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No genetic causality between appendectomy and gastrointestinal cancers: a Mendelian randomization study and meta-analysis in European population

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The impact of appendectomy on the risk of gastrointestinal cancers remains unknown. We aimed to systematically estimate the causal relationship between appendectomy and gastrointestinal cancers in the European population using two-sample Mendelian randomization (TSMR) study methods and meta-analysis. As part of the discovery cohort analysis, we identified independent genetic variants strongly associated with appendectomy from the UK Biobank (50,105 cases) to serve as instrumental variables (IVs). Summary-level data for gastrointestinal cancers were obtained from the FinnGen study. As the replication cohort, IVs associated with appendectomy were extracted in the FinnGen study (28,601 cases). The data for gastrointestinal cancers were obtained from the UK Biobank. Finally, meta-analyses were conducted to evaluate the combined causal effects of the MR results. We found no causal relationship between appendectomy and gastrointestinal cancers in both the discovery and replication cohorts. Finally, the meta-analysis revealed no causal association between appendectomy and gastrointestinal cancers. Our findings suggest no causal relationship exists between appendectomy and gastrointestinal cancers in the European population. This genetic evidence supports the conclusion from other observational studies that appendectomy does not affect the risk of gastrointestinal cancers in the European population.

Keywords Mendelian randomization, Appendectomy, Gastrointestinal cancers, Colorectal cancer

Acute appendicitis is a common cause of acute abdominal pain worldwide. The lifetime risk of developing the disease is estimated to be 7–8%[1]. Appendectomy is the standard treatment for appendiceal diseases such as acute appendicitis[2]. Throughout history, the appendix has been considered an organ degenerating with human evolution and considered unimportant[3].

However, as early as the 1960s, studies showed an increased risk of cancer after appendectomy[4,5]. For example, an association between appendectomy and colorectal cancer (CRC) was first identified in 1964 by McVay JR[5]. Many researchers have continued to focus on this issue to this day. The meta-analysis by Liu et al.[3] showed that appendectomy increased the risk of CRC. However, the relationship is inconsistent when focusing on geographic and demographic differences. Appendectomy is a risk factor for CRC in Asian populations and Americans, but no causal relationship was found in European populations. There have also been many studies focusing on the association between appendectomy and cancer of the gastrointestinal tract, such as the esophagus[6], stomach[6–8], pancreas[9–17], liver[17], and small intestine[17,18]. However, the findings have not been consistent. For example, a study using the Swedish Patient and Cancer Register (1965–1993) found a significant increase in the risk of gastric cancer (GC) after appendectomy[7]. Meanwhile, another subsequent study of Swedish patients by Song H et al.[6] did not find such an association.

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It is difficult to measure the true risk of gastrointestinal cancers in appendectomy patients due to the inevitable confounding factors of traditional epidemiological studies. Therefore, the present study was based on the European population and used the research methodology of two-sample Mendelian randomization (TSMR) combined with meta-analysis to comprehensively assess the risk of appendectomy and gastrointestinal cancers including esophageal cancer (EC), GC, small intestine cancer (SIC), CRC, liver cancer (LC), pancreatic cancer (PC) in the European population.

MR is an emerging method of epidemiological analysis that uses genetic variation to assess causal relationships between exposures and clinical outcomes[19,20].The method is based on the principle of random distribution in biology, making its results independent of potential confounders and reverse causation. The TSMR method is widely used in MR research. The exposure and result data of TSMR should be measured in different (or only partially overlapping) samples[21]. This study selects different databases for analysis to avoid overlapping samples. Because the distribution of genetic variants across generations is random, the MR approach can provide strong evidence to support the causal role of risk factors on outcomes. For example, some studies have explored the relationship between appendectomy and neurodegenerative diseases by using the TSMR method. The results show that appendectomy can reduce the risk of Parkinson's disease and amyotrophic lateral sclerosis[22]. Some studies have also explored the relationship between appendectomy and inflammatory bowel disease, indicating that there is no causal relationship between appendectomy and inflammatory bowel disease[23]. Moreover, several studies have used TSMR methods to explore the relationship between the gut microbiome or plasma ghrelin and gastrointestinal cancers[24,25]. Single nucleotide polymorphisms (SNPs) are a type of genetic variation known to be valuable. SNP was chosen as an instrumental variable (IV) in this study. Finally, the causal relationship between appendectomy and gastrointestinal cancers was systematically assessed in conjunction with meta-analysis. The results of this study can provide evidence for observational research at the genetic level. In addition, the results of this study may suggest guidance on the need for long-term surveillance of gastrointestinal cancers in patients undergoing appendectomy.

