Research Paper

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

Chi-Ya Yang,1, Meng-Che Wu,b,1, Mei-Chen Lin,c,d, James Cheng-Chung Wei,e,f,g,h,*

a School of Medicine, Chung Shan Medical University, Taichung, Taiwan
b Division of Gastroenterology, Children’s Medical Center, Taichung Veterans General Hospital, Taichung, Taiwan
c Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan
d College of Medicine, China Medical University, Taichung, Taiwan
e Department of Rheumatology, BenQ Medical Center, The Affiliated BenQ Hospital of Nanjing Medical University, Nanjing, China
f Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China
g Department of Allergy, Immunology & Rheumatology, Chung Shan Medical University Hospital; Institute of Medicine, College of Medicine, Chung Shan Medical University, Taichung, Taiwan
h Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan

ARTICLE INFO

Article History:
Received 7 December 2019
Revised 1 May 2020
Accepted 1 May 2020
Available online 20 June 2020

Keywords:
Appendectomy
IBS
Irritable bowel syndrome
Nation-wide
Insurance
Population
Cohort

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 microbiota 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 undergone this surgery. Further research on the pathogenesis of this association is required.

Funding: This work was supported by grants from the Ministry of Health and Welfare, Taiwan (MOHW108-TDU-B-212-133004), China Medical University Hospital, Academia Sinica Stroke Biosignature Project (BM10701010021), MOST Clinical Trial Consortium for Stroke (MOST 108-2321-B-039-003-), Tseng-Lien Lin Foundation, Taichung, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.

© 2020 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/)

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 system.
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: 577.91), 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 years (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 a 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, 1.12–2.17). 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), diabetes (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 male 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                      | Non-appendectomy | Appendectomy | p-value |
|-------------------------------|------------------|--------------|---------|
| Gender                        | Before PSM       | After PSM    |         |
|                               | n=615955 | n=9236 |         | n=9236 | n=9236 |         |
|                               | n (%) | mean (SD) | n (%) | mean (SD) | n (%) | mean (SD) |         |
| Female                        | 306,515 | 49.8    | 4450  | 48.2    | <0.001 | 4447  | 48.1    | 4450   | 48.2 |
| Male                          | 309,080 | 50.2    | 4786  | 51.8    |         | 4789  | 51.9    | 4786   | 51.8 |
| Age at baseline               |                  |              |        |         |         |        |         |        |      |
| < 40                           | 278,654 | 45.3    | 4650  | 50.3    | <0.001 | 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  | 12.0    | <0.001 | 1097  | 11.9    | 1111   | 12.0 |
| Mean(SD)                      | 442    | 16.1    | 42.7  | 16.3    |         | 42.8  | 16.2    | 42.8   | 16.3 |
| Baseline comorbidity           |                  |              |        |         |         |        |         |        |      |
| Diabetes mellitus             | 63,908  | 10.4    | 932   | 10.1    | <0.06  | 934   | 10.1    | 932    | 10.1 |
| Hypertension                  | 126,895 | 20.6    | 1917  | 20.8    | 0.74   | 1911  | 20.7    | 1917   | 20.8 |
| Hyperlipidemia                | 80,240  | 13.0    | 1185  | 12.8    | <0.06  | 1145  | 12.4    | 1185   | 12.8 |
| Obesity                       | 4661   | 0.8     | 77    | 0.8     | 0.40   | 67    | 0.7     | 77     | 0.8 |
| Intestinal cystitis           | 53,606  | 8.7     | 1008  | 10.9    | <0.001 | 1012  | 11.0    | 1008   | 10.9 |
| Fibromyalgia                  | 119,633 | 19.4    | 1953  | 21.1    | <0.001 | 1965  | 21.3    | 1953   | 21.1 |
| Gastroesophageal reflux disease | 3235   | 0.5     | 61    | 0.7     | 0.08   | 58    | 0.6     | 61     | 0.7 |
| Diarrhea                      | 1741   | 0.3     | 39    | 0.4     | <0.01  | 31    | 0.3     | 39     | 0.4 |
| Urinary stones                | 38,024  | 6.2     | 716   | 7.8     | <0.001 | 718   | 7.8     | 716    | 7.8 |
| Asthma                        | 40,390  | 6.6     | 648   | 7.0     | 0.08   | 629   | 6.8     | 648    | 7.0 |

*p*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.*
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

| Characteristics          | Event Person IR Univariable Mutivariable |
|--------------------------|------------------------------------------|
| Appendectomy             |                                         |
| No                       | 239                                      |
| Yes                      | 335                                      |
| Gender                   |                                         |
| Female                   | 309                                      |
| Male                     | 265                                      |
| Age at baseline          |                                         |
| <40                      | 212                                      |
| 40–65                    | 257                                      |
| 65                       | 105                                      |
| Baseline comorbidity     |                                         |
| Diabetes mellitus        | 100                                      |
| Hypertension             | 200                                      |
| Hyperlipidemia           | 113                                      |
| Obesity                  | 11                                       |
| Intestinal cystitis      | 86                                       |
| Fibromyalgia             | 168                                      |
| Gastroesophageal reflux disease | 5                        |
| Diarrhea                 | 4                                        |
| Urinary stones           | 76                                       |
| Asthma                   | 57                                       |

