explore the causal relationship between 1,400 serum metabolites and CD. SNPs significantly associated with exposure factors were used as IVs to eliminate confounders, enhancing confidence in the results using heterogeneity tests, pleiotropy tests, and sensitivity analysis. MR analysis followed the following three basic assumptions: (1) a strong correlation between IVs and exposure factors; (2) IVs were not associated with any confounding factors; and (3) IVs affected the outcome only through exposure factors.

2.2 Data sources

The serum metabolite dataset was derived from pooled data from a Canadian aging longitudinal aging cohort GWAS study that included 8 299 participants, identifying a total of 1 091 metabolites and 309 metabolite ratios available for genetic analysis[6]. The CD dataset, from the GWAS statistics of the Liu JZ team, including 20 833 samples of 5 956 patients and 14 927 healthy controls, involving a total of 12 276 506 SNPs[12]. The study populations for serum metabolites and CD were all derived from European populations, including men and women, to avoid bias caused by race-related

confounding factors.

2.3 Filter of the tool variables

To select SNPs strongly associated with and highly significant for the exposure factors, the following criteria were strictly applied:

(1) At P <110-5 selected SNPs strongly associated with exposure factors for the criteria; (2) with linkage disequilibrium region width Kb=10000, threshold r2=0.001 is the standard, keeping the SNPs with the highest significance; (3) with the F test value> 10 is the standard, remove weak tool variables. Finally, SNPs strongly associated and relatively independent with exposure factors were obtained as IVs.

2.4 MR analyse

This study used MR analysis using "TwoSampleMR" package in R 4.3.2, using inverse variance weighted method (inverse-variance weighted, IVW), MR-Egger regression method, weighted median method (Weighted median, WME), simple model method (Simple mode, SM) and weighted model method (Weighted mode, WM). Among them, IVW method is the main analysis method of the study, which is widely used in MR analysis by infer the causal association between exposure factors and outcome factors by combining the Word ratio of all SNPs[13]. The remaining four methods were used as supplements to the IVW method, and indicated when the β values of these four methods were consistent with the β values of IVW[14]. In MR analysis results, β value> 0 indicates risk factor and β value <0 indicates exposure factor as protective factor; OR value> 1 indicates risk factor and OR value <1 indicates protective factor. The heterogeneity was assessed by Cochran Q test when P <0.05; pleiotropy was assessed by MR-Egger intercept for pleiotropy, P <0.05 for IVs. 05; MR (MR pleiotropy RESidual sum and outlier, MR-PRESSO) to identify outliers of SNPs, and MR analysis was performed after removing the outlier. The effect of individual SNPs on the results of MR analysis was examined using leave-one-out sensitivity analysis[15].

3. Results

3.1 Tool variable screening

IVs of 1 400 serum metabolites (including 12 276 506 SNPs) followed the screening criteria used in this study and resulted in 34 843 SNPs strongly associated with high significance with serum metabolites. Among them, the F test value corresponding to a single SNPs in this study is> 10, indicating that there is no weak instrumental variable offset, and the results are relatively reliable.

3.2 Causal effect of serum metabolites associated with Crohns disease

Using the results of the IVW method as the main judgment condition to evaluate the causal effect between serum metabolites and CD, four known metabolites and one unknown metabolite had a significant causal association with CD. IVW results show: high citrulline {OR (95% CI): 0.845 (0.761~0.939), P=0.002}, X-17325{OR(95% CI): 0.825(0.733~0.928), P=0.001}, 1-palmitoyl-2-arachidoyl-glycerol phosphatidylcholine {OR (95% CI): 0.842 (0.783~0.906), P<0.001}, The increase of these three metabolites can reduce the risk of CD; Plasma lactate {OR (95% CI): 1.308 (1.112~ 1.537), P=0.001}, Ratio of oleacyl linoacylglycerol / arachidacylglycerol {OR (95% CI): 1.206 (1.115 to 1.304), P<0.001}, Elevation of these 2 metabolites could increase the risk of developing CD. In addition, the results of MR-Egger regression, WME, WM, WM and IVW method

were consistent (see Table 1, Figure 1). The effect of SNPs related to the exposure factors on CD was assessed by drawing a forest map, and the results suggested that the direction of the integrated effect values of SNPs was consistent (see Figure 2). Cochran Q Test results showed no heterogeneity among SNPs highly associated with the five serum metabolites (P> 0.05); MR-Egger intercept showed no pleiotropy among SNPs highly correlated with the five serum metabolites (P> 0.05); MR-PRESSOThe results showed that there was no outlier (P> 0.05) among the SNPs highly correlated with the five serum metabolites (see Table 2). Moreover, by mapping the robustness of the results, the funnel plots indicate that the included SNPs are basically symmetrically distributed, suggesting that there is no potential shift in the causal effect (see Figure 3). The results of the leave-one-out sensitivity analysis showed that removal of single SNPs had no impact on the MR analysis, further demonstrating the stability and reliability of the results (see Figure 4)

