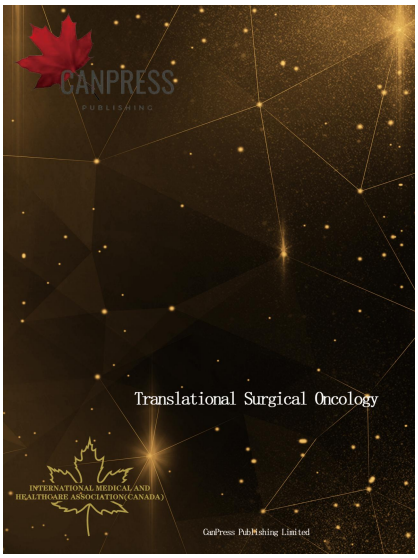
Inguinal hernia combined with colorectal cancer: 8 cases report and Mendelian Randomization



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Abstract

Background The colorectal cancer (CRC) and inguinal hernia association has been long debated. Here, we describe eight cases of patients with inguinal hernia simultaneously combined with CRC. We applied Mendelian randomization (MR) analysis to estimate the bidirectional causal relations between CRC and inguinal hernia.**Methods** Data of the clinical manifestations, diagnosis, and treatments of eight patients with inguinal hernia combined with CRC, six of whom were incarcerated, from January 2012 to December 2022, have been collected. Two-sample Mendelian randomization was conducted. Fifty-three colorectal cancer-associated single-nucleotide polymorphisms (SNPs) and 38 inguinal hernia-associated SNPs were used as genetic instrument variables (IV), derived from publicly available genome-wide association studies (GWAS) summary meta-analysis. The primary estimation was based on the inverse-variance weighted approach (IVW); the MR-Steiger method was used to detect the reverse effect. MR Pleiotropy RESidual Sum and Outlier, MR-Egger, and weighted median methods were utilized for heterogeneity and pleiotropy evaluation.**Results** Surgery was performed in all eight cases. Postoperative pathology confirmed the combination of inguinal hernia and colorectal cancer in all patients Eventually, seven of them were cured, whereas one died; Mendelian randomization showed no evidence of bidirectional causal effect between CRC and inguinal hernia. Inguinal hernia did not cause CRC (OR = 0.999 (0.992,1.006), P = 0.802, OR = 1.039 (0.998, 1.081), P = 0.409), neither did inguinal hernia could induce CRC (OR = 1.015 (0.909, 1.134), P = 0.784, OR = 1.039 (0.985, 1.233), P = 0.097), colon cancer (OR = 0.999 (0.877, 1.140), P = 0.999, OR = 1.001 (0.999, 1.004), P = 0.137), or rectal sigmoid junction cancer (OR = 1.001 (0.999, 1.001), P = 0.343). The sensitivity analysis showed no pleiotropy or heterogeneity among SNPs. **Conclusions** MR study found no bidirectional association between CRC and inguinal hernia. More treatment suggestions should be concluded by collecting a large number of cases.

Keywords: inguinal hernia, CRC, casual effect, Mendelian randomization

Introduction

The association between colorectal cancer (CRC) and inguinal hernia has been long debatable. The first systematic study of the combination of inguinal hernia and CRC was conducted by Nick et al. in 1963. They reported that 28% of the CRC patients in their hospital suffered from inguinal hernia or have had an inguinal hernia repaired in recent 2 years[1]. In 1973, Polterauer et al. published a paper in which they claimed that patients with inguinal hernia were more likely to develop CRC[2]. Lovett et al. then supported this view revealing 26% incidence of malignant and premalignant lesions in inguinal hernia patients by colonoscopy screening [3].

Conversely, a single-arm study conducted by Brendel et al. suggested no connection between inguinal hernia and CRC [4]. A prospective screening trial performed by Avidan et al. found that the presence of an inguinal hernia did not automatically indicate the existence of CRC [5]. A colonoscopy screening study of 644 cases carried out by Benjamin et al. indicated that colonoscopy screening is not necessary for inguinal patients aged <50 years[6]. Furthermore, a recent meta-analysis done by Shreya et al. found no evidence in the collected data of 1462 patients from 4 studies that inguinal hernia can induce CRC[7].

