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Research Paper

Risk of irritable bowel syndrome in patients who underwent appendectomy: A nationwide population-based cohort study

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ABSTRACT

Background: Appendectomy is one of the most common surgical procedures; however, the possible long-term consequences have not been fully explored. The appendix has been associated with microflora of the gut and immune functions. However, literature examining the relationship between prior appendectomy and the risk of irritable bowel syndrome (IBS) is lacking. The aim of this study was to evaluate the risk of irritable bowel syndrome for patients who underwent appendectomy by using a nationwide longitudinal population-based cohort.

Methods: Data from this study was collected from Taiwan's National Health Insurance Research Database (NHIRD), a population-based database. We identified 12,760 patients who underwent appendectomy between January 1, 2000 and December 31, 2012. A total of 9236 patients who had appendectomy (case group) were randomly matched with 9236 patients who had not undergone appendectomy (control group) in a ratio of 1:1 by means of propensity scores. The hazard ratio (HR) of IBS was calculated by multiple Cox regression. Furthermore, sensitivity test and stratified analysis were performed.

Findings: The incidence rate of IBS was 51.30 per 10,000 person-years in patients having appendectomy, more than the 35.28 per 10,000 person-years in patients not having appendectomy. Patients who underwent appendectomy had 1.46-fold risk of IBS compared to patients not having appendectomy (HR, 1.46; 95% CI, 1.24−1.72). Stratified analysis revealed that the higher HR of 1.55 (95% CI, 1.18−2.04) in patients <40 years old, and particularly within the first 5 years follow-up period of undergoing appendectomy. In addition, patients diagnosed with fibromyalgia had a greater risk of suffering IBS after appendectomy (HR, 1.41; 95% CI, 1.04−1.92).

Interpretation: Patients with appendectomy have a higher incidental risk of IBS than the control population. The risk is higher for patients under 40 years old and those who received appendectomy within 5 years. Physicians could take this into consideration for treatment plans of patients who have underwent this surgery. Further research on the pathogenesis of this association is required.

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1. Introduction

Appendectomy is one of the most frequently performed surgical interventions worldwide. Previous research that was conducted using the NHIRD has shown that the overall incidence of appendicitis in Taiwan was 107.76 per 100,000 per year [1]. However, studies have shown that the appendix can be an important part of the immune

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Research in context

Evidence before this study

Before the start of this study in August 2019, we searched PubMed with combinations of the terms "appendectomy" and "IBS" without language restrictions. Appendectomy is a very common surgery, and there are quite a numberof studies on IBS. Literature suggests that certain surgeries such as hysterectomy and cholecystectomy increase risk of IBS. To date, research to evaluate the relationship between appendectomy and IBS risk is scarce.

Added value of this study

This study showed a significantly increased risk of IBS after appendectomy, especially for patients under 40 years old. To our knowledge, this is the first epidemiological study to use a nationwide longitudinal population-based dataset to identify an association between prior appendectomy and IBS risk.

Implications of all the available evidence

Our research provides evidence of an association between prior appendectomy and subsequent risk of IBS. Clinicians should be aware of IBS among patients undergoing appendectomy and provide appropriate monitoring for any symptoms of IBS following appendectomy. Future research with metagenomic approaches to investigate the role of the gut microbiome in patients undergoing appendectomy is suggested to elucidate the underlying mechanism of this association.

functioning of humans [2]. The appendix has been significantly associated with recurrent Clostridium difficile infection [3], as well as being able to provide support for growth of commensal microbiota and possibly facilitate re-inoculation of the gut following gastrointestinal infections. So the appendix is known as a "safe house" for normal gut flora [4,5]. Moreover, gut-associated lymphoid tissue (GALT) is highly concentrated in the appendix of multiple species, including homosapiens [6,7]. Appendectomy might also alter the immune function, studies have examined the association between antecedent removal of appendix and the risk of autoimmune disease such as systemic lupus erythematosus [8], rheumatoid arthritis [9], inflammatory bowel disease [10] and cancers [11,12].