Table 1. MR analysis of causality between five serum metabolites and CD

Exposure factors	The outcome factor	method	SNPs quantity	*β*	*OR*	95% CI	*P price*
		MR-Egger regression	28	-0.067	0.935	0.761~1.149	0.529
		WME	28	-0.167	0.846	0.722~0.991	0.039
Homocitrulline	Crohns disease	IVW	28	-0.168	0.845	0.761~0.939	0.002
		SM	28	-0.091	0.913	0.684~1.219	0.544
		WM	28	-0.154	0.857	0.731~1.005	0.069
		MR-Egger regression	25	-0.288	0.750	0.574~0.979	0.046
		WME	25	-0.227	0.797	0.663~0.959	0.016
X-17325	Crohns disease	IVW	25	-0.192	0.825	0.733~0.928	0.001
		SM	25	-0.364	0.695	0.501~0.964	0.039
		WM	25	-0.275	0.759	0.601~0.960	0.030
		MR-Egger regression	31	-0.147	0.863	0.778~0.958	0.010
1-palmitoyl-2-peanut		WME	31	-0.185	0.831	0.772~0.895	<0.001
Tetrenenoyl-glycerophospholipids	Crohns disease	IVW	31	-0.172	0.842	0.783~0.906	<0.001
Acylcholine		SM	31	-0.054	0.947	0.729~1.232	0.690
		WM	31	-0.181	0.835	0.771~0.903	<0.001
		MR-Egger regression	18	0.294	1.342	0.948~1.901	0.118
		WME	18	0.234	1.264	1.007~1.586	0.043
Plasma lactate	Crohns disease	IVW	18	0.268	1.308	1.112~1.537	0.001
		SM	18	0.219	1.245	0.868~1.786	0.251
		WM	18	0.228	1.256	0.907~1.739	0.188
		MR-Egger regression	26	0.223	1.249	1.102~1.416	0.002
Linoyl-Linoylglycerol /		WME	26	0.246	1.280	1.159~1.412	<0.001
Linoacyl arachidene	Crohns disease	IVW	26	0.187	1.206	1.115~1.304	<0.001
Acyl glycerol		SM	26	0.122	1.130	0.858~1.488	0.393
		WM	26	0.244	1.277	1.147~1.422	<0.001