Methods

Research design

This TSMR analysed the causal relationship between appendectomy and EC, GC, SIC, CRC, LC and PC. Firstly, as a discovery cohort, we selected IVs strongly associated with appendectomy in the UK Biobank and then obtained genome-wide association study (GWAS) data for gastrointestinal cancers in the FinnGen study for analysis. As a replication cohort, we selected IVs strongly associated with appendectomy in the Finnish database and then obtained GWAS data for gastrointestinal cancers in the UK Biobank for analysis. Finally, meta-analysis was used to synthesise our results. This study was conducted according to the STROBE-MR guidelines (Supplementary Table S1).

In MR research, IVs must meet three basic requirements: (1) IV must be directly related to exposure factors. (2) IVs are not affected by any potential confounding factors. (3) IVs do not influence outcomes other than the exposure pathways that influence outcomes (Fig. 1)[26]. There was no need to get informed consent or ethical approval for this study again because all of the data were taken from published sources, and the informed consent and approval were received.

Exposure data acquisition

The GWAS data of appendectomy (50,105 cases) in the discovery cohort were obtained from the UK Biobank study. The UK Biobank study is an ongoing cohort study initiated by recruiting about 500,000 adults between 2006 and 2010. It is a large-scale open database with hundreds of thousands of individuals' genotype data paired with electronic health records and survey measures.GWAS summary statistics can be downloaded from the UK Biobank study (https://pan.ukbb.broadinstitute.org/)[27]. Detailed information is provided in Table 1 and Supplemental Table S4.

GWAS data of appendectomy (28,601 cases) in the replication cohort were obtained from the FinnGen study. The FinnGen study includes data on more than 300,000 Finnish individuals, combining genotype data from Finnish biobanks and digital health record data from Finnish health registries. GWAS summary statistics can be downloaded from the FinnGen study (https://www.finngen.fi/en)[28]. Detailed information is provided in Table 1 and Supplemental Table S4.

Outcome data acquisition

In the discovery cohort, data for OC (619 cases), GC (1,423 cases), SIC (525 cases), CRC (6,847 cases), LC (648 cases), and PC (1,626 cases) were all obtained from the FinnGen study.

In the replication cohort, data for OC (975 cases), GC (764 cases), SIC (244 cases), CRC (5,693 cases), LC (539 cases), and PC (933 cases) were obtained from the UK Biobank study.

The above GWAS data are from the most recent data publicly available from the UK Biobank and FinnGen study. Specific definitions and download links for all disease data can be found in Supplementary Table S4.

Selection of instrumental variables

In constructing IVs, genome-wide significant SNPs ($P < 5e-08$) were extracted from the GWAS pooled data, and those with a longer physical distance (≥ 10000 kb) and less possibility of linkage disequilibrium ($R^2 < 0.001$) were retained. We queried the possible phenotypes for each SNP associated with gastrointestinal cancers by LDtrait (https://ldlink.nci.nih.gov/?tab=ldtrait)[29], and SNPs possibly confounding factors related to gastrointestinal cancers were removed, such as waist circumference adjusted for body mass index[30] (SNP: rs2484697) and insomnia[31] (SNP: rs224029). To avoid weak instrumental variable bias, we evaluated the SNP-exposure association strengths using the $F = BETA^2/SE^2$[32,33] (Supplemental Tables S2 and S3) for each SNP.

