International Journal of Colorectal Disease (2024) 39:149
https://doi.org/10.1007/s00384-024-04726-4

RESEARCH

The causal relationship between cholecystectomy and IBD/IBS and the role of bile acids and gut microbiota: a two-sample Mendelian randomization study

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Accepted: 16 September 2024 / Published online: 24 September 2024
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Abstract

Objective This study aims to explore the causal relationship between cholecystectomy and inflammatory bowel disease (IBD)/irritable bowel syndrome (IBS) and the role of serum bile acids and gut microbiota in this context.

Methods Utilizing genetic variant data from previous Genome-Wide Association Studies (GWAS), this study employed a two-sample MR approach to assess the causal effect of cholecystectomy on IBD/IBS.

Results The MR analysis suggested a potential negative causal relationship between cholecystectomy and UC ($p = 0.0233$, OR 0.9773, 95%CI 0.9581–0.9969) and a positive causal relationship between cholecystectomy and IBS ($p = 0.0395$, OR 4.077, 95%CI 1.0699–15.5362). Various sensitivity analyses reinforced the reliability of the causal relationship. However, the analysis did not find definitive results between serum bile acids or gut microbiota and cholecystectomy or IBD/IBS, possibly due to insufficient statistical power. MVMR find a causal relationship between bile acids and IBS ($p = 0.0015$, $b = 0.4085$) and UC ($p = 0.0198$, $b = 0.0029$).

Conclusion This study provides evidence of a causal relationship between cholecystectomy and IBD/IBS, highlighting the potential risk reduction for UC and increased risk for IBS following cholecystectomy. The role of bile acids and gut microbiota in this relationship remains unclear, necessitating further research to validate the causality and explore underlying mechanisms.

Keywords Cholecystectomy · IBD · IBS · Bile acids · MR

Inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) are two common gastrointestinal disorders that significantly impact patients' quality of life. IBD is characterized by chronic inflammation of the intestines and primarily includes Crohn's disease (CD) and ulcerative colitis (UC). The etiology of IBD is complex, involving genetics, immune responses, environmental factors, and imbalances in the gut microbiome [1]. IBS, on the other hand, is a functional gastrointestinal disorder marked by abdominal pain and changes in bowel habits [2]. Cholecystectomy, a common surgical procedure for treating gallbladder diseases, generally leads to good postoperative recovery for most patients. However, some may experience post-cholecystectomy syndrome (PCS) or complications such as diarrhea [3].

Recent studies have increasingly focused on the potential link between cholecystectomy and IBD/IBS. One study found a higher proportion of cholecystectomy among IBD patients, with some experiencing aggravated IBD conditions post-surgery [4]. Conversely, another study highlighted a significant increase in IBS risk, particularly diarrhea-predominant IBS (IBS-D), among patients with post-cholecystectomy [5]. Changes in bile acid metabolism following cholecystectomy are considered a potential mechanism leading to the onset or exacerbation of IBD/IBS [6, 7].

Although existing research provides evidence of a potential link between cholecystectomy and IBD, this field is still in its early stages, requiring further investigation to understand the precise relationship and underlying mechanisms. This article aims to explore the causal relationship between cholecystectomy and IBD/IBS by a two-sample Mendelian

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randomization study and then examine the role of serum bile acids in this process.

Method

Study design

This study employed a two-sample Mendelian randomization (MR) approach to investigate the causal relationship between cholecystectomy and IBD/IBS, as well as the role of bile acids in this process. The MR method uses genetic variants as instrumental variables (IVs) to assess the causal effect of the exposure factor (cholecystectomy) on the outcome variables (IBD/IBS), while minimizing the interference of confounding factors. This MR analysis is based on three critical assumptions: (1) IVs must be strongly associated with cholecystectomy, (2) IVs must not be associated with confounders, and (3) IVs cannot influence IBD/IBS unless through their effects on cholecystectomy (Fig. 1).

Data sources

The genetic variant data required for this study were obtained from previous Genome-Wide Association Studies (GWAS). This includes data from the GWAS Catalog (https://www.ebi.ac.uk/gwas), the Dutch Project (https://dutchmicrobiomeproject.molgeniscloud.org/), and the GWAS summary data (https://gwas.mrcieu.ac.uk).