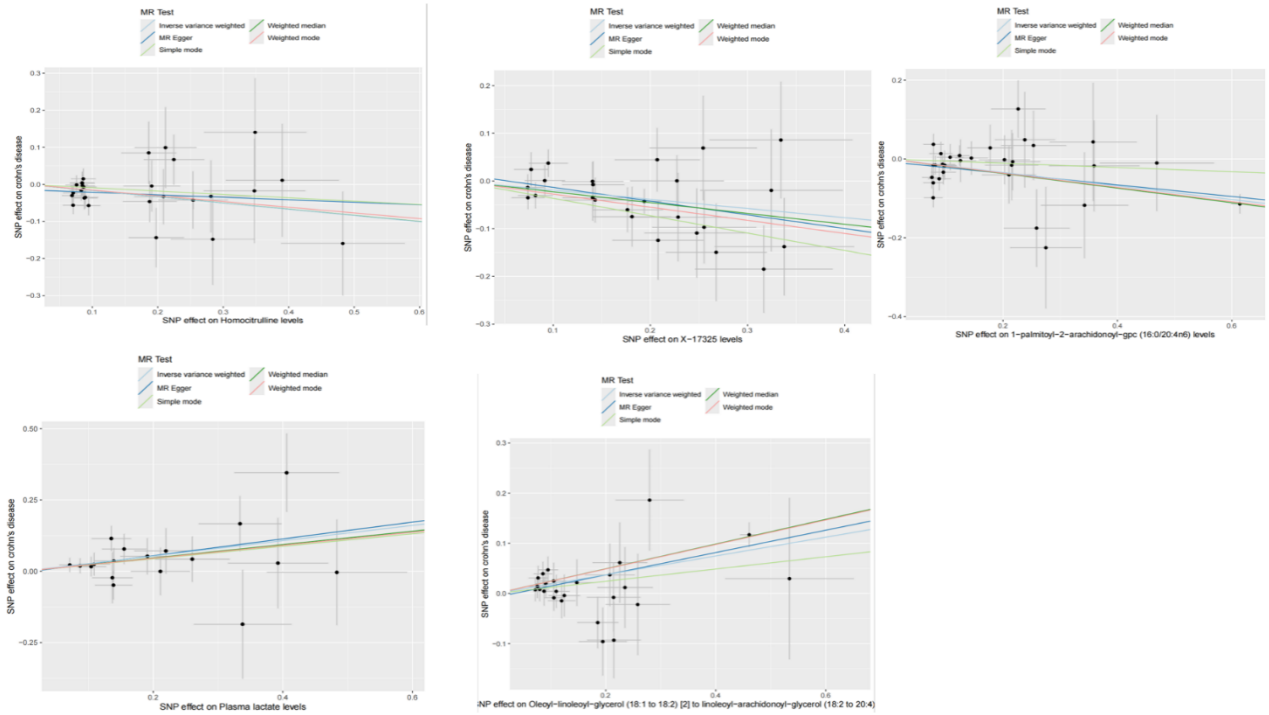

Figure 1 5 MR scatter plots of serum metabolites associated with the risk of Crohns disease

A: high citrulline; B: X-17325; C: 1-palmitoyl-2-arachidoyl-glycerol phosphatidylcholine; D: plasma lactic acid; E: ratio of linacylglycerol / linacacylarachidacylglycerol

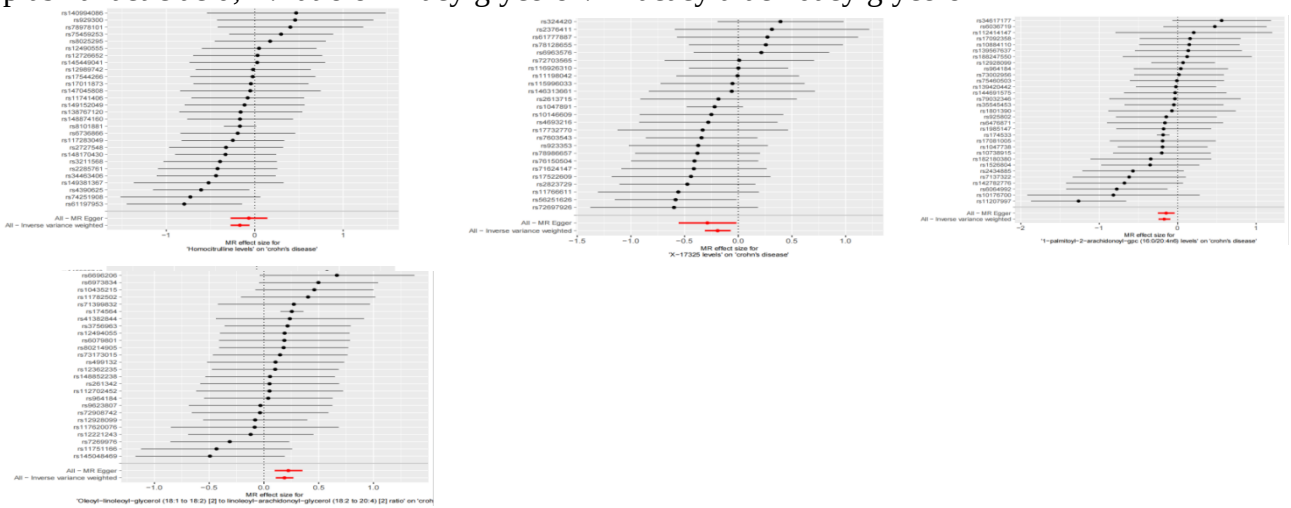

Figure 2 5 Forest plot of SNPs related to CD causal effects

A: high citrulline; B: X-17325; C: 1-palmitoyl-2-arachidoyl-glycerol phosphatidylcholine; D: plasma lactic acid; E: ratio of linacylglycerol / linacacylarachidacylglycerol

Table 2.Results of heterogeneity, pleiotropic, comprehensive outlier test of five SNPs with highly correlated serum metabolites