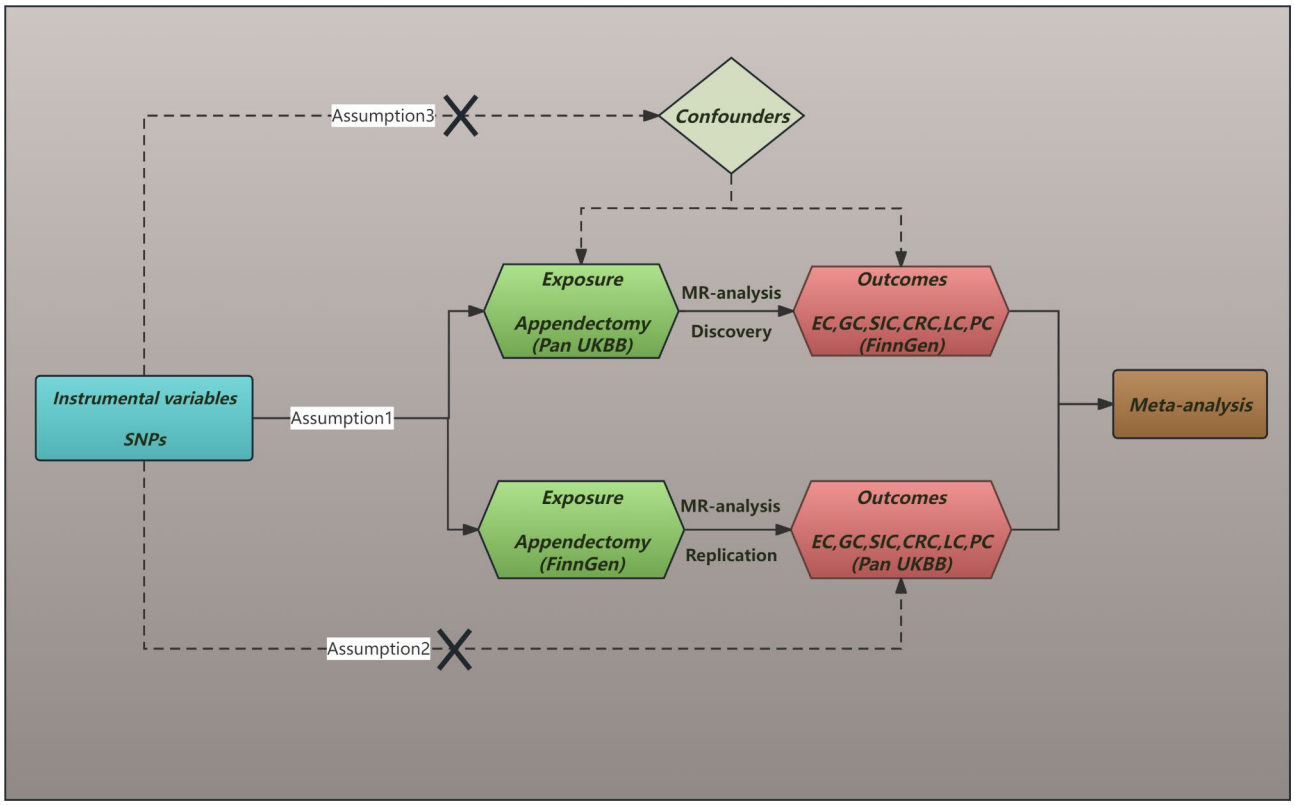

Fig. 1. The diagram of Mendelian randomization assumption. SNPs: single nucleotide polymorphisms; EC: esophageal cancer; GC: gastric cancer; SIC: small intestine cancer; CRC: colorectal cancer; LC: liver cancer; PC: pancreatic cancer.

Characteristic	Resource	Sample size	Population
Appendectomy (discovery cohort)	Pan UKBB	50,105 cases and 370,368 controls	European
EC (discovery cohort)	FinnGen (R10)	619 cases and 314,193 controls	European
GC (discovery cohort)	FinnGen (R10)	1,423 cases and 314,193 controls	European
SIC (discovery cohort)	FinnGen (R10)	525 cases and 314,193 controls	European
CRC (discovery cohort)	FinnGen (R10)	6,847 cases and 314,193 controls	European
LC (discovery cohort)	FinnGen (R8)	648 cases and 259,583 controls	European
PC (discovery cohort)	FinnGen (R10)	1,626 cases and 314,193 controls	European
Appendectomy (replication cohort)	FinnGen (R10)	28,601 cases and 383,580 controls	European
EC (replication cohort)	Pan UKBB	975 cases and 419,556 controls	European
GC (replication cohort)	Pan UKBB	764 cases and 419,767 controls	European
SIC (replication cohort)	Pan UKBB	244 cases and 420,287 controls	European
CRC (replication cohort)	Pan UKBB	5,693 cases and 386,740 controls	European
LC (replication cohort)	Pan UKBB	539 cases and 419,992 controls	European
PC (replication cohort)	Pan UKBB	933 cases and 419,598 controls	European

Table 1. Information of genome-wide association summary data. EC: esophageal cancer; GC: gastric cancer; SIC: small intestine cancer; CRC: colorectal cancer; LC: liver cancer; PC: pancreatic cancer; R10: Release 10; R8: Release 8.