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder that is characterized by recurrent abdominal pain and altered bowel habit, with occurrences of diarrhea, constipation, or both [13–15]. IBS poses negative impacts on patients' quality of life, manifested by poorer physical, mental and social functions [16–18]. Health-related Quality of Life impairment in IBS patients have been shown to be comparable or even more severe than other severe chronic organic diseases like inflammatory bowel disease, gastroesophageal reflux disease, diabetes, hypertension and end-stage renal failure [19–22]. A study has shown that IBS symptoms severity is associated with lower richness of intestinal microbiota such as Bifidobacterium and Faecalibacterium [23]. Studies have also suggested that those who have changes in the gut microbiome and promote increased intestinal permeability seem more likely to develop IBS [24].

A study showed that symptoms suggestive of IBS arise de novo in 10% after women went through hysterectomy [25]. Another study also showed that IBS followed after hysterectomy and tubular ligation in 5% and 8% of cases respectively [26]. This suggests that there may be possibility of IBS arising post-surgery. Also, a study in the UK showed that cholecystectomy might cause IBS-like symptoms [27]. Most data exist on hysterectomy and cholecystectomy but there is little information about appendectomy. The short-term complications of appendectomy are well-researched, whereas limited long-term complications have been investigated [28]. The aim of this study was to evaluate the risk of IBS diagnosis after going through appendectomy by analyzing a nationwide population-based retrospective cohort from the National Health Insurance Research Database (NHIRD).

2. Methods

2.1. Data source

National Health Insurance Research Database (NHIRD) has been being built since 1995. The Longitudinal Health Insurance Database (LHID) is a randomly selected subset of the NHIRD, which consists of comprehensive de-identified medical records of 1 million people who participated in government-run single-payer National Health Insurance (NHI). The database contains data on demographics, medical history of outpatients and inpatients, details of use of prescription drugs and other medical services. Diagnoses and procedures were defined based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9CM) codes. The Research Ethics Committee of China Medical University and Hospital in Taiwan approved the study (CMUH-104-REC2-115-R3).

2.2. Study population

To assess the association of appendectomy (ICD-9-CM Procedure Code: 47.0 and 47.1) with irritable bowel syndrome (ICD-9-CM: 564.1), 12,760 patients who underwent appendectomy between January 1, 2000 and December 31, 2012 were identified, and patients with medical records of colon cancer (ICD-9-CM: 140–208), inflammatory bowel disease (ICD-9-CM: 555 and 556) before appendectomy and during the timeframe 2000–2012 or aged less than 20 years were excluded. In order to assure the validity of inclusion of patients who suffered from IBS after appendectomy, patients who were diagnosed with IBS at least twice in outpatient visits or at least once in hospitalization after the index date, which was the date of the appendectomy and the starting date of the follow-up period, were recognized as IBS patients after appendectomy.

The covariates of comorbidity comprised of diabetes mellitus (ICD-9-CM: 250), hypertension (ICD-9-CM: 401–405), hyperlipidemia (ICD-9-CM: 272.0–272.4), obesity (ICD-9-CM: 278), interstitial cystitis (ICD-9-CM: 595), fibromyalgia (ICD-9-CM: 729.1), gastroesophageal reflux disease (ICD-9-CM: 530.81), diarrhea (ICD-9-CM: 787.91), urinary stones (ICD-9-CM: 592 and 594), and asthma (ICD-9-CM: 493), and patients diagnosed with any of the comorbidities more than once in outpatient visits or at least once in hospitalization before the index date were included in the study.

2.3. Statistical analysis

A total of 9236 patients who had appendectomy (case group) were randomly matched with 9236 patients who had not underwent appendectomy (control group) in a ratio of 1:1 by means of propensity scores, which were made up of gender, age, year of index date, and comorbidities listed above. The end date of the follow-up period was the date on which IBS occurred in patients, patients died, or patients withdrew from NHIRD, or Dec.31, 2012.