Exposure factors	Cochran Q Heterogeneity test				Multipleiotropy test		Comprehensive outliers	
	IVW		MR-Egger regression		MR-Egger regression		MR-PRESSO	
	Q price	*P price*	*Q price*	*P price*	nodal increment	*P price*	RSSobs	*P price*
Homocitrulline	21.569	0.759	20.323	0.776	-0.015	0.276	23.649	0.790
X-17325	18.275	0.709	17.665	0.775	0.015	0.443	19.625	0.822
1-palmitoyl-2-arachididy l-glycerophosphatidylcho line	30.895	0.129	30.336	0.115	-0.007	0.520	41.122	0.225
Plasma lactate	14.421	0.637	14.394	0.569	-0.004	0.072	16.079	0.675
Linoacylglycerol / linoacyl arachidacylglycerol	21.203	0.681	20.696	0.657	-0.007	0.483	29.531	0.521

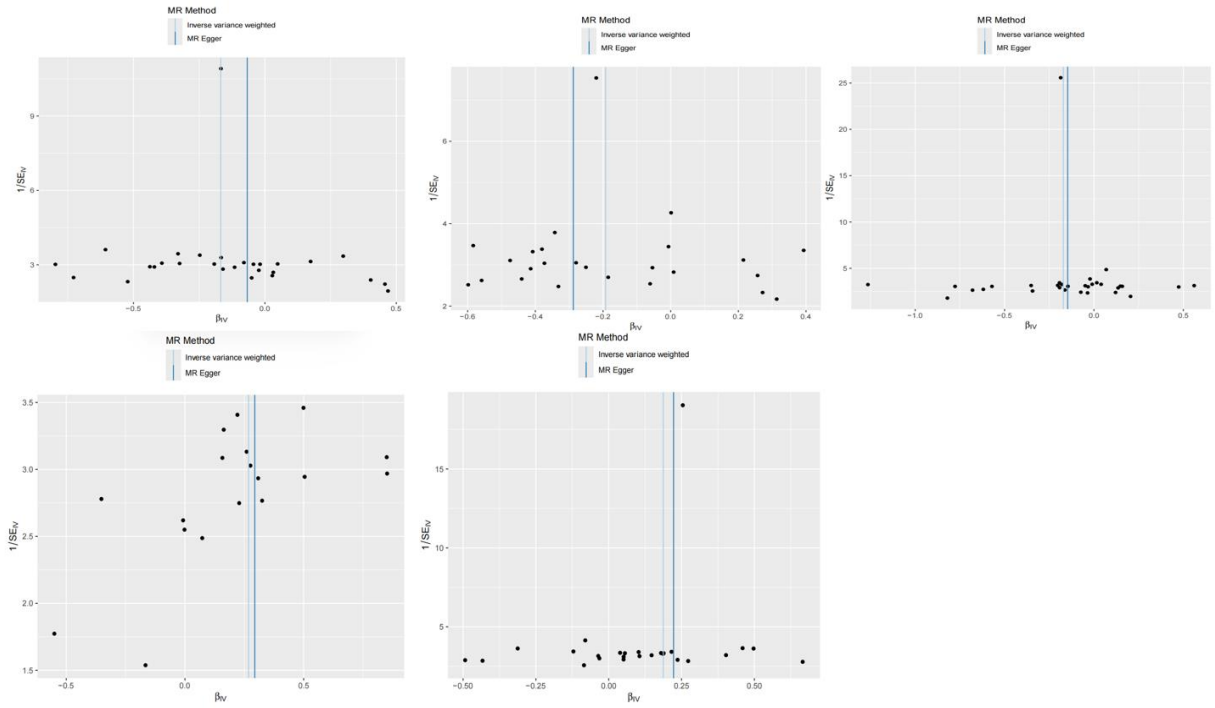

Figure 3 A funnel plot of the Mendelian randomization results

A: high citrulline; B: X-17325; C: 1-palmitoyl-2-arachidoyl-glycerol phosphatidylcholine; D: plasma lactic acid; E: ratio of linacylglycerol / linacacylarachidacylglycerol