The aforementioned results seemed to confirm that inguinal hernia does not increase the risk of CRC. However, those studies were designed to estimate a one-directional causal effect between these two diseases. As a result, it is challenging to determine which disease occurred first and subsequently led to the development of the other. Whether an inguinal hernia increases the likelihood of CRC due to the aberrant bowel anatomical structure, or the CRC induces an inguinal hernia because of the abnormal abdominal pressure caused by it. The etiology of this combination of diseases could be bidirectional. Inguinal hernia combined with CRC is not common. From 2012 to 2022, we had only eight such cases. Two of them were admitted to the hospital for a long-term inguinal mass, and six of them were admitted for inguinal hernia incarceration.

In this study, we present the clinical statistics of eight cases of inguinal hernia combined with CRC. We performed MR analysis to estimate the bidirectional causal effect between inguinal hernia and CRC.

Materials and Methods

Case information

In this study, we report the data of eight cases of patients who had inguinal hernia combined with CRC and were admitted in our General Surgery Department of the First Affiliated Hospital of Soochow University from January 2012 to December 2022. The cohort comprised of six males and two females aged 61–92 (mean age, 71, SD value 12.51) years. The final diagnosis was confirmed by intraoperative and postoperative pathological examinations.

Data on the co-existing diseases, clinical classification, pathological diagnosis, site of inguinal hernia, and CRC, and the preoperative diagnosis are presented in Table 1.

The medical history of the included cases showed that the duration of the inguinal mass of the eight patients was all longer than 3 months. One patient had had unexplained weakness recently; three suffered from hematochezia and two from constipation. Physical examinations revealed abdominal muscle rigidity in three cases, a left palpable abdominal mass in one case, and hyperactive bowel sounds in four cases. Additionally, we performed digital rectal examination in six patients, and blood was detected on the gloves post-examination in two of them, without determination of the bleeding area. Then, B-ultrasound was performed on all eight patients. The results indicated that the inguinal mass initially detected was a hernia. Computed tomography (CT) examination was next conducted in 6 of them, whose results showed that the colorectal-bowel wall was irregularly thickened, and the lymph nodes near the lesion were enlarged, indicating a neoplasm (Figure 1). Stenosis in the sigmoid colon was detected in one of the patients, indicating a neoplasm (Figure 2). All patients with CT examination were diagnosed with incarcerated inguinal hernia with a colorectal mass, whereas the other two cases were diagnosed with inguinal hernia only.

Treatment

Three of the patients had a severe hernia incarceration combined with a sigmoid colon mass and a bad general condition. After tumor resection, we simultaneously performed a Hartmann's procedure and inguinal hernia ring closure. One incarcerated inguinal hernia patient with an ascending colon mass and bowel perforation underwent right hemicolectomy, ileostomy, and inguinal hernia ring closure. Laparoscopic inguinal hernia one-stage repair was performed in another patient. During the laparoscopic exploration, we found a mass on the sigmoid colon. A week later, colonoscopy findings confirmed that it was sigmoid colon cancer. Then, we performed two-stage laparoscopic sigmoid colectomy.

One patient had a tumor in the descending colon, and the hernia content consisted of a metastatic tumor of the omentum. We also detected a metastatic tumor of the liver. Due to the advanced cancer stage and the severe bowel obstruction, we performed transverse colon colostomy instead of tumor

removal and inguinal hernia repair simultaneously. One patient underwent left hemicolectomy with primary anastomosis and internal ring closure at the same time. Another was subjected to left hemicolectomy with ileostomy and internal ring closure simultaneously. All patients who underwent stage I tumor resection and anastomosis were given gastrointestinal decompression and irrigation. Incarcerated inguinal hernia combined with CRC was confirmed by intraoperative and postoperative pathological examinations.

Notably, two of the patients were preoperatively misdiagnosed. Of all eight patients, seven were cured, but one died. The deceased patient was the one with perforation, who underwent Hartman surgery and internal ring closure operation along with ileostomy. Due to the poor general condition, septic shock, multiple organ failure occurred four days postoperatively. One patient had incision dehiscence and was treated with anti-infection therapy and incision re-suture. Three patients with respiratory infection were treated with anti-infection and atomization inhalation therapy to dispel the phlegm and were finally cured. The remaining soon recovered and were discharged.