IV selection

A relaxed threshold ($p < 5 \times 10^{-6}$) was used to identify SNPs, a common practice in similar studies [8, 9]. To obtain independent SNPs, we collected SNPs at linkage disequilibrium (LD) r^2 threshold at $r^2 < 0.001$ and kb > 10,000 based on European ancestry reference data, which come from the 1000 Genomes Project [10]. The parameters, including the effect allele (EA), non-effect allele (NEA), effect allele frequency (EAF), effect size (ES or β), standard error (SE), and p value, were extracted. F values > 10 indicated no weak tool bias. And the following formula was used to calculate the F statistic: F statistic $= R^2(N-2)/(1-R^2)$. $R^2 = 2 \times \mathrm{EAF} \times (1 - \mathrm{EAF}) \times \beta 2$.

Statistical analysis and sensitivity analysis

This study employed three different MR analysis methods. The MR analysis utilized the random-effect Inverse Variance Weighted (IVW) method, which aggregates the Wald ratio estimates from each single nucleotide polymorphism (SNP) on the outcome to provide a combined causal estimate. This approach offers high statistical power. Additionally, results were calculated based on both random-effect and fixed-effect models [11]. Cochran's Q test was used to assess heterogeneity. For IVW analyses where heterogeneity was present, results from the random-effect model were used, while the fixed-effect model was applied in the absence of heterogeneity. The weighted median and simple median methods were employed to corroborate the findings from the IVW analysis.

Sensitivity analysis was conducted using MR-Egger intercept tests to detect the presence of pleiotropy and assess the robustness of the results. A leave-one-out sensitivity analysis was also performed to evaluate the stability of the effect size (ES) through IVW, where each SNP was sequentially removed to determine its impact on the other SNPs. The MR Steiger test was utilized to assess the potential for reverse causality.

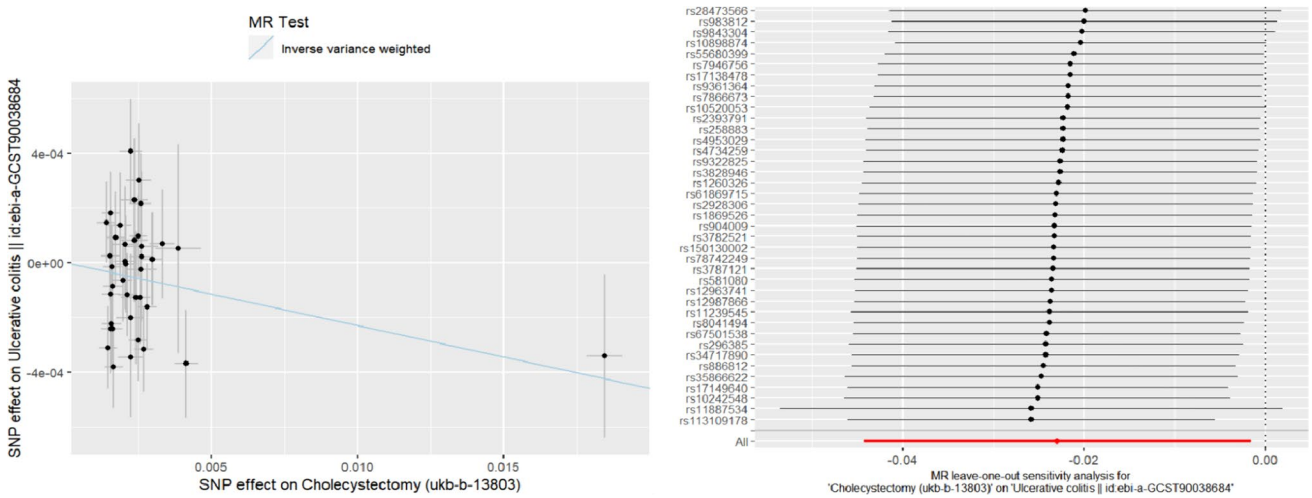

Fig. 1 MR leave-one-out analysis and scatter plot for cholecystectomy on UC

Software and tools

Statistical analyses were performed using R software (version 4.2.1). A two-sample Mendelian randomization (TSMR) analysis was conducted utilizing the "TwoSampleMR" packages within R software. A two-tailed p value of less than 0.05 was deemed to indicate statistical significance.