When the SNPs had an F value > 10, we considered a strong association between the selected IVs and exposure. We excluded SNPs with a minor allele frequency ≤ 0.01 and removed palindromic sequences in IVs. Finally, we removed outliers using the MR-PRESSO test before each TSMR analysis.

TSMR analysis

The TSMR analyses in this study were performed in R 4.2.1 software using the TwoSampleMR package. In this study, we used the inverse variance weighting (IVW) method as the most dominant method for calculating

causal effects. The IVW model is the most powerful method for detecting causality in TSMR analysis[34]. The Mg-Egger and weighted median complemented the IVW results. Cochran's Q-test assessed the heterogeneity of the IVW model. Cochran's Q-test of $p < 0.05$ indicates heterogeneity[35]. If there is no heterogeneity, we use a fixed effects model. Otherwise, a random effects model is used[36]. MR-Egger intercept test was performed to assess whether the included SNPs were potentially horizontally pleiotropic, and a p-value of < 0.05 indicated the presence of pleiotropy[37]. The leave-one-out sensitivity test eliminates SNPs to determine the sensitivity of individual SNPs in this TSMR study. This study also used scatter, forest, and funnel plots for visualization and analysis[38]. Finally, to present a comprehensive and accurate picture of the causal relationship between appendectomy and gastrointestinal cancers, we used meta-analyses to assess the combined causal effects of TSMR outcomes. $P < 0.05$ was considered statistically significant (two-sided). We used the odds ratio (OR) and 95% confidence interval (CI) to assess the relative risk between appendectomy and gastrointestinal cancers.

Results

Results of the discovery cohort

First, we used a discovery cohort to determine the association of appendectomy with six gastrointestinal cancers. Appendectomy Heterogeneity in TSMR results with CRC was observed, so we used a random-effects model to assess causal associations between the two. The final IVW results showed no causal association between appendectomy and any of the gastrointestinal cancers, including EC (OR: 0.893, 95% CI: 0.435–1.831, $P = 7.565E-01$), GC (OR: 0.742, 95% CI: 0.461–1.195, $P = 2.193E-01$), SIC (OR: 1.185, 95% CI: 0.545–2.579, $P = 6.684E-01$), CRC (OR: 0.931, 95% CI: 0.674–1.287, $P = 6.661E-01$), LC (OR: 1.203, 95% CI: 0.596–2.426, $P = 6.060E-01$), PC (OR: 1.015, 95% CI: 0.650–1.583, $P = 9.494E-01$) (Tables 2 and Supplemental Table S7). Neither the weighted median method nor the MR-Egger method found a causal relationship between appendectomy and gastrointestinal cancers (Tables 2 and Supplemental Tables S5-S6). None of these associations were pleiotropic, and the leave-one-out method, scatterplot, and funnel plot further supported these results (Supplemental Figures).

Results of the replication cohort

The IVW method showed no causal association between appendectomy and the six gastrointestinal cancers in the replication cohort, including EC (OR: 1.064, 95% CI: 0.574–1.973, $P = 8.442E-01$), GC (OR: 0.902, 95% CI: 0.450–1.808, $P = 7.716E-01$), SIC (OR: 1.213, 95% CI: 0.356–4.136, $P = 7.581E-01$), CRC (OR: 1.271, 95% CI: 0.981–1.648, $P = 6.981E-02$), LC (OR: 0.595, 95% CI: 0.260–1.357, $P = 2.170E-01$), PC (OR: 0.645, 95% CI: 0.312–1.455, $P = 3.149E-01$). Weighted median and MR-Egger methods also found no association between appendectomy and gastrointestinal cancers (Tables 3 and Supplemental Table S7). There was no heterogeneity or pleiotropy in any of the results (Tables 3 and Supplemental Tables S5-S6), and the leave-one-out method, scatterplot, and funnel plot further supported these results (Supplemental Figs).