Methods

An overview of the study design is presented in Figures 3 and 4. SNPs were used as the instrument variables in this MR analysis. We based this research on the following MR assumptions: (1) IV were robustly associated with risk factors; (2) IV were associated only with outcomes through risk factors; (3) IV were not associated with the confounders of the risk factor-outcome association. The primary estimation was based on the inverse-variance weighted approach, and the MR-Steiger method was implemented to detect the reverse effect. The heterogeneity and pleiotropy were analyzed using the MR Pleiotropy RESidual Sum and Outlier, MR-Egger, and the weighted median methods.

Genetic variants associated with inguinal hernia and colorectal cancer

The instrumental variables for genetic analysis of CRC were obtained by extracting the summary data from a recent meta-analysis of GWAS, which included 58,131 cases and 67,347controls[8]. 78 SNPs were reported to be significantly related with CRC ($P < 5 \times 10-8$). We then evaluated the linkage disequilibrium (LD) based on LD $r2 < 0.001$ and excluded 21 SNPs. To avoid violations of the Mendelian assumption, we searched the GWAS catalog to exclude the SNPs reported to be associated with inguinal hernia. Few reports were found, and only four SNPs were reportedly associated with BMI, which were excluded[9].

GWAS summary data regarding the inguinal hernia outcome

The data of two inguinal hernia variants were analyzed. One part of them was obtained in a latest genome-wide association study based on UK Biobank (UKB) research, which included 18,791 cases and 93,955 controls [12]. Another portion of data was obtained from FinnGen GWAS database, which had 29,087 cases and 293,793 controls. A number of 53 SNPs were retrieved from those two inguinal hernia outcome data sources, all 53 SNPs associated with CRC were extracted. For UKB data, 4 SNPs were removed due to palindromy with intermediate allele frequencies. As for FinnGen data, two SNPs were removed for same reason, and another two SNPs were removed by MR-PRESSO analysis. Eventually, 49 SNPs were included in the UKB inguinal hernia outcome data, and 45 SNPs were used in the FinnGen inguinal hernia data.

GWAS summary data regarding the CRC outcome

The summarized data of the variants of CRC and colon cancer were derived from the UKB and FinnGen GWAS databases. The summarized data of the variants of rectal-sigmoid junction cancer were obtained from UKB. No SNPs were excluded after the retrieval of 38 SNPs from those data. However, nine SNPs were removed from the UKB data due to palindromy with intermediate allele frequencies. Besides, two SNPs for CRC and colon cancer data were removed by MR-PRESSO analysis due to horizonal pleiotropy. Three SNPs were removed from the FinnGen data due to palindromy. Finally, 27 SNPs were used for CRC and colon cancer UKB data analysis, and 29 SNPs were included in the rectal-sigmoid junction cancer analysis. We assessed 35 SNPs in the CRC and colon cancer FinnGen data analysis.

Mendelian randomization

After removing the SNPs which failed to clump and harmonize, and related to confounders, we used bidirectional Mendelian randomization to analyze the casual association between CRC and inguinal hernia. The IVW, weighted median, and MR-Egger methods were applied. The primary outcome measure was the inverse-variance weighted meta-analysis of the Wald ratio for individual SNPs. This method assumes that the instrumental variables can only affect the outcome through the exposure of interest and not through any other alternative pathway[13]. In addition to the IVW estimates, MR-Egger and weighted median methods were employed to provide more robust estimates in a wider range of scenarios. However, these approaches are less efficient and may lead to wider confidence intervals.

Sensitivity analysis has played a pivotal role in Mendelian randomization studies. MR pleiotropy residual sum and outlier (MR-PRESSO) global tests have also been implemented to identify significant horizontal pleiotropy and remove the outliers detected. To verify if there was potential reverse effect in each analysis, we used MR Steiger analysis to check the causal effect directions, and no reverse causal effect was found[14-16]. The R packages used were TwoSampleMR package (v0.5.6) [17] and MRPRESSO (v1.0) [18].