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

*Abbreviation: HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.
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 promotes their elimination [32]. Nevertheless, it also binds to the commensal 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, the NHIRD uses the Rome III criteria after 2006 and Rome II criteria before 2006 to allow the diagnosis of IBS. Thus, there may be inaccuracies in the diagnosis of IBS, which could lead to potential bias in this study.
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 discrepancies. 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 postoperative consultation may increase the probability of IBS diagnosis of pre-existing symptoms. Fourthly, the NHIRD does not include histological assessments, therefore pathophysiological 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.

Acknowledgements

This work was supported by grants from the Ministry of Health and Welfare, Taiwan (MOHW108-TDU-B-212-133004), China Medical University Hospital, Academia Sinica Stroke Biosignature Project (BM10701010021), MOST Clinical Trial Consortium for Stroke (MOST 108-2321-B-039-003-), Tseng-Lien Lin Foundation, Taichung, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.

References

[1] Lin K-K, Lai RR, Yang N-P, et al. Epidemiology and socioeconomic features of appendicitis in Taiwan: a 12-year population-based study. World J Emerg Surg 2015;10:42.
[2] Kooij IA, Sahami S, Meijer SL, Buskens CJ, Te Velde AA. The immunology of the vermiform appendix: a review of the literature. Clin Exp Immunol 2016;186 (1):1–9.
[3] Im GY, Modayil RJ, Lin CT, et al. The appendix may protect against clostridium difficile recurrence. Clin Gastroenterol Hepatol 2011;9(12):1072–7.
[4] Laurin M, Everett ML, Parker W. The cecal appendix: one more immune component with a function disturbed by post-industrial culture. Anatom Record 2011;294(4):567–79.
[5] Randal Bollinger R, Barbhas AS, Bush EL, Lin SS, Parker W. Biolumines in the large bowel suggest an apparent function of the human vermiform appendix. J Theor Biol 2007;249(4):826–31.
[6] Berry RJ. The true caecal apex, or the vermiform appendix: its minute and comparative anatomy. J Anat Physiol 1900;35(Pt 1):93–1005.
[7] Smith HF, Parker W, Kotzé SH, Laurin M. Morphological evolution of the mammalian cecum and cecal appendix. Compont Rend Palevol 2017;16(1):39–57.
[8] Chung WS, Lin CH, Hsu CY. Women who had appendectomy have increased risk of systemic lupus erythematosus: a nationwide cohort study. Clin Rheumatol 2018;37(11):3009–16.
[9] Tseng YM, Kao LT, Kao S, Lin HC, Tsai MC, Lee CZ. An appendectomy increases the risk of rheumatoid arthritis: a five-year follow-up study. PLoS One 2015;10(5):e0126816.
[10] Rasmussen T, Fonnes S, Rosenberg J. Long-term complications of appendectomy: a systematic review. Scand J Surg 2018;107(3):189–96.
[11] Mohammad M, Song H, Cao Y, et al. Risk of lymphoid neoplasms in a Swedish population-based cohort of 337,437 patients undergoing appendectomy. Scand J Gastroenterol 2016;51(5):583–9.
[12] Wu SC, Chen WT, Muo CH, Ke TW, Fang CW, Sung FC. Association between appendectomy and subsequent colorectal cancer development: an Asian population study. PLoS One 2015;10(2):e0118411.
[13] Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clin Epidemiol 2014;6:71–80.
[14] Lacy BE, Patel NK. Rome criteria and a diagnostic approach to irritable bowel syndrome. J Clin Med 2017;6(11):99.
[15] Saha L. Irritable bowel syndrome: pathogenesis, diagnosis, treatment, and evidence-based medicine. World J Gastroenterol 2014;20(22):6759–73.
[16] Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. Digestion 1999;60(1):77–81.
[17] Koloski NA, Talley NJ, Boyce PM. The impact of functional gastrointestinal disorders on quality of life. Am J Gastroenterol 2000;95(1):67–71.
[18] Munchies H. Quality of life in patients with irritable bowel syndrome. J Clin Gastroenterol 2011;45:598–5101.
[19] Liang AM, Tien Y. Quality of life in irritable bowel syndrome: a narrative overview. J Arch Mil Med 2016;4(1):e36624.
[20] Pace F, Molteni P, Bollani S, et al. Inflammatory bowel disease versus irritable bowel syndrome: a hospital–based, case–control study of disease impact on quality of life. Scand J Gastroenterol 2003;38(10):1031–8.