Exposure	Outcome	Method	SNP(n)	OR(95%CI)	pval	$P_{heterogeneity}$	$P_{pleiotropy}$
Appendectomy (Pan UKBB)	EC (FinnGen)	IVW (fixed effects)	11	0.893(0.435 to 1.831)	7.565E-01	2.492E-01	6.004E-01
	EC (FinnGen)	MR Egger	11	0.446(0.032 to 6.238)	5.637E-01		
	EC (FinnGen)	Weighted median	11	1.012(0.378 to 2.704)	9.817E-01		
	GC (FinnGen)	IVW (fixed effects)	11	0.742(0.461 to 1.195)	2.193E-01	5.876E-01	2.883E-01
	GC (FinnGen)	MR Egger	11	1.689(0.375 to 7.612)	5.125E-01		
	GC (FinnGen)	Weighted median	11	0.904(0.474 to 1.725)	7.593E-01		
	SIC (FinnGen)	IVW (fixed effects)	11	1.185(0.545 to 2.579)	6.684E-01	7.925E-02	6.563E-01
	SIC (FinnGen)	MR Egger	11	2.481(0.090 to 68.387)	6.043E-01		
	SIC (FinnGen)	Weighted median	11	1.849(0.625 to 5.468)	2.666E-01		
	CRC (FinnGen)	IVW (multiplicative random effects)	11	0.931(0.674 to 1.287)	6.661E-01	1.873E-02	2.948E-01
	CRC (FinnGen)	MR Egger	11	0.541(0.197 to 1.484)	2.632E-01		
	CRC (FinnGen)	Weighted median	11	0.891(0.639 to 1.242)	4.963E-01		
	LC (FinnGen)	IVW (fixed effects)	11	1.203(0.596 to 2.426)	6.060E-01	9.498E-01	6.475E-01
	LC (FinnGen)	MR Egger	11	1.997(0.218 to 18.318)	5.557E-01		
	LC (FinnGen)	Weighted median	11	1.041(0.425 to 2.552)	9.295E-01		
	PC (FinnGen)	IVW (fixed effects)	11	1.015(0.650 to 1.583)	9.494E-01	1.357E-01	1.100E-01
	PC (FinnGen)	MR Egger	11	3.865(0.813 to 18.370)	1.233E-01		
	PC (FinnGen)	Weighted median	11	0.886(0.478 to 1.646)	7.027E-01		

Table 2. Causal effects of appendectomy on six gastrointestinal cancers risk in the discovery cohort. SNPs: single nucleotide polymorphisms; EC: esophageal cancer; GC: gastric cancer; SIC: small intestine cancer; CRC: colorectal cancer; LC: liver cancer; PC: pancreatic cancer; IVW: inverse variance weighting; OR: odds ratio; CI: confidence interval.

Exposure	Outcome	Method	SNP(*n*)	OR(95%CI)	pval	$P_{heterogeneity}$	$P_{pleiotropy}$
Appendectomy (FinnGen)	EC (Pan UKBB)	IVW (fixed effects)	5	1.064(0.574 to 1.973)	8.442E-01	7.388E-01	7.050E-01
	EC (Pan UKBB)	MR Egger	5	0.709(0.095 to 5.287)	7.590E-01		
	EC (Pan UKBB)	Weighted median	5	0.869(0.406 to 1.858)	7.173E-01		
	GC (Pan UKBB)	IVW (fixed effects)	5	0.902(0.450 to 1.808)	7.716E-01	2.274E-01	3.695E-01
	GC (Pan UKBB)	MR Egger	5	3.499(0.247 to 49.531)	4.226E-01		
	GC (Pan UKBB)	Weighted median	5	1.235(0.516 to 2.958)	6.359E-01		
	SIC (Pan UKBB)	IVW (fixed effects)	5	1.213(0.356 to 4.136)	7.581E-01	8.253E-01	9.575E-01
	SIC (Pan UKBB)	MR Egger	5	1.084(0.020 to 58.695)	9.709E-01		
	SIC (Pan UKBB)	Weighted median	5	1.025(0.231 to 4.552)	9.740E-01		
	CRC (Pan UKBB)	IVW (fixed effects)	5	1.271(0.981 to 1.648)	6.981E-02	1.822E-01	1.601E-01
	CRC (Pan UKBB)	MR Egger	5	0.593(0.255 to 1.381)	3.125E-01		
	CRC (Pan UKBB)	Weighted median	5	1.331(0.949 to 1.868)	9.728E-02		
	LC (Pan UKBB)	IVW (fixed effects)	5	0.595(0.260 to 1.357)	2.170E-01	1.318E-01	2.226E-01
	LC (Pan UKBB)	MR Egger	5	5.931(0.270 to 130.211)	3.408E-01		
	LC (Pan UKBB)	Weighted median	5	0.832(0.291 to 2.379)	7.317E-01		
	PC (Pan UKBB)	IVW (fixed effects)	5	0.645(0.344 to 1.210)	1.717E-01	6.602E-01	5.208E-01
	PC (Pan UKBB)	MR Egger	5	0.314(0.041 to 2.428)	3.479E-01		
	PC (Pan UKBB)	Weighted median	5	0.674(0.312 to 1.455)	3.149E-01		