Mendelian randomization results

The IVW results indicated a lack of evidence for a causal bidirectional relationship between inguinal hernia and CRC (CRC, colon cancer, or rectal-sigmoid junction cancer). OR was consistent in different outcome databases (Table 2). Sensitivity analysis showed no significant heterogeneity or pleiotropy or directional pleiotropy. (Table 2). The casual estimates from IVW, MR-Egger and weighted median methods were generally consistent, illustrating the robustness of the MR assumptions.

Discussion

In the past decade, we have had eight cases of patients, age was 56–92 (mean age: 71) years, who had inguinal hernia combined with CRC simultaneously. Six of them came to hospital for hernia incarceration and two for long-term inguinal area mass history. The intra-operative and pathological findings confirmed that all of them had inguinal hernia combined with CRC. Generally, collagen content within the transverse abdominal fascia diminishes as individuals age[19]. Concurrently, in the context of colorectal cancer, the occurrence of incomplete intestinal obstruction or impaired peristaltic movement can precipitate a notable elevation in intraabdominal pressure[20]. We agree with the hypothesis that the neoplasm of the colon may promote a reversible hernia into an irreducible hernia [21], mainly due to the abdominal pressure change.

CT examination was performed in five of these patients. Two patients were misdiagnosed, in whom colon mass was not noticed until the surgery, which significantly changed our surgical plan. Therefore, comprehensive examinations, especially CT, are important for the detection of such unexpected cases. Cancer resection was performed in five of the other six patients. Hartmann procedure was preferred over single-stage anastomosis.

Polterauer et al. reported that patients with inguinal hernia were more likely to develop CRC[2]. As described before, the causal relationship between CRC and inguinal hernia is complex and could be reversed and bidirectional. Thus, we utilize Mendelian Randomization analysis, which uses genetic variants to estimate the causal effect of an exposure on an outcome, to avoid the reverse effect and collider bias [14,16,22].

To the best of our knowledge, this study is the first MR study to access the bidirectional causal relationship between CRC and inguinal hernia by applying the MR method. Our IVW results showed no causal association between CRC and inguinal hernia. SNPs were used as instrumental variables (IV), and the cornerstone of IV was based on three main assumptions: (1) SNPs must be robustly associated with exposure (our dataset fulfills the criterion of $P < 5 \times 10{-}8$ and $F > 10$, as per assumption)[23]; (2) SNPs do not affect exposure directly (confirmed by our MR-Egger intercept test)[24]; (3) SNPs do not associate with confounders involved in the exposure-outcome association (the confound risk factors associated with SNPs were removed in to meet that assumption criterion)[25].No heterogeneity was not found, confirming that the IV estimate is consistent with the average causal effect[26]. Furthermore, we performed a MR Steiger analysis to prevent the reverse effect in the analysis[14-16]. All aforementioned analyses and results make our results reliable and compelling.

Few reports have described that cancer was predominantly located in the sigmoid colon[20]. Given this, we analyzed the bidirectional causal effect between rectal-sigmoid junction colon cancer colonic colon cancer, and inguinal hernia, respectively. Our results showed no relation between these two diseases.

Several limitations of this study are to be acknowledged. First, the data on the cases of inguinal hernia combined with CRC we collected were too limited to conclude statistically significant evidence for diagnosis and treatment. Second, the possible mechanism for CRC development in the case of an inguinal hernia could be the abdominal pressure caused by the latter. Unfortunately, no GWAS data correlated with abdominal pressure were available. Third, different stages of CRC may affect inguinal hernia to a different degree. Due to the limited available datasets, we were unable to conduct a stratified analysis based on different CRC stages. Finally, the statistical power of several analyses did not meet the threshold criterion of 80%, mainly due to the too-low case/control ratio in the data. Further MR analysis should be focused on the causal effect between the CRC and inguinal hernia stratified by the different stages of the former.

This is the first MR study to evaluate the existence of a bidirectional causal association between inguinal hernia and CRC. MR analysis showed no evidence of a causal effect between inguinal hernia and CRC. Two misdiagnosed cases indicate that a possibility of a combined disease is need to be excluded in the clinical evaluation of long-term inguinal hernia or sudden incarcerated inguinal hernia, and CT might have a possible role in that. More cases are needed to provide a more convinced treatment suggestion.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

This study was approved by the First Affiliated Hospital of Soochow University Ethical Committee. The Mendelian randomization study is a re-analysis of previously collected and published data, no additional ethics approval was needed.