To allow the case group to be comparable with the control group and to reduce confounding bias between them, propensity score matching (PSM) was performed. Logistic regression was used to estimate each patient's propensity score, which is a probability of allocating a patient to one of the groups. Analysis of categorical and continuous data was conducted by Chi-square test and Student's *t*-test to address hypothesis testing for differences between groups,

respectively. Sub-analyses stratified by sex, age group, comorbidity and years of follow-up were also performed to assess the association between appendectomy and the subsequent risk of IBS.

Probability were estimated by Kaplan–Meier method, and differences in time-to-event distributions between groups were compared by log-rank tests. Hazard ratios (HRs), adjusted hazard ratios (aHRs), and 95% confidence intervals (95% CIs) for the association between appendectomy, including the subgroup stratified by age and time since appendectomy and the incidental risk of IBS were calculated by Cox proportional hazard models. The significant criterion was set at a 2-tailed p-value < 0.05. All data were analyzed using SAS 9.4 software (SAS Institute Inc., Cary, NC) and cumulative incidence curves were plotted in R software.

2.4. Role of funding

The funders had no role in study design, data collection, data analysis, data interpretation, and the writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

2.5. STROBE guidelines

This article adheres to STROBE guidelines.

3. Results

In Table 1, 18,472 patients were included in the analysis, among which 8897 patients were female (48.2%) and 9575 patients were male (51.8%). Age was classified into three categories as < 40 years, 40–65 years, and ≥ 65 years, and there were 9287 patients in the < 40 years age group (50.3%), 6977 patients in the 40–65 years age group (37.6%), and 2208 patients in the ≥ 65 years age group (12.0%).

In terms of comorbidities, there were 1953 patients with fibromyalgia (21.1%), 1917 patients with hypertension (20.8%), 1185 patients with hyperlipidemia (12.8%), 1008 patients with interstitial cystitis (10.9%), 932 patients with diabetes mellitus (10.1%), 716 patients with urinary stones (7.8%), 648 patients with asthma (7%), 77 patients with obesity (0.8%), 61 patients with gastroesophageal reflux disease (0.7%), and 39 patients with diarrhea (0.4%) in appendectomy group before propensity score matching. All the above are listed in Table 1. The Kaplan–Meier curves are shown in Fig. 1. The probability of IBS was higher in patients that had appendectomy than in patients that did not undergo appendectomy, and the log-rank test for comparison of probability curves gave a p-value of <0.001. There were 239 events of IBS without appendectomy, and 335 events of IBS after undergoing appendectomy. The incidence rate of IBS was 51.30 per 10,000 person-years in patients having appendectomy, more than the 35.28 per 10,000 person-years in patients not having appendectomy. The median of follow-up year (to the first occurrence of IBS) are shown as median (Q1, Q3), for the appendectomy cohort it is 6.90 (3.92, 10.70), for without appendectomy it is 7.30 (3.64, 10.50).

Table 2 displays results of Cox proportional hazard models in several demographic characteristics. After adjustment, patients who underwent appendectomy had 1.46-fold risk of IBS compared to patients not having appendectomy (HR, 1.46; 95% CI, 1.24–1.72), and the risk of suffering from IBS was less in males (HR, 0.88; 95% CI, 0.74–1.05) than females. There was a trend that older patients were at a higher risk of IBS, those that were 40–65 years old (HR, 1.36; (95% CI, 1.11–1.66) and over 65 years old (HR, 1.63; 95% CI, 1.23–2,17). Moreover, patients diagnosed with hypertension (HR, 1.52; 95% CI, 1.22–1.91), obesity (HR, 2.26; 95% CI, 1.23–4.14), fibromyalgia (HR, 1.47; 95% CI, 1.22–1.77), diarrhea (HR, 2.98; 95% CI, 1.11–7.99), and urinary stones (HR, 1.54; 95% CI, 1.20–1.98), had greater risks of suffering IBS.