Ethical considerations.

This study was based on publicly available GWAS summary data and did not involve any identifiable personal information, adhering to ethical standards. Informed consent and ethical approval were obtained in the original studies, and these publicly available datasets (UK Biobank 11/NW/0382/ and University Medical Center Groningen 2017/152) complied with all ethical requirements.

Data availability statement

No datasets were generated during the current study.

Result

IV selection

In this study, GWAS data related to cholecystectomy, bile acid, IBS, ulcerative colitis, and Crohn's disease were obtained from various public datasets (Table 1). We selected related SNPs from the cholecystectomy and bile acid cohorts, adhering to screening criteria of $p < 5 \times 10^{-6}$, $r^2 < 0.001$, kb = 10,000, F-statistics > 10, and clustering in the European population (S. Table 1, S. Table 2, and S. Table 3). The average IV F-statistics for cholecystectomy was 57.95 and 26.08 for bile acid.

MR analysis and sensitivity analysis

The results of the MR analysis suggest a potential causal relationship between cholecystectomy and UC, cholecystectomy and IBS, and serum bile acid levels and cholecystectomy (Table 2). In the causal relationship between cholecystectomy and UC, no heterogeneity was found, so the fixed-effect model results were adopted ($p = 0.0233$, OR 0.9773, 95%CI 0.9581–0.9969). The weighted median (OR 0.982, 95%CI 0.952–1.0129) and simple median (OR 0.9909, 95%CI 0.9582–1.0248) results also confirmed a negative causal relationship between the two. In the causal relationship between cholecystectomy and IBS, heterogeneity was found among the samples, so the random-effect model results were adopted ($p = 0.0395$, OR 4.077, 95%CI 1.0699–15.5362). The weighted median (OR 5.6624, 95%CI 1.3842–23.1626) and simple median (OR 6.1944, 95%CI 1.0751–35.6893) results also confirmed a positive causal relationship between the two. Although the IVW fixed-effect model suggested a negative causal relationship between serum bile acid levels and cholecystectomy ($p < 0.0001$), the heterogeneity test result was positive ($p < 0.0001$), and the random-effect model results did not indicate a meaningful causal relationship ($p = 0.0799$).

Second, we conducted several sensitivity analyses to assess the robustness of our results (Table 3). The MR-Egger intercept test indicated no horizontal pleiotropy. The leave-one-out test supported a causal relationship between cholecystectomy and UC (Fig. 1) and cholecystectomy and IBS (Fig. 2). Excluding each SNP individually, the overall error line remained largely unchanged, suggesting the reliability of the causal relationship. The MR Steiger test confirmed that the causal relationship was unidirectional.

Gut microbiota

We further evaluated the role of gut microbiota in this context. The results are presented in Supplementary Tables S. Table 4 and S. Table 5. Cholecystectomy has a causal relationship with the following gut microbiota. The gut microbiota associated with a causal relationship with IBD, UC, and CD are specified as follows. Specifically, cholecystectomy has a negative causal relationship with Ruminococcus torques ($p = 0.0392$, OR 0.0415, 95%CI 0.0020–0.8549), and Ruminococcus torques also has a negative causal relationship with UC ($p = 0.0008$, OR 0.9984, 95%CI 0.9973–0.9996).

Table 1 Basic information of population in the study

Phenotype	N	Population	Consortium	GWAS ID
Cholecystectomy	463,010	European	MRC-IEU	ukb-b-13803
Bile acid	13,814	European	GWAS Catalog	GCST90060135
Irritable bowel syndrome	486,601	European	GWAS Catalog	GCST90016564
Ulcerative colitis	484,598	European	GWAS Catalog	GCST90038684
Crohn's disease	40,266	European	GWAS Catalog	GCST004132
Gallbladder disease	484,598	European	GWAS Catalog	GCST90038628