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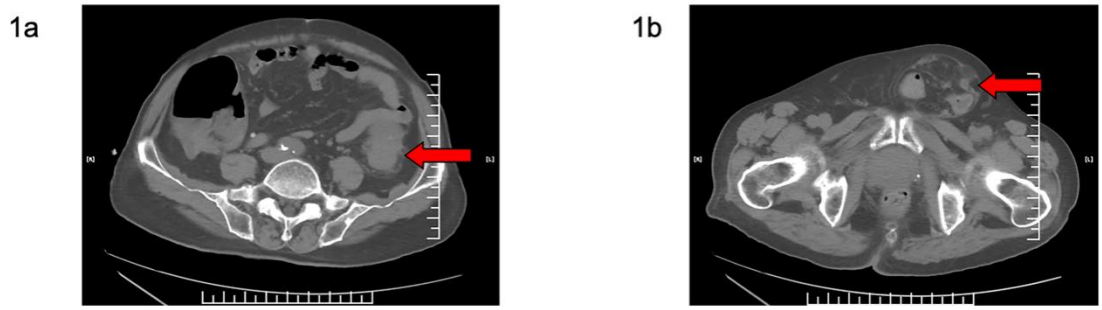

Figure 1. (a) The colon bowel wall is irregularly thickened, and the lymph nodes near the lesion are enlarged, indicating a neoplasm (marked in Figure 1a); (b) Irreducible hernia in the left groin (marked in Figure 2b).

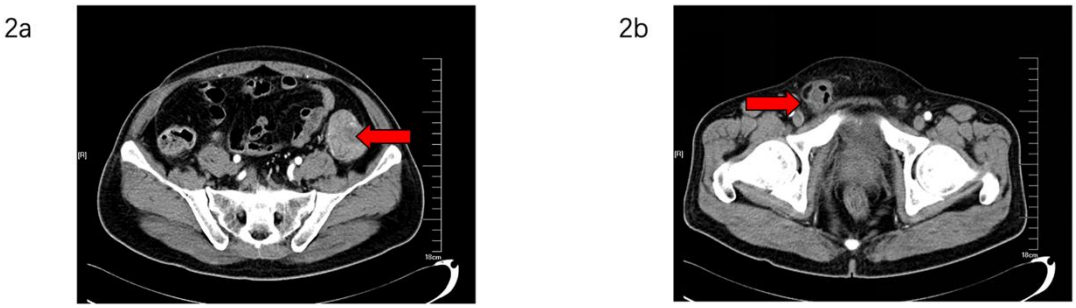

Figure 2. (a) Stenosis in the sigmoid colon indicated tumor presence (marked in 2a); (b) Hernia in the right groin (marked with an arrow in 2b).

