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Increased risk of appendectomy in patients with asthma

A nested case-control study using a national sample cohort

So Young Kim, MD[a], Dong Jun Oh, MD[b], Bumjung Park, MD[c], Il-Seok Park, MD, PhD[d], Hyo Geun Choi, MD[c,e,*]

Abstract

The study aimed to expand previous data regarding an association between asthma and appendectomy in children compared with the population of all ages.

The Korean Health Insurance Review and Assessment Service—National Sample Cohort from 2002 through 2013 was used. In all, 22,030 participants who underwent appendectomy were matched for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia with 88,120 participants who were included as a control group. In both the appendectomy and control groups, previous history of asthma was investigated. Appendectomy for appendicitis was identified based on a surgical code (International Classification of Disease-10 [ICD-10]: K35). Asthma was classified using an ICD-10 code (J45 and J46) and medication history. The crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of asthma for appendectomy were analyzed using conditional logistic regression analysis. Subgroup analyses were conducted according to age and sex.

Approximately 15.2% (3358/22,030) of individuals in the appendectomy group and 13.3% (11,749/88,120) of those in the control group had asthma ($P < .001$). The appendectomy group demonstrated a higher adjusted odds of asthma than the control group (adjusted OR 1.18, 95% CI 1.13–1.23, $P < .001$). This result was consistent in the subgroups divided according to age and sex.

The odds for asthma were higher in the appendectomy group than in the control group.

Abbreviations: CIs = confidence intervals, COPD = chronic obstructive pulmonary disease, LAMA = long-acting muscarinic antagonists, NHIS = Korean National Health Insurance Service, ORs = odds ratios.

Keywords: appendectomy, asthma, case-control studies, cohort studies, risk factors

1. Introduction

Acute appendicitis is 1 of the most common surgical emergencies with an estimated lifetime risk of approximately 7% to 8% worldwide.[1,2] In Korea, a lifetime risk of appendicitis of approximately 16% has been reported.[3] The pathophysiologic mechanism underlying appendicitis is still elusive. Direct obstruction of the appendicular lumen can cause elevated luminal pressure and subsequent inflammation, which result in appendicitis.[1] However, luminal obstruction is presumed to be the minor cause in most cases of appendicitis. Instead, intraluminal inflammation including acute mucosal and submucosal inflammation has been suggested to be the main pathological cause of appendicitis.[4] The submucosa of the human appendix is composed of a large number of lymphoid follicles. Thus, immune reactions can result in lymphoid hyperplasia and inflammation, and subsequent appendicitis. In line with this phenomenon, a relationship between appendicitis and immune disorders has been suggested in a few genetic studies.[5,6]

Asthma is 1 of the most common chronic airway disorders and is accompanied by inflammation and immune dysregulation. Approximately 4.3% of the adult population worldwide have asthma diagnosed by doctor.[7] In Korea, approximately 5.7% of adults suffer from asthma.[8] The pathophysiology of asthma is complex and has heterogeneous characteristics. In terms of immunologic causes, not only Th2 immune responses but also Th1-predominant inflammatory factors, such as tumor necrosis factor-alpha, are known to contribute to the development of asthma.[9] In addition to classical airway remodeling disorders, recent studies have suggested that systemic immune dysregulation and infection are involved in asthmatic patients and can lead to systemic inflammatory responses.[10–12]

Because appendicitis is also associated with inflammation and immune dysregulation, it can be postulated that asthma may influence the risk of appendicitis. Indeed, we have encountered

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[a] Department of Otorhinolaryngology-Head & Neck Surgery, CHA Bundang Medical Center, CHA University, Seongnam, [b] Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul Hospital, [c] Department of Otorhinolaryngology-Head & Neck Surgery, Hallym University College of Medicine, Anyang, [d] Department of Otorhinolaryngology-Head & Neck Surgery, Hallym University College of Medicine, Dongtan, [e] Hallym Data Science Laboratory, Hallym University College of Medicine, Anyang, Republic of Korea.

[*] Correspondence: Hyo Geun Choi, Department of Otorhinolaryngology-Head & Neck Surgery, Hallym University Sacred Heart Hospital, 22, Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang-si, Gyeonggi-do 14068, Republic of Korea (e-mail: pupen@naver.com).

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some asthmatic patients who suffered from abdominal pain and were diagnosed with acute appendicitis in the clinics. When the PubMed and Embase databases were searched for studies using the keywords "(asthma) AND ([appendicitis] OR [appendectomy] OR [appendix])," only 1 study reported an association between asthma and appendicitis through June, 2018.[13] A population case-control study described an increased risk of appendicitis in asthma patients compared with children in a control group.[13] However, few previous studies have investigated the risk of appendicitis in asthma patients in adult populations.

The running hypothesis of the present study was that asthma might increase the risk of acute appendicitis in adults, and also young individuals. To prove this hypothesis, a population encompassing all ages of individuals was analyzed for the risk of appendectomy among asthma patients. In addition, the control group was matched for age, sex, income, region of residence, and past medical history to minimize potential confounders.

2. Patients and methods

2.1. Ethical considerations

The Ethics Committee of Hallym University (2017-I102) approved the use of these data. The requirement for written informed consent was waived by the institutional review board.

This national cohort study relied on data from the Korean National Health Insurance Service (NHIS)-National Sample Cohort. The detailed description of this data was described in our previous studies.[14,15]

2.2. Study population and data collection

Among 1,125,691 patients with 114,369,638 medical claim codes, we included individuals who underwent appendectomy. Appendectomies were identified based on surgical codes (Q2860-Q2863); only appendectomies performed for appendicitis (International Classification of Disease-10 [ICD-10]: K35) were included (n=22,047). The appendectomies for other causes were excluded (n=640).

Asthma was considered if a diagnosis of asthma (ICD-10: J45) or status asthmaticus (J46) was recorded. We selected participants who were treated ≥2 times with corticosteroids, a steroid inhaler, long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists, or xanthine (n=230,764). This method has been modified from a previous study.[8] In addition, to investigate the influence of severity of asthma on the odds of appendectomy, asthma patients who were treated ≥3, 4, and 5 times with asthmatic medications were selected.

The appendectomy participants were matched at a 1:4 ratio with patients (control group) in this cohort who had not undergone appendectomy from 2002 through 2013. The control group was selected from the original population (n=1,103,004). These subjects were matched for age, group, sex, income, region of residence, and past medical history (hypertension, diabetes, and dyslipidemia). To prevent a selection bias when selecting the matched participants, the control group participants were sorted using a random number order, and they were then selected from top to bottom. The matched control participants were assumed to be involved at the same time as each matched appendectomy participant (index date). Therefore, the control group subjects who died before the index date were excluded. Appendectomy participants for whom we could not identify enough matched participants were excluded (n=17). Finally, 1:4 matching resulted in the inclusion of 22,030 appendectomy participants and 88,120 control participants (Fig. 1). However, they were not matched for ischemic heart disease, cerebral stroke, depression, and chronic obstructive pulmonary disease (COPD) because