[21] Wells NEJ, Hahn BA, Whorwell PJ. Clinical economics review: irritable bowel syndrome. Alim Pharmacol Therap 1997;11(6):1019–30.

[22] Whitehead WE, Burnett CK, Cook 3rd EW, Taub E. Impact of irritable bowel syndrome on quality of life. Diges Dis Sci 1996;41(11):2248–53.

[23] Pittayanon R, Lau JT, Yuan Y, et al. Gut microbiota in patients with irritable bowel syndrome: a systematic review. Gastroenterology 2019;157(1):97–108.

[24] Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol 2016;1(2):133–46.

[25] Prior A, Stanley KM, Smith AR, Read NW. Relation between hysterectomy and the irritable bowel: a prospective study. Gut 1992;33(6):814.

[26] Khoshbaten M, Melli MS, Fattahi MJ, Sharifi N, Mostafavi SA, Pourhoseingholi MA. Irritable bowel syndrome in women undergoing hysterectomy and tubal ligation. Gastroenterol Hepatol Bed Bench 2011;4(3):138–41.

[27] Kennedy TM, Jones RH. Epidemiology of cholecystectomy and irritable bowel syndrome in a UK population. BJS (Br J Surg) 2000;87(12):1658–63.

[28] Rasmussen T, Fonnes S, Rosenberg J. Long-term complications of appendectomy: a systematic review. Scand J Surg 2018;107(3):189–96.

[29] Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications. Gastroenterology 2002;122(4):1140–56.

[30] Veale D, Kavanagh G, Fielding JF, Fitzgerald O. Primary fibromyalgia and the irritable bowel syndrome: different expressions of a common pathogenetic process. Rheumatology 1991;30(3):220–2.

[31] Masahata K, Umemoto E, Kayama H, et al. Generation of colonic IgA-secreting cells in the caecal patch. Nat Commun 2014;5:3704.

[32] Girard-Madoux MJH, Gomez de Aguero M, Ganal-Vonarburg SC, et al. The immunological functions of the Appendix: an example of redundancy. Semin Immunol 2018;36:31–44.

[33] Hall NJ, Eaton S. Non-operative management of appendicitis in children. Arch Dis Child 2018;103(5):498–502.

[34] Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol 2016;1(2):133–46.

[35] Wang L, Alammar N, Singh R, et al. Gut microbial dysbiosis in the irritable bowel syndrome: a systematic review and meta-analysis of case–control studies. J Acad Nutr Dietet.

[36] Hsieh C-Y, Su C-C, Shao S-C, et al. Taiwan's National health insurance research database: past and future. Clin Epidemiol 2019;11:349–58.

[37] Pan C-H, Chang C-C, Su C-T, Tsai P-S. Trends in irritable bowel syndrome incidence among taiwanese adults during 2003–2013: a population-based study of sex and age differences. PLoS one 2016;11(11):e0166922.

[38] Tan T-K, Saps M, Lin C-L, Wei C-C. Is long-term ambient air pollutant exposure a risk factor for irritable bowel syndrome in children? A 12-year longitudinal cohort study. J Neurogastroenterol Motil 2019;25(2):241–9.

[39] Yang T-Y, Chen C-S, Lin C-L, Lin W-M, Kuo C-N, Kao C-H. Risk for irritable bowel syndrome in fibromyalgia patients: a national database study. Medicine 2015;94(10):e616.

[40] Almansa C, Rey E, Sánchez RG, Sánchez AA, Díaz-Rubio M. Prevalence of functional gastrointestinal disorders in patients with fibromyalgia and the role of psychologic distress. Clin Gastroenterol Hepatol 2009;7(4):438–45.

[41] Chalaye P, Coffaux P, Bourgault P, et al. Comparing pain modulation and autonomic responses in fibromyalgia and irritable bowel syndrome patients. Clin J Pain 2012;28(6):519–26.

[42] Albusoda A, Ruffle JK, Friss KA, et al. Systematic review with meta-analysis: conditioned pain modulation in patients with the irritable bowel syndrome. Alim Pharmacol Therapeutics 2018;48(8):797–806.

[43] Chung W-S, Chen Y, Chen W, Lin C-L. Incidence and risk of venous thromboembolism in patients following appendectomy: a nationwide cohort study. J Thromb Thrombolysis 2019;48(3):481–90.

[44] Lee Y-M, Kor C-T, Zhou D, Lai H-C, Chang C-C, Ma W-L. Impact of age at appendectomy on development of type 2 diabetes: a population-based cohort study. PLOS ONE 2018;13(10):e0205502.

[45] Salininen V, Aki EA, You JJ, et al. Meta-analysis of antibiotics versus appendectomy for non-perforated acute appendicitis. Br J Surg 2016;103(6):656–67.