Age	Sex	Site of hernia	Site of tumor	Incarcerated	Pre-operative Diagnose	History Illness	Combined symptoms	Digital rectal examination	CT	Treatment	Pathology Diagnose	Duke`s stage	Post-operative complication	Hospital time(days)
56	M	Left	Sigmoid	Incarcerated	Incarcerated left inguinal hernia, Sigmoid colon mass	non	severe abdominal pain and hematochezia	not touch the mass but found blood	Y	Hartmanns+ Internal hernia ring closure (one stage)	differentiated adenocarcinoma	D	non	7
61	M	Right	Ascending	Incarcerated	Incarcerated right inguinal hernia, Right colon perforation, Right colon mass	hypertension, Parkinson's disease	severe abdominal pain	non	Y	Right hemicolectomy + ileostomy Internal ring closure (one stage)	poorly differentiated adenocarcinoma	D	septic shock, multiple organ failure	20
63	M	Right	Sigmoid	non	Right inguinal hernia	coronary heart disease	constipation and weakness	not touch the mass not found blood	N	Stage I Laparoscopic Tension free hernia repair +Stage II Laparoscopic Sigmoid-dectomy (two stage)	poorly differentiated adenocarcinoma	B	non	14
67	F	Left	Transverse	Incarcerated	Incarcerated left inguinal hernia, Transverse colon mass	non	severe abdominal pain	non	Y	Transverse colostomy+ Tension free hernia repair (one stage)	moderately differentiated adenocarcinoma	C	non	8
68	M	Right	Descending	Incarcerated	Incarcerated left inguinal hernia, Left colon mass	hypertension, diabetes	severe abdominal pain	not touch the mass not found blood	Y	Left hemicolectomy + Internal hernia ring closure (one stage)	differentiated adenocarcinoma	C	incision dehiscence	16
75	M	Left	Sigmoid	Incarcerated	Incarcerated left inguinal hernia	hypertension	hematochezia, severe abdominal pain	not touch the mass not found blood	N	Hartmanns+ Internal hernia closure (one stage)	differentiated adenocarcinoma	B	respiratory infection	10
86	M	Left	Sigmoid	Incarcerated	Incarcerated left inguinal hernia, Sigmoid colon mass	hypertension	hematochezia, severe abdominal pain	not touch the mass but found blood	Y	Hartmanns + Inguinal hernia ring closure (one stage)	moderately differentiated adenocarcinoma	C	respiratory infection	11
92	F	Right	Descending	non	Left inguinal hernia, Left colon mass	hypertension	constipation	non	Y	Left hemicolectomy+ Ileostomy + Internal ring closure (one stage)	mucous adenocarcinoma	C	respiratory infection	13

Table 1. The basic conditions and treatments of the eight patients.

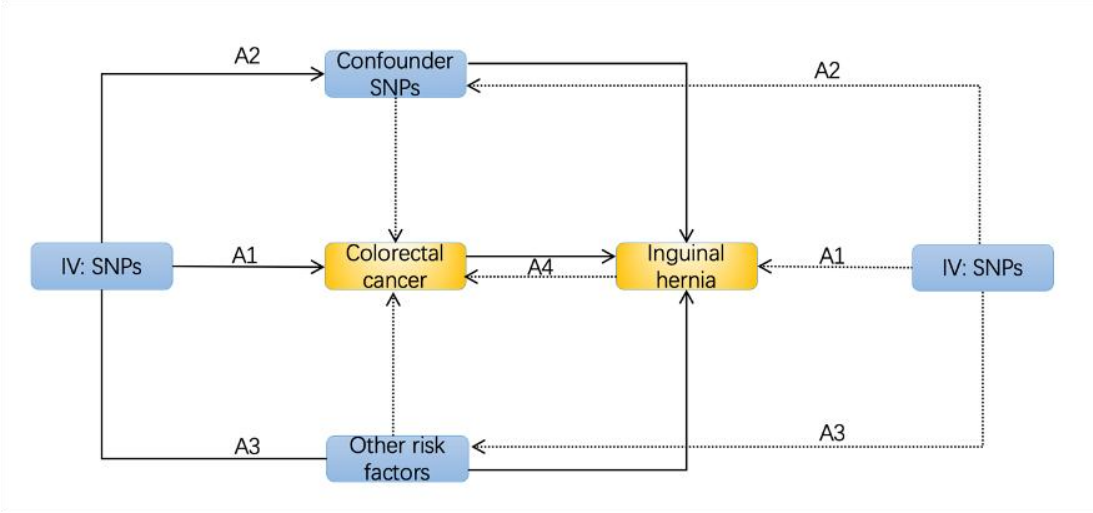

Figure 3. A1: IV is robustly associated with exposure. A2: IV does not include the SNP directly lead to outcome. A3: IV influence the risk of outcome only through exposure. A4: the direction of the causal effect must be correct. Abbreviation: IV, instrument variables; SNPs, single-nucleotide polymorphisms;