Table 3. Causal effects of appendectomy on six gastrointestinal cancers risk in the replication cohort. SNPs: single nucleotide polymorphisms; EC: esophageal cancer; GC: gastric cancer; SIC: small intestine cancer; CRC: colorectal cancer; LC: liver cancer; PC: pancreatic cancer; IVW: inverse variance weighting; OR: odds ratio; CI: confidence interval.

Combined results from the meta-analysis

Finally, we used meta-analysis to more fully assess the causal association between appendectomy and the six gastrointestinal cancers. meta-analysis showed no association between appendectomy and any of the gastrointestinal cancers, including EC (OR: 0.987, 95% CI: 0.618–1.577, $P=9.576E-01$), GC (OR: 0.790, 95% CI: 0.533–1.170, $P=2.390E-01$), SIC (OR: 1.193, 95% CI: 0.619–2.301, $P=5.984E-01$), CRC (OR: 1.125, 95% CI: 0.919–1.378, $P=2.528E-01$), PC (OR: 0.872, 95% CI: 0.607–1.254, $P=4.606E-01$), LC (OR: 0.895, 95% CI: 0.524–1.528, $P=6.844E-01$) (Fig. 2).

Discussion

This is the first TSMR study to assess the causal relationship between appendectomy and gastrointestinal cancers systematically. Based on two TSMR analyses and a final meta-analysis, we found no causal relationship between appendectomy and any of the six gastrointestinal cancers. Our findings further support the conclusions of most observational studies at the genetic level.

As the third most common cancer in the world, CRC, researchers have paid particular attention to the association between appendectomy and CRC. For Asian populations and Americans, numerous studies have found appendectomy to be a risk factor for cancer[39–45]. However, it is very surprising that none of the studies on European populations have found such an association[18,46–48]. Moreover, a meta-analysis by Liu Z et al.[3] showed that appendectomy was a risk factor for CRC in Asian populations (OR: 1.46, 95% CI: 1.04–2.05) versus Americans (OR: 1.68, 95% CI: 1.15–2.44). In contrast, for the European population, this association was not significant (OR:0.94,95%CI:0.87–1.02) in 2022.

In 2023, a study based on a Hong Kong, China population, Shi F et al.[49] found that appendectomy caused gut microbial dysbiosis with significant enrichment of cancer-promoting bacteria and depletion of beneficial commensals, and altered the correlations among bacteria and their functional pathways, which contribute in part to the appendectomy-associated increased CRC development. Therefore, further research is needed on the association between appendectomy and gastrointestinal cancers in different populations. When the study took into account CRC staging and gender stratification, Rothwell JA et al.[48] found, based on three large prospective studies of more than 590,000 participants from Europe, that appendectomy was associated with a reduced risk of CRC in women. However, not men, and they also found that appendectomy was associated with a reduced risk of colon cancer and distal colon cancer in women. Due to data limitations, we were not able to conduct an TSMR study of appendectomy and CRC stratified and typed by gender. We also need more studies to determine this association, which would be very meaningful.

Observational studies have reached different conclusions regarding the causal relationship between appendectomy and GC. In 2003, Cope JU et al.[7] showed an increased incidence of GC after appendectomy in Swedish children. Song H et al.[6] later found no association between appendectomy and GC, also based on a Swedish population. A study by Wu S-C et al.[17] on an Asian population also found that appendectomy was not associated with GC. Our study also found no causal association between appendectomy and GC.