Furthermore, comparison of incidence rates of IBS between the case group and the control group in stratified analysis are summarized in Table 3. Patients who had appendectomy had significantly higher risk of IBS than who did not have appendectomy regardless of gender (HR, 1.48; 95% CI, 1.18–1.86; p-value < 0.001 in female and HR, 1.41; 95% CI, 1.11–1.80; p-value < 0.01 in male). Patients aged < 40 years and aged between 40 and 65 years in the case group also had significantly higher risk of IBS than those in the control group (HR, 1.55; 95% CI, 1.18–2.04; p-value < 0.01 in < 40 years and HR, 1.42; 95% CI, 1.11–1.82; p-value < 0.01 in 40–65 years). However, it was not found in patients aged > 65 years. Patients <40 years have the highest risk of IBS when compared with patients in the 40–65 years and >65 years age groups. Patients with fibromyalgia in the case group were at

Table 1
Demographic characteristics and comorbidities of patients with appendectomy in Taiwan during 2000-2012

Variable	Before PSM			After PSM		
	Non-appendectomy n=615595 n (%)/mean (SD)	Appendectomy n=9236 n (%)/mean (SD)	p value	Non-appendectomy n=9236 n (%)/mean (SD)	Appendectomy n=9236 n (%)/mean (SD)	p value
Gender			0.002			0.96
Female	306,515 (49.8)	4450 (48.2)		4447 (48.1)	4450 (48.2)	
Male	309,080 (50.2)	4786 (51.8)		4789 (51.9)	4786 (51.8)	
Age at baseline			<0.001			0.90
<40	278,654 (45.3)	4650 (50.3)		4637 (50.2)	4650 (50.3)	
40–65	260,418 (42.3)	3475 (37.6)		3502 (37.9)	3475 (37.6)	
≥65	76,523 (12.4)	1111 (12)		1097 (11.9)	1111 (12.0)	
Mean(SD)‡	44.2 (16.1)	42.7 (16.3)	<0.001	42.8 (16.2)	42.8 (16.3)	0.87
Baseline comorbidity						
Diabetes mellitus	63,908 (10.4)	932 (10.1)	0.36	934 (10.1)	932 (10.1)	0.96
Hypertension	126,895 (20.6)	1917 (20.8)	0.74	1911 (20.7)	1917 (20.8)	0.91
Hyperlipidemia	80,240 (13)	1185 (12.8)	0.56	1145 (12.4)	1185 (12.8)	0.38
Obesity	4661 (0.8)	77 (0.8)	0.40	67 (0.7)	77 (0.8)	0.40
Interstitial cystitis	53,606 (8.7)	1008 (10.9)	<0.001	1012 (11.0)	1008 (10.9)	0.92
Fibromyalgia	119,633 (19.4)	1953 (21.1)	<0.001	1965 (21.3)	1953 (21.1)	0.83
Gastroesophageal reflux disease	3235 (0.5)	61 (0.7)	0.08	58 (0.6)	61 (0.7)	0.78
Diarrhea	1741 (0.3)	39 (0.4)	0.01	31 (0.3)	39 (0.4)	0.34
Urinary stones	38,024 (6.2)	716 (7.8)	<0.001	718 (7.8)	716 (7.8)	0.96
Asthma	40,390 (6.6)	648 (7)	0.08	629 (6.8)	648 (7.0)	0.58

*Chi-square test, Student's t test‡
*Abbreviate: SD, standard deviation;
*Gender, age and comorbidities as covariates listing in Table 1 were included in the matching model.