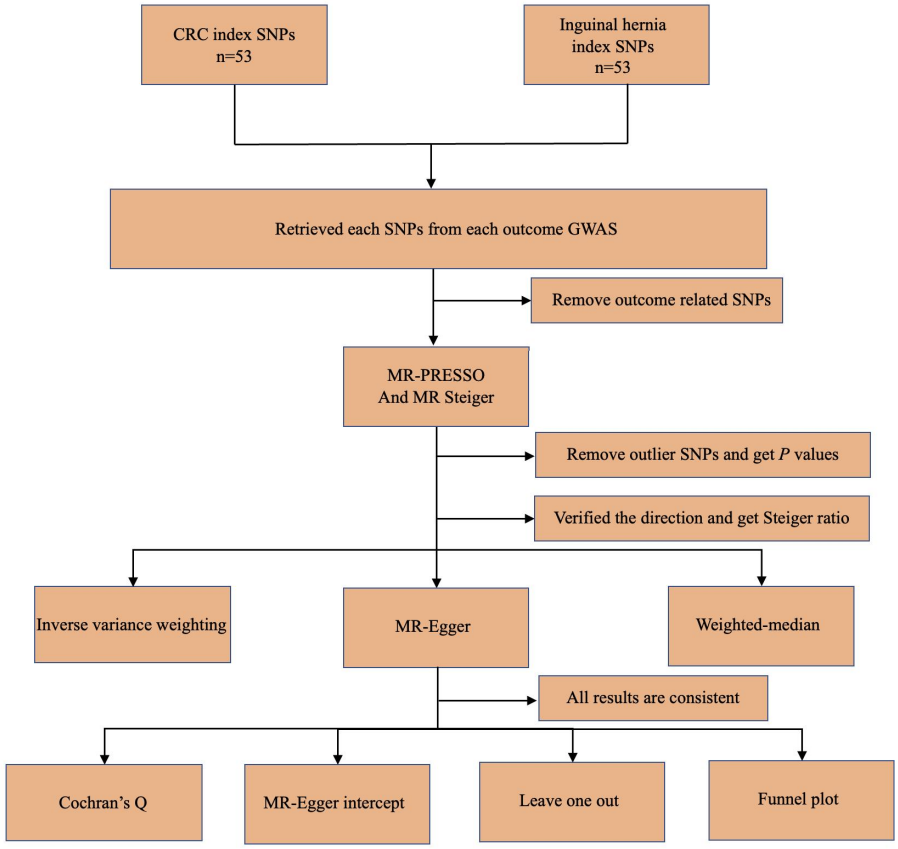

Figure 4: Process diagram of Mendelian randomization study estimating the bidirectional causal effect between CRC and inguinal hernia. Abbreviation: CRC, colorectal cancer.

Table 2. Summary of mendelian randomization study.

Exposure	Outcome	No. of SNPs	R^2	F-statistics	OR(95%CI)	*P*-value	IVW Q (*P*-value)	MR-Egger intercept (*P*-value)	MR-PRESSOR RSSobs (*P*-value)
Colorectal cancer	Inguinal hernia_UKB	49	0.119	14970.221	0.999(0.992,1.006)	0.802	61.631(0.074)	`-0.0007(0.430)	65.497(0.072)
	Inguinal hernia_Finngenn	45	0.113	14281.535	1.039(0.998,1.081)	0.409	49.861(0.251)	`-0.00015(0.776)	52.151(0.267)
Inguinal hernia	Colorectal cancer_UKB	27	0.067	35062.664	1.015(0.909,1,134)	0.784	27.604(0.378)	`-0.0068(0.526)	53.030(0.504)
	Rectal-Sigmoid junction_UKB	29	0.069	35062.664	1.001(0.999,1.001)	0.343	16175(0.963)	`-2.2e-5(0.683)	24.165(0.667)
	Coloncancer_UKB	27	0.067	35062.664	0.999(0.877,1.140)	0.999	22.802(0.644)	`-0.019(0.166)	17.345(0.964)
	Colorectal cancer_Finngenn	35	0.07	45397.928	1.102(0.985,1.233)	0.097	40.280(0.212)	`-0.00419(0.718)	42.402(0.223)
	Coloncancer_Finngenn	35	0.07	45397.928	1.001(0.999,1.004)	0.137	40.423(0.207)	`-0.444(0.764)	42.403(0.220)

UKB, UK Biobank; CI, confidence interval; IVW, inverse-variance weighting; MR, Mendelian randomization; MR-PRESSO, MR pleiotropy residual sum and outlier; OR, odds ratio; RSSobs, observed residual sum of squares; SNP, single-nucleotide polymorphism.

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