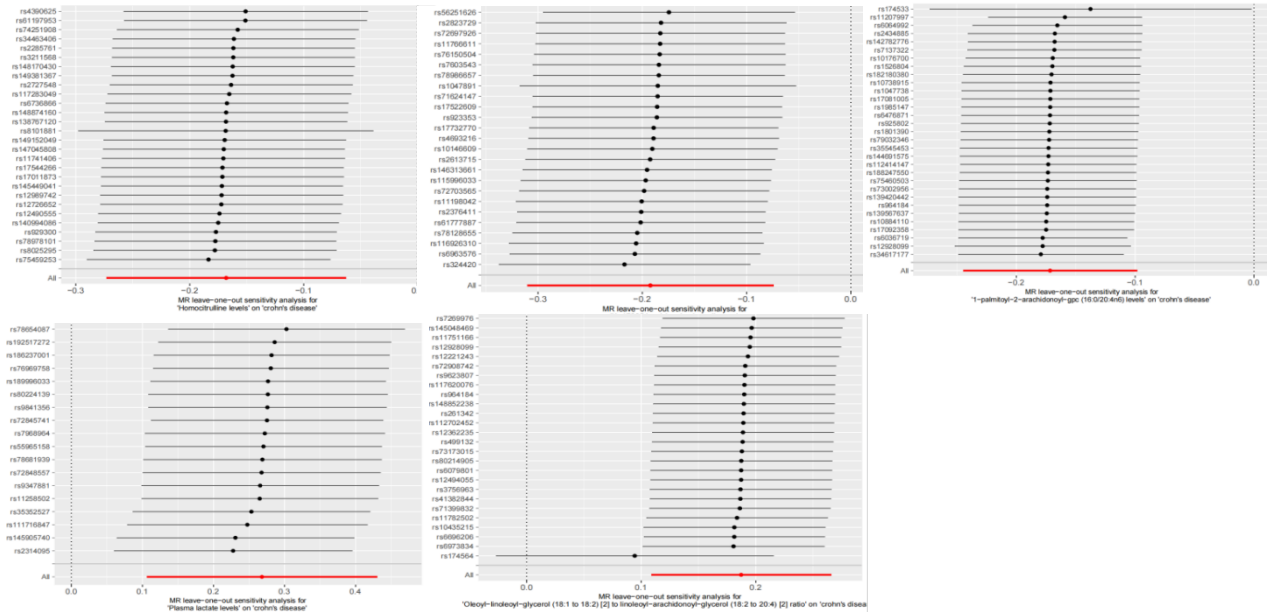

Figure 4 5 Results of sensitivity analysis of serum metabolites and CD

A: high citrulline; B: X-17325; C: 1-palmitoyl-2-arachidoyl-glycerol phosphatidylcholine; D: plasma lactic acid; E: ratio of linacylglycerol / linacacylarachidacylglycerol

3.3 Reverse MR analysis results

Negative MR analysis by setting Crohns disease as an exposure factor and serum metabolites as outcome factors showed no obvious causal relationship between CD and the ratio of hypercitrulline, X-17325, 1-palmitoyl-21-phosphoridacylglyceroline, MAL (P> 0.05) (see Table 3).

Table 3 MR analysis results of causality between CD and 5 serum metabolites

Exposure factors	The outcome factor	method	SNPs quantity	β	OR	95% CI	P price
Crohns disease	Homocitrulline	MR-Egger regression	50	−0.0 15	0.9 85	0. 935~ 1. 038	0. 573
		WME	50	0. 011	1.011	0. 976~ 1.047	0. 549
		IVW	50	−0. 009	0. 991	0. 960~ 1.014	0. 432
		SM	50	0.0 23	1.023	0. 963~ 1. 097	0.5 31
		WM	50	0.010	1.010	0. 970~ 1.0 60	0. 470
Crohns disease	X-17325	MR-Egger regression	50	0.040	1.041	0. 984~ 1.100	0. 166
		WME	50	0.022	1.022	0. 986~ 1.059	0 .227
		IVW	50	0.003	1.002	0. 979~ 1.026	0. 841
		SM	50	0.029	1.029	0. 951~ 1.113	0. 477
		WM	50	0.031	1.032	0. 985~ 1.081	0. 194
Crohns disease	1-palmitoyl-2-arachidoyl-glycerophosphatidylcholine	MR-Egger regression	50	− 0.003	0. 997	0. 946~ 1.052	0. 918
		WME	50	0. 001	1.001	0. 966~ 1.038	0 .942
		IVW	50	−0. 006	0. 994	0. 970~ 1.017	0 .597
		SM	50	0.0 03	1.003	0. 941~ 1. 070	0. 920
		WM	50	0. 003	1.003	0. 962~ 1047	0 .879
Crohns disease	Plasma lactate	MR-Egger regression	50	0. 016	1.016	0.9 64~ 1.071	0. 552
		WME	50	−0.009	0.991	0.956~ 1. 026	0. 597
		IVW	50	−0.018	0.983	0.960~ 1. 006	0. 143
		SM	50	−0.047	0.954	0.8 86~ 1.028	0.2 26
		WM	50	−0.001	0.999	0.9 55~ 1. 044	0. 948
Crohns disease	Linoacyl linacylglycerol / linoacyl arachidacylglycerol	MR-Egger regression	50	<0 .001	1. 000	0.942~ 1. 061	0. 999
		WME	50	0. 011	1. 011	0.972~ 1. 052	0 .596
		IVW	50	0. 014	1. 014	0.988~ 1. 041	0 .302
		SM	50	− 0. 010	0.982	0. 916~ 1. 053	0. 616
		WM	50	0. 001	1. 001	0.957~ 1. 047	0.970