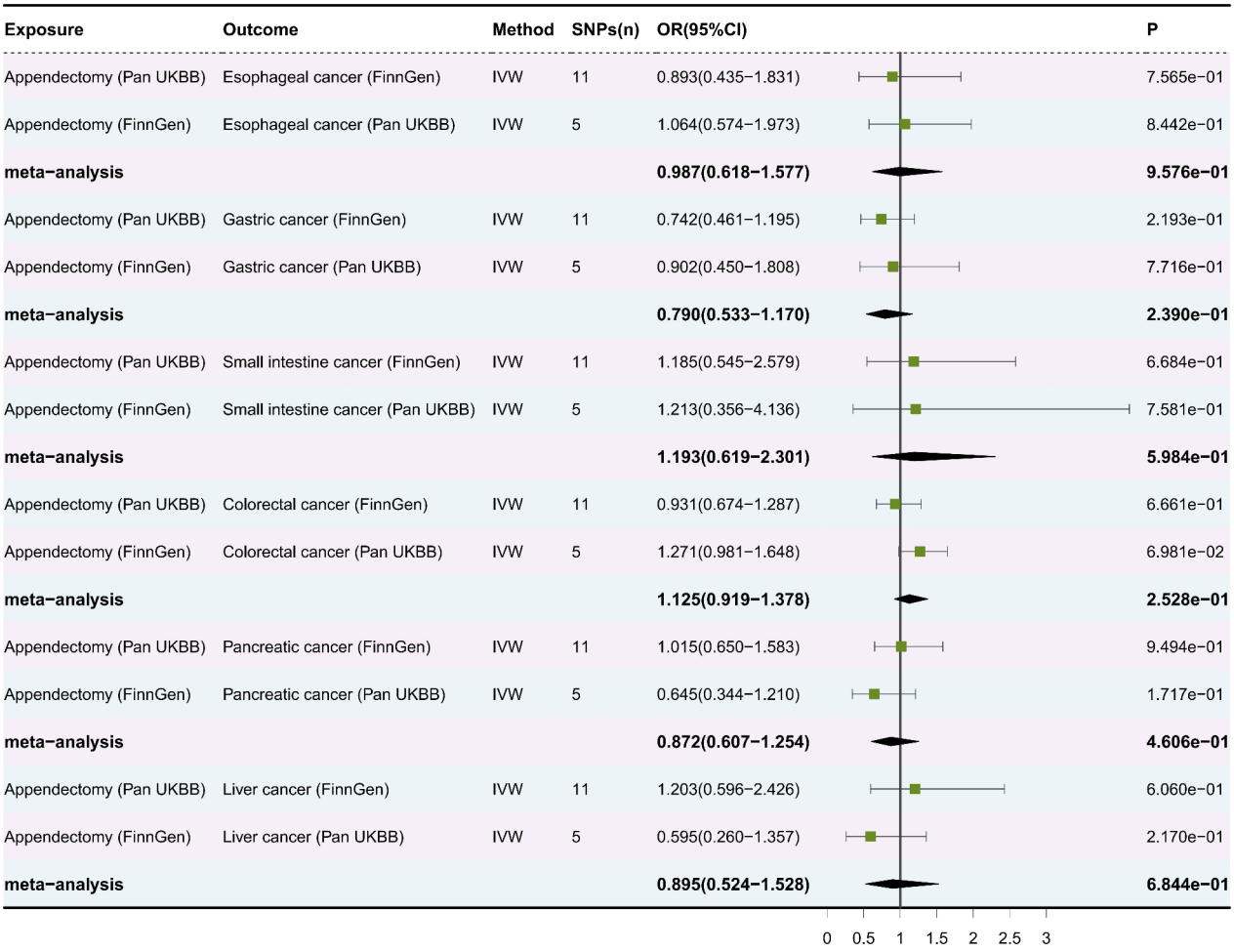

Fig. 2. Forest plot of meta-analysis of causal estimation of appendectomy for six gastrointestinal cancers. SNPs: single nucleotide polymorphisms; OR: odds ratio; CI: confidence interval; IVW: inverse variance weighting; P: pval.

Regarding the relationship between appendectomy and PC, the results of all observational studies were consistent and no causal relationship was found between appendectomy and PC[16], which is consistent with our findings.

Fewer studies have examined appendectomy and EC, LC, and SIC, but the available studies are consistent with our results, and none have found a causal association. However, after Song H et al.[6] analysed subtypes of EC, they found that patients with appendectomy had an increased risk of esophageal adenocarcinoma but a decreased risk of oesophageal squamous cell carcinoma. This may be because Song H et al. did not adjust for important confounders such as body weight and smoking. This association may require further study.