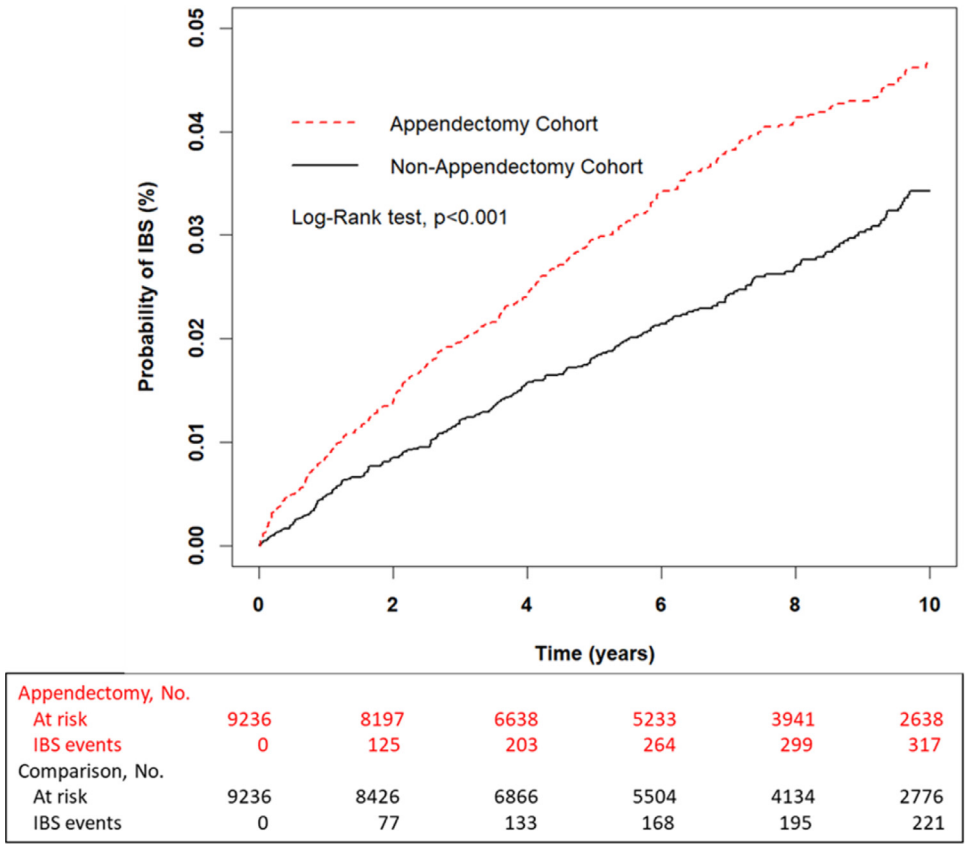

Fig. 1. Probability of irritable bowel syndrome in patients with appendectomy.

significantly greater risk of IBS than those in the control group as well (HR, 1.41; 95% CI, 1.04–1.92; *p*-value < 0.05).

In Table 4, comparison between the case group and the control group was performed in the follow-up years and among different age groups. In < 40 years age group, the case group had significantly higher risk of IBS than the control group in the first 2-years follow-up group. (HR, 1.83 95% CI, 1.09–3.07; *p*-value < 0.05 in the first 2-year follow-up). In the 40–65 years age group, the case group had significantly higher risk of IBS than the control group in the first 2-year and 2 to 5-year follow-up. (HR, 1.56; 95% CI, 1.04–2.36; *p*-value< 0.05 in the first 2-year follow-up and HR, 1.76; 95% CI, 1.13–2.74; *p*-value < 0.05 in the 2 to 5-year follow-up).

4. Discussion

We noted that there was a 1.46-fold higher risk of IBS, especially higher in patients aged < 40 years and particularly within the first

Table 2
Multiple Cox proportional hazard regression for the estimation of hazard ratios for irritable bowel syndrome.