4. Discussion

To explore the potential effects of serum metabolites on CD development, this study systematically evaluated 1400 serum metabolites and CD using a genome-wide association dataset, identifying a total of 5 metabolites with causal association with CD. These findings have important implications for the diagnosis, prevention, and treatment of CD.

Among the metabolites that lead to a reduced risk of CD development, hypercitrulline is a compound formed by carbamylation of the lysine amino group[16].It has been shown that high expression levels of high citrulline are closely related with aging and seborrheic keratosis in the skin and may be its potential biomarker[17]. Furthermore, the presence of abnormal expression of hypercitrulline in patients with RA may be associated with the activity and severity of the disease and has important implications for the diagnosis of RA[18]. Previous studies have found that hypercitrulline also plays an important role in the pathogenesis of chronic diseases such as chronic kidney disease and non-alcoholic fatty liver disease[19,20]. 1-palmitoyl-2-arachidyl-glycerol phosphatidylcholine is a specialized phospholipid involved in the composition of cell membranes associated with biological processes such as oxidative stress response and endothelial cell activation[21], And it has been reported to have a protective effect on CD risk[22], Is more consistent with our study. Moreover, this study identified 1 unknown serum metabolite X-17325 with causal association with CD, which requires further investigation to reveal the biological function of this metabolite.

Among the metabolites that lead to an increased risk of CD, plasma lactate, which is a product of glucose anaerobic metabolism and can be used as an indicator of organ hypoperfusion and tissue hypoxia[23]. With the deepening of research, more effects of lactic acid have also been found, which can acidify the tumor microenvironment, inhibit the immune system, and regulate the proliferation of tumor cells, which is of great significance for the occurrence and development of tumors[24]. Moreover, lactate can also serve as a substrate for histone lactfication modification to regulate expression of macrophage genes[25].An increase in intracellular lactate levels in macrophages can be found in diseases such as pulmonary fibrosis and ulcerative colitis[26,27]. The level of lactate after cardiac surgery can be used as a valid indicator for the assessment of disease severity and prognosis, and is an independent predictor of in-hospital mortality[28]. In addition, obese diabetic patients had higher fasting lactate levels than obese non-diabetic patients[29]. Linoleacylglycerol belongs to one of triglycerides and has a significant correlation with the GCKR gene that maintains blood glucose homeostasis[30].And the increased ratio of vitamin A to oleacylglycerol can reduce the risk of aplastic anemia[31]. Some studies have shown that linoyl arachididyl glycerol has a strong correlation with vitamin E concentration in serum[32], And were associated with lower levels of coronary artery calcification in European Americans[33].

In conclusion, the results of this study are partially consistent with previous studies, which provides a new theoretical basis for the treatment of CD in clinical practice. However, this study has some limitations: (1) the genome-wide association analysis data of the included studies are all derived from European populations, Lack of applicability, More comprehensive studies between samples from different regions are needed; (2) GAWS summary data lack data from different groups by sex and age, Unable not compare the causal effect between different groups and CD; (3) the presence of unknown metabolites in the metabolites with a causal effect with CD, Currently, the structure and function of these metabolites are unknown, Further analysis and research cannot be conducted; (4) Studies have initially revealed a causal association between serum metabolites and CD, But the exact mechanism is still unclear, This needs to be confirmed by further studies.

In conclusion, this paper uses a two-sample MR method to find five serum metabolites with CD risk, which may be biomarkers to predict the occurrence and progression of CD, providing new ideas

for early prevention and treatment of CD.

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