Table 2 MR analysis

Exposure	Outcome	Method	*B*	SE	pval	OR	95%CI
Cholecystectomy	Crohn's disease	Weighted median	−0.7638	2.6931	0.7767	0.4659	0.0024–91.3399
		Simple median	−3.3317	2.7309	0.2225	0.0357	0.0002–7.5442
		IVW (m)	−1.2634	3.4964	0.7178	0.2827	0.0003–267.6312
		IVW (f)	−1.2634	1.6368	0.4402	0.2827	0.0114–6.9924
	Irritable bowel syndrome	Weighted median	1.7338	0.7187	0.0158	5.6624	1.3842–23.1626
		Simple median	1.8236	0.8935	0.0412	6.1944	1.0751–35.6893
		IVW (m)	1.4054	0.6826	0.0395	4.077	1.0699–15.5362
		IVW (f)	1.4054	0.4781	0.0033	4.077	1.5973–10.4060
	Ulcerative colitis	Weighted median	−0.0182	0.0158	0.2502	0.982	0.9520–1.0129
		Simple median	−0.0091	0.0172	0.5953	0.9909	0.9582–1.0248
		IVW (m)	−0.0229	0.0109	0.0353	0.9773	0.9567–0.9984
		IVW (f)	−0.0229	0.0101	0.0233	0.9773	0.9581–0.9969
	Bile acid	Weighted median	2.4973	1.1628	0.0317	12.1492	1.2437–118.6801
		Simple median	−3.3149	3.0016	0.2694	0.0363	0.0001–13.0423
		IVW (m)	1.5048	1.2911	0.2438	4.5034	0.3586–56.5623
		IVW (f)	1.5048	1.1178	0.1782	4.5034	0.5036–40.2710
Bile acid	Crohn's disease	Weighted median	−0.2303	0.1641	0.1606	0.7943	0.5758–1.0957
		Simple median	−0.0620	0.1661	0.7088	0.9398	0.6787–1.3016
		IVW (m)	−0.0717	0.1641	0.6623	0.9308	0.6747–1.2841
		IVW (f)	−0.0717	0.1217	0.5559	0.9308	0.7332–1.1816
	Irritable bowel syndrome	Weighted median	0.0566	0.0864	0.5124	1.0583	0.8933–1.2537
		Simple median	0.0409	0.0809	0.6130	1.0418	0.8890–1.2208
		IVW (m)	0.0622	0.1226	0.6120	1.0642	0.8369–1.3532
		IVW (f)	0.0622	0.0506	0.2191	1.0642	0.9637–1.1751
	Ulcerative colitis	Weighted median	−0.0006	0.0015	0.7034	0.9994	0.9965–1.0024
		Simple median	−0.0006	0.0014	0.6656	0.9994	0.9966–1.0022
		IVW (m)	0.0007	0.0013	0.6119	1.0007	0.9981–1.0032
		IVW (f)	0.0007	0.0010	0.5330	1.0007	0.9986–1.0027
	Cholecystectomy	Weighted median	−0.0035	0.0037	0.3415	0.9965	0.9894–1.0037
		Simple median	−0.0035	0.0040	0.3820	0.9965	0.9887–1.0044
		IVW (m)	−0.0135	0.0077	0.0799	0.9866	0.9719–1.0016
		IVW (f)	−0.0135	0.0024	< 0.0001	0.9866	0.9820–0.9913

Table 3 Sensitivity analysis

Exposure	Outcome	Egger intercept	SE	pval	Steiger pval	*Q*	*Q* pval
Bile acid	Crohn's disease	−1.10E−02	5.42E−02	0.8493	1.67E−20	9.09E+00	0.1055
	Irritable bowel syndrome	−5.58E−03	3.77E−02	0.8897	2.17E−30	2.93E+01	< 0.0001
	Ulcerative colitis	2.96E−04	3.56E−04	0.4521	9.60E−33	7.55E+00	0.1831
	Cholecystectomy	−8.60E−04	3.27E−03	0.8097	2.08E−22	4.09E+01	< 0.0001
Cholecystectomy	Crohn's disease	−5.10E−02	2.82E−02	0.0820	3.77E−02	1.23E+02	< 0.0001
	Irritable bowel syndrome	3.34E−05	3.30E−03	0.9920	7.54E−164	7.54E+01	0.0002
	Ulcerative colitis	−2.57E−05	5.27E−05	0.6289	1.38E−186	4.42E+01	0.2276
	Bile acid	−1.62E−02	6.68E−03	0.0600	8.37E−03	8.01E+00	0.2377