Characteristics	Event	Person	IR	Univariable		Mutivariable	
	(*n*=574)	years		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Appendectomy							
No	239	67,747	35.28	Ref.		Ref.	
Yes	335	65,305	51.30	1.45(1.23–1.71)	<0.001	1.46(1.24–1.72)	<0.001
Gender							
Female	309	64,763	47.71	Ref.		Ref.	
Male	265	68,289	38.81	0.81(0.69–0.95)	0.012	0.88(0.74–1.05)	0.156
Age at baseline							
<40	212	71,981	29.45	Ref.			
40–65	257	48,519	52.97	1.77(1.48–2.12)	<0.001	1.36(1.11–1.66)	0.003
≥65	105	12,552	83.65	2.72(2.15–3.44)	<0.001	1.63(1.23–2.17)	<0.001
Baseline comorbidity							
Diabetes mellitus	100	11,329	88.27	2.20(1.77–2.73)	<0.001	1.22(0.95–1.57)	0.118
Hypertension	200	23,448	85.30	2.43(2.05–2.89)	<0.001	1.52(1.22–1.91)	<0.001
Hyperlipidemia	113	13,403	84.31	2.10(1.71–2.58)	<0.001	1.16(0.91–1.47)	0.232
Obesity	11	748	147.02	3.26(1.79–5.92)	<0.001	2.26(1.23–4.14)	0.008
Interstitial cystitis	86	12,849	66.93	1.61(1.28–2.02)	<0.001	1.22(0.96–1.55)	0.112
Fibromyalgia	168	23,087	72.77	1.89(1.58–2.27)	<0.001	1.47(1.22–1.77)	<0.001
Gastroesophageal reflux disease	5	399	125.36	2.52(1.04–6.08)	0.040	1.60(0.66–3.89)	0.298
Diarrhea	4	229	175.00	3.45(1.29–9.24)	0.014	2.98(1.11–7.99)	0.030
Urinary stones	76	9179	82.80	2.02(1.58–2.57)	<0.001	1.54(1.20–1.98)	<0.001
Asthma	57	7696	74.06	1.74(1.32–2.28)	<0.001	1.17(0.88–1.56)	0.268

*Abbreviation: HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Table 3
Subgroup analysis of hazard ratios (95% CI) stratified by age, sex and comorbidities groups.

Variables	Non-Appendectomy cohort			Appendectomy cohort			HR
	n=9236			*n*=9236			
	Event	Person years	IR	Event	Person years	IR	(95% CI)
Gender							
Female	127	32,978	38.51	182	31,785	57.26	1.48(1.18−1.86)***
Male	112	34,769	32.21	153	33,519	45.65	1.41(1.11−1.80)**
Age at baseline							
<40	84	36,336	23.12	128	35,645	35.91	1.55(1.18−2.04)**
40-65	109	24,851	43.86	148	23,668	62.53	1.42(1.11−1.82)**
≥65	46	6560	70.12	59	5992	98.46	1.39(0.95−2.04)
Baseline comorbidity							
Diabetes mellitus	49	5840	83.91	51	5489	92.91	1.11(0.75−1.64)
Hypertension	93	12,132	76.66	107	11,316	94.55	1.22(0.93−1.62)
Hyperlipidemia	56	6778	82.62	57	6625	86.04	1.03(0.71−1.49)
Obesity	5	370	135.15	6	378	158.63	1.18(0.36−3.89)
Interstitial cystitis	42	6585	63.78	44	6264	70.25	1.10(0.72−1.68)
Fibromyalgia	71	11,775	60.30	97	11,312	85.75	1.41(1.04−1.92)*
Gastroesophageal reflux disease	2	196	102.20	3	203	147.66	1.49(0.25−8.95)
Diarrhea	1	102	98.44	3	127	236.25	2.54(0.26−24.48)
Urinary stones	32	4694	68.18	44	4486	98.09	1.43(0.91−2.26)
Asthma	24	3905	61.46	33	3791	87.05	1.40(0.83−2.37)

*Abbreviation: IR, incidence rates, per 100,000 person-years; HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.
*p-value <0.05; * *p-value <0.01; ***p-value<0.001.