Results in our discovery and replication cohorts were consistent, with neither finding a causal relationship between appendectomy and gastrointestinal cancers. This finding remains stable after meta-analysis combining their causal associations. Moreover, our findings are consistent with those of most observational studies. However, it is very important to note that the association between appendectomy and gastrointestinal cancer subtypes needs to be determined in larger studies.

Studies have shown that the appendix may play a more important role than previously thought, and keeping the appendix may have a biological role. Considering these reasons, it is prudent for clinicians to reconsider various alternative methods of appendectomy to treat acute appendicitis to turn to internal medicine and preserve the appendix. The 2020 update of the World Society of Emergency Surgery Jerusalem guidelines presents non-operative management of appendicitis with antibiotics as a safe alternative to surgery in adult and pediatric populations in selected patients with uncomplicated acute appendices and an absence of appendix[50,51]. Recent trials and meta-analyses show that people who only use antibiotics for drug treatment may increase complications and recurrence rates[52,53]. Some studies show that the risk of malignant tumors still increases after non-surgical treatment of appendicitis, which is attributed to the fact that appendicitis may be secondary to tumor lesions, and surgical intervention can play a role in the definitive management of possible precancerous lesions[54,55]. Our study did not find an association between appendectomy and gastrointestinal cancer in the European population. This is more likely to suggest that clinicians should use surgical intervention rather than

medication when treating European populations. Of course, given the contradictory evidence, the surgeon still needs to weigh the decision to treat acute appendicitis to make a personalized management plan, considering the factors of disease, surgeon, and patient. However, for non-European people, it is difficult for our research to give straightforward suggestions. In the future, more relevant research is needed to explore the causal relationship between appendectomy and gastrointestinal cancer in non-European populations. At the same time, our research suggests that researchers and clinicians should pay attention to the heterogeneity of the population in their research or clinical treatment.

Much effort was put into preventing instrumental variables from influencing the study results through confounding factors. We screened SNPs with very stringent criteria. SNPs associated with confounders that may lead to gastrointestinal cancers, such as insomnia and waist circumference adjusted for body mass index, were excluded through LDtrait website screening. Therefore, we excluded them to ensure reliable results. In addition, we performed MR-PRESSO to remove aberrant SNPs, Cochran's Q-test to detect heterogeneity, and MR-Egger intercept test to detect the presence of horizontal pleiotropy. The stability of our results was also further demonstrated by using the leave-one-out method and other methods. Finally, meta-analysis was used to assess the combined causal effect of appendectomy and gastrointestinal cancers comprehensively. The above methods are mainly effective in reducing potential bias and ensuring the reliability of the results.

Our study has several strengths. First, this study is the first TSMR study to assess the causal relationship between appendectomy and gastrointestinal cancers, and the advantage of the MR design in directly detecting causality avoids confounders and reverse causality compared with observational studies. Second, almost all common gastrointestinal cancers were included in this study. This study provides the most systematic assessment of the risk of developing gastrointestinal cancers in appendectomised patients. Third, we used meta-analyses to comprehensively assess causal effects to ensure the reliability of our results.

Of course, we recognize that our study has some limitations. Firstly, due to GWAS data limitation, we did not obtain a large number of SNPs when selecting IVs, which may have impacted the results. Second, our study was conducted in populations of European descent, while the situation in non-European descent remains to be determined. Therefore, caution is needed when using our findings in populations of different races and ethnicities. Finally, due to data limitations, we could not conduct further subgroup analyses for variables such as gender, age, and region.

Conclusion

This comprehensive TSMR analysis shows that appendectomy is not associated with gastrointestinal cancers in the European population. Patients undergoing appendectomy need not be overly concerned about this risk. There is also no need for deliberate, long-term monitoring of the risk of gastrointestinal cancers beyond the normal physical examination to avoid additional psychological and financial burdens. Surgeons still need to weigh the decision to treat acute appendicitis. However, for non-European populations, more studies must determine this association, which should not be overlooked.

Data availability

Data Availability: The data used in this paper were obtained from free database downloads and have been described explicitly in the text. Further inquiries can be directed to the corresponding author.

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Author contributions

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Declarations

Conflict of interest

The authors declare that they have no conflicts of interest to declare.

Ethical approval

There was no need to get informed consent or ethical approval for this study again because all of the data were taken from published sources, and the informed consent and approval were received.

Additional information

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