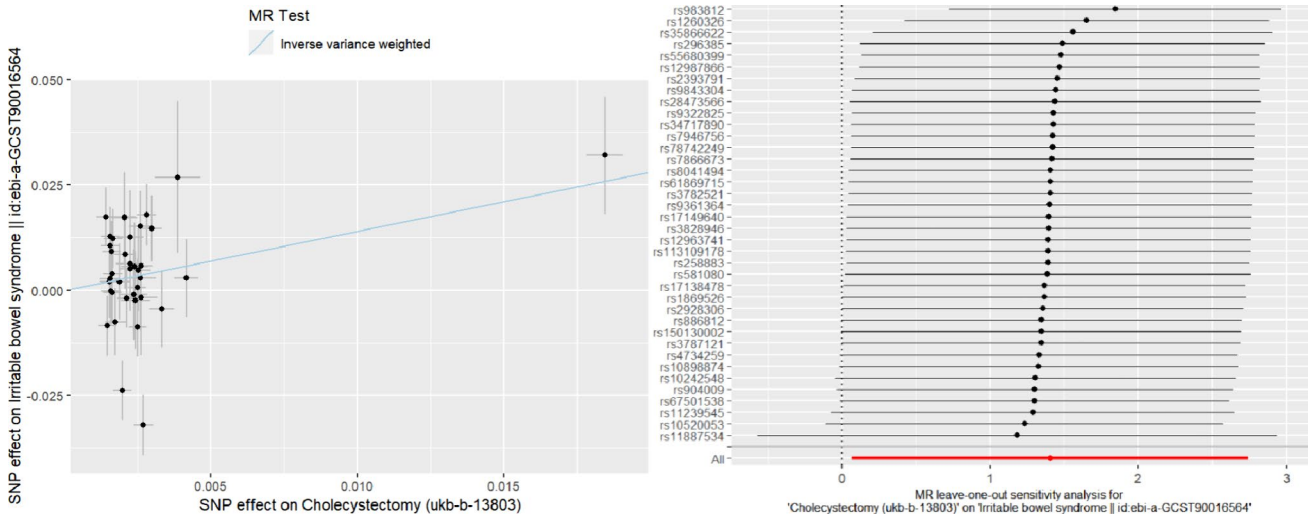

Fig. 2 MR leave-one-out analysis and scatter plot for cholecystectomy on IBS

MVMR

Considering the dubious causal relationship between serum bile acid levels and cholecystectomy, we further analyzed the causal relationship between bile acid levels, Ruminococcus torques, cholecystectomy, and outcomes using MVMR (Table 4), adjusting for the impact of gallbladder. We did not find a causal relationship between cholecystectomy or gallbladder disease and outcome, but we found that the causal relationship between bile acids and IBS ($p = 0.0015$, $b = 0.4085$) and UC ($p = 0.0198$, $b = 0.0029$) still exists.

Discussion

This study marks the inaugural Mendelian randomization (MR) exploration into the causal relationship between cholecystectomy and IBD/IBS, while also delving into the role of bile acids in this context. We discovered a negative causal relationship between cholecystectomy and UC and a positive causal relationship between cholecystectomy and IBS. A significant strength of our study lies in the MR design, which assesses the independent causal effects of cholecystectomy on multiple outcomes, devoid of reverse causality or residual

Table 4 MVMR

Exposure	Outcome	*B*	SE	pval
Gallbladder disease	Ulcerative colitis	0.0670	0.0595	0.2603
Bile acid		0.0029	0.0012	0.0198
Cholecystectomy		−0.0887	0.0562	0.1140
Gallbladder disease	Crohn's disease	−8.1920	70.9399	0.9081
Bile acid		0.3985	0.9322	0.6690
Cholecystectomy		9.5684	57.4880	0.8678
Gallbladder disease	Irritable bowel syndrome	3.7942	6.1283	0.5358
Bile acid		0.4085	0.1285	0.0015
Cholecystectomy		−3.6070	5.7767	0.5324
Gallbladder disease	Ulcerative colitis	−0.0215	0.0609	0.7247
Ruminococcus_torques		−0.0010	0.0006	0.1105
Cholecystectomy		−0.003	0.0566	0.9580
Gallbladder disease	Crohn's disease	−1.2894	17.9175	0.9426
Ruminococcus_torques		0.1012	0.2123	0.6336
Cholecystectomy		3.4970	15.2301	0.8184
Gallbladder disease	Irritable bowel syndrome	1.7450	4.2164	0.6790
Ruminococcus_torques		0.0273	0.0447	0.5412
Cholecystectomy		−0.4023	3.9142	0.9181

confounding. Although the multivariable MR results did not further confirm the causal relationship between cholecystectomy and IBD/IBS, positive results were obtained in bile acid metabolism. Therefore, cholecystectomy may affect IBD/IBS by affecting bile acid metabolism. This maximizes the reliability and validity of our study's findings. Moreover, the considerable sample size facilitated a robust MR analysis.