5 years follow-up period of undergoing appendectomy. Patients with fibromyalgia were at higher risk of IBS after appendectomy. Studies have highly associated IBS and fibromyalgia, and suggest common pathogenetic mechanism [29,30]. Therefore, development of IBS post-appendectomy may be associated with fibromyalgia. To the best of our knowledge, this is the first epidemiological study to use a nationwide longitudinal population-based dataset to identify an increased IBS risk among patients with prior appendectomy. These results highlight that physicians should be aware of IBS among patients undergoing appendectomy.

The pathophysiology underlying the relationship between an appendectomy and subsequent IBS remains uncertain. The appendix is the primary site of production of secretory immunoglobulin A [31], which binds to pathogenic bacteria with high affinity and promoting their elimination [32]. Nevertheless, it also binds to the commensal gut flora with low affinity and has a crucial role in host protection. Therefore, the appendix plays an important role in regulating the size and composition of the gut microbiota [32]. The function of the appendix is to act as a reservoir of commensal flora to rapidly re-inoculate the gut through biofilm regeneration and shedding after diarrheal infections [32,33]. By removal of the appendix, an immune organ and a reservoir of beneficial flora, may change the mucosal immunity, resulting in low-grade mucosal inflammation and altered gut permeability that contribute to the pathogenesis of IBS [34,35]. More research needs to be done on the causation between the absence of appendix and gut health.

The strength of our study is that the population-based data from National Research Insurance Research Database (NHIRD) is representative of the general population. Nonetheless, there are several limitations to be noted. Firstly, the NHIRD does not contain information regarding lifestyles and habits of patients, such as diet preference and body mass index, which may be associated risk factors for the development of IBS. However, we have accounted for comorbidities that may be the consequences of lifestyle and habits that could be associated risk factors. For example, COPD may be associated with smoking habits and cardiovascular diseases could be associated with diet. However, these unmeasured confounding factors could have led to potential bias from this retrospective cohort study when compared with randomized trials.

Secondly, there may be inaccuracy in the diagnosis of IBS. While there is no confirmatory test for IBS, according to our observations about general practice patterns in Taiwan, most clinicians using Rome III criteria after 2006 and Rome II criteria before 2006 to allow

Table 4
Incidence and hazard ratio of IBS stratified by follow-up year.

Variables	Non-Appendectomy cohort			Appendectomy cohort			HR
	n=9236			*n*=9236			
	Event	Person years	IR	Event	Person years	IR	(95% CI)
Patients less than 40 years of age							
<2	22	9073	24.25	40	9021	44.34	1.83(1.09−3.07)*
2-5	28	11,445	24.46	40	11,276	35.47	1.45(0.89−2.35)
≥5	34	15,817	21.50	48	15,348	31.27	1.46(0.94−2.26)
Patients aged 40−64 years							
<2	38	6803	55.85	58	6630	87.48	1.56(1.04−2.36)*
2-5	31	8138	38.09	52	7775	66.88	1.76(1.13−2.74)*
≥5	40	9910	40.36	38	9263	41.02	1.02(0.65−1.59)
Patients more than 65 years of age							
<2	17	2064	82.35	27	1966	137.33	1.66(0.91−3.05)
2−5	12	2260	53.11	22	2083	105.62	1.99(0.98−4.02)
≥5	17	2236	76.03	10	1943	51.46	0.68(0.30−1.48)

*Abbreviation: IR, incidence rates, per 10,000 person-years; HR, hazard ratio; CI, confidence interval.
*p-value <0.05; * *p-value <0.01; ***p-value<0.001.

diagnoses to be made [14]. The diagnosis of IBS was entirely dependent on the ICD-9 codes in the administrative dataset. Therefore, validation of the accuracy of diagnosis could not be verified by personal review of medical records and may have resulted in misclassification. Although a large database could potentially solve this problem [36], it is still worth noting that these misclassifications are more likely to be random, and the associations are often underestimated rather than overestimated. Moreover, Taiwan's NHI administration has established an ad hoc committee to monitor the accuracy of claims data to prevent violations. In addition, we only selected subjects that were repeatedly coded to increase the validity and accuracy of the diagnoses. Based on the published epidemiologic study of IBS in Taiwan's NHIRD [37], we believed that including patients with a single diagnosis of IBS in an outpatient visit or a hospitalization may increase the rate of false-positives of IBS patients, and 3 or more diagnoses might increase the rate of false-negative diagnoses in both cohorts. Other studies using the NHIRD dataset have also used the same code of IBS and similar criteria of at least 2 consensus diagnoses [37–39]. Nonetheless, this study might apply to patients with moderate to severe IBS with presentable symptoms. Some IBS patients with milder symptoms who did not seek repeated medical visits were not enrolled and might reduce the number of patients with IBS, thereby reducing the power in statistical analysis. We can only ensure that patients with IBS diagnostic code before appendectomy were excluded. However, we cannot account for mild IBS or patients who do not seek healthcare support, this might bias the results. Moreover, we have excluded patients with colon cancer and inflammatory bowel disease but IBS-like cases such as symptomatic diverticular disease might have been misclassified into the IBS event in our study. Since diverticular disease is uncommon in Taiwan, the effect on our results may be limited.

Thirdly, our research has included some patients with fibromyalgia in the study population that might affect the interpretation. Previous studies have shown that IBS is highly correlated with fibromyalgia, where prevalence of fibromyalgia in IBS patients can range from 28% to 65% [40]. Research has also shown that fibromyalgia and IBS have common pain inhibitory dysfunctions [41]. The reduced conditioned pain modulation can be an important part of the pathophysiology in IBS [42]. A previous study also using the NHIRD found that fibromyalgia was associated with increased risk for IBS [39]. Fibromyalgia patients who were not diagnosed with IBS prior to surgery may indicate mild IBS with symptoms that were not severe enough to be diagnosed by clinicians. We have used propensity score matching, including this comorbidity, to minimize discrepancy. However, it cannot be completely ruled out that some fibromyalgia were cases of mild IBS that were not diagnosed. This might be interpreted as appendectomy would increase severity of IBS leading to an IBS diagnosis or postsurgical consultation may increase the probability of IBS diagnosis of pre-existing symptoms. Fourthly, the NHIRD does not include histological assessments, therefore pathological findings upon appendectomy cannot be provided. Relevant clinical information, such as laboratory data, imaging findings, or gut microbiota assessment were unavailable for further validation. Another limitation is that it cannot be proven whether the removed appendices were inflamed. Based on the research using similar diagnostic criteria of appendectomy events in recently published Taiwan's NHIRD studies [8,9,12,43,44], the appendectomy procedure codes recorded by the NHIRD database were reliable. Nevertheless, our research cannot provide answers to the problem of unnecessary appendectomy. Finally, it remains uncertain whether the finding in our study can be extended to other ethnic groups, as the majority of the patients were Taiwanese. Clinical studies should be conducted in patients from other races and countries to support the relationship.

There is growing evidence that show that non-operative management with antibiotics may be an effective and safe treatment for acute uncomplicated appendicitis in children and adults [33,45]. Our research provides evidence of an association between prior appendectomy and subsequent risk of IBS. Hence, we recommend that the optimal management for appendicitis should be chosen and a need for thoughtful consideration before performing incidental or prophylactic appendectomy. Furthermore, patients undergoing appendectomy should be monitored and followed-up for any symptoms of IBS.

Patients who have undergone appendectomy have a higher incidental risk of IBS than the control population. The risk is higher for patients under 40 years old and those who received appendectomy within 5 years. Future prospective studies with metagenomic approaches to investigate the role of the gut microbiome in patients undergoing appendectomy are warranted to elucidate the possible pathogenetic mechanisms underlying these associations.

Declaration of Competing Interest

None.

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