Our MR analysis results indicate a negative causal relationship between cholecystectomy and UC, suggesting that cholecystectomy may reduce the risk of UC. This finding is consistently supported by the fixed-effect model and sensitivity analysis results. Research by Liu et al. has shown that cholecystectomy may decrease the risk of UC by increasing the accumulation of secondary bile acids, which alleviate colonic inflammation by inhibiting the recruitment of monocytes/macrophages. Secondary bile acids possess anti-inflammatory properties and can reduce intestinal inflammation by activating the LXRα signaling pathway, thereby inhibiting the recruitment and activation of monocytes and macrophages[12]. However, further analysis using univariable and multivariable MR to assess the role of bile acids or the gut microbiota (Ruminococcus torques) revealed results that are difficult to explain. This may indicate the presence of more complex causal relationships.

The MR analysis results of this study indicate a positive causal relationship between cholecystectomy and IBS, suggesting that cholecystectomy may increase the risk of IBS. Research by Zhao et al. has found that cholecystectomy directly affects bile acid metabolism, which is a key factor in the pathology of IBS. After cholecystectomy, the circulation and metabolism of bile acids change, potentially leading to an accumulation of bile acids in the intestines. This accumulation can stimulate intestinal motility, thereby triggering IBS [5]. The MVMR analysis in this study also supports this conclusion, suggesting that bile acids may be a key mediating factor in the development of IBS following cholecystectomy.

Although previous studies have suggested that bile acid metabolism may be a potential mechanism by which cholecystectomy increases or decreases the risk of IBD/IBS, the MR analysis in this paper did not find definitive positive results between serum bile acids and cholecystectomy or IBD/IBS. After rigorous sensitivity analysis, the random-effect model of IVM did not yield statistically significant results. This is most likely due to insufficient statistical power resulting from an inadequate sample size, because of the positive results in the causal relationship between bile acids and IBD/IBS in MVMR analysis. It is also necessary to consider factors other than bile acid levels, as there may be other potential mechanisms in the causal relationship between cholecystectomy and IBD/IBS. The role of the gut microbiome cannot be overlooked. Research by Keren et al. has shown that after cholecystectomy, the bidirectional interaction between bile acids and the gut microbiome changes, leading to an increase in total bile acid concentration and a reduction in microbial diversity [13].

This research was subject to several limitations. Firstly, to incorporate more instrumental variables (IVs), we relaxed the statistical threshold to $p < 5 \times 10^{-6}$, which allowed for the inclusion of additional SNPs. Secondly, the association between genetic variants and study outcomes might not directly reflect causal mechanisms but could be influenced indirectly through complex biological pathways. The specific biological mechanisms remain unclear. Thirdly, due to the MR study design, there was a lack of long-term follow-up data, leading to uncertainties regarding the long-term effects of cholecystectomy. Finally, findings are based on genetic data from European populations, potentially limiting generalizability to other ethnic groups. Given these limitations, future studies are necessary to validate the causality and delve into the underlying mechanisms, which are essential for developing relevant clinical recommendations.

Conclusion

Our findings reveal a negative causal relationship between cholecystectomy and UC, suggesting that cholecystectomy may potentially reduce the risk of UC. Conversely, a positive causal relationship was identified between cholecystectomy and IBS, indicating that cholecystectomy might elevate the risk of developing IBS. However, more research is needed to clarify the role of bile acids and gut microbiota (especially Ruminococcus torques).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00384-024-04726-4.

Author contributions Peng Ding is responsible for data statistics and writing, while Zhai Huihong is responsible for reviewing, Shuang Yang provided assistance in revising the article.

Data availability No datasets were generated during the current study.

Declarations

Competing interests The authors declare no competing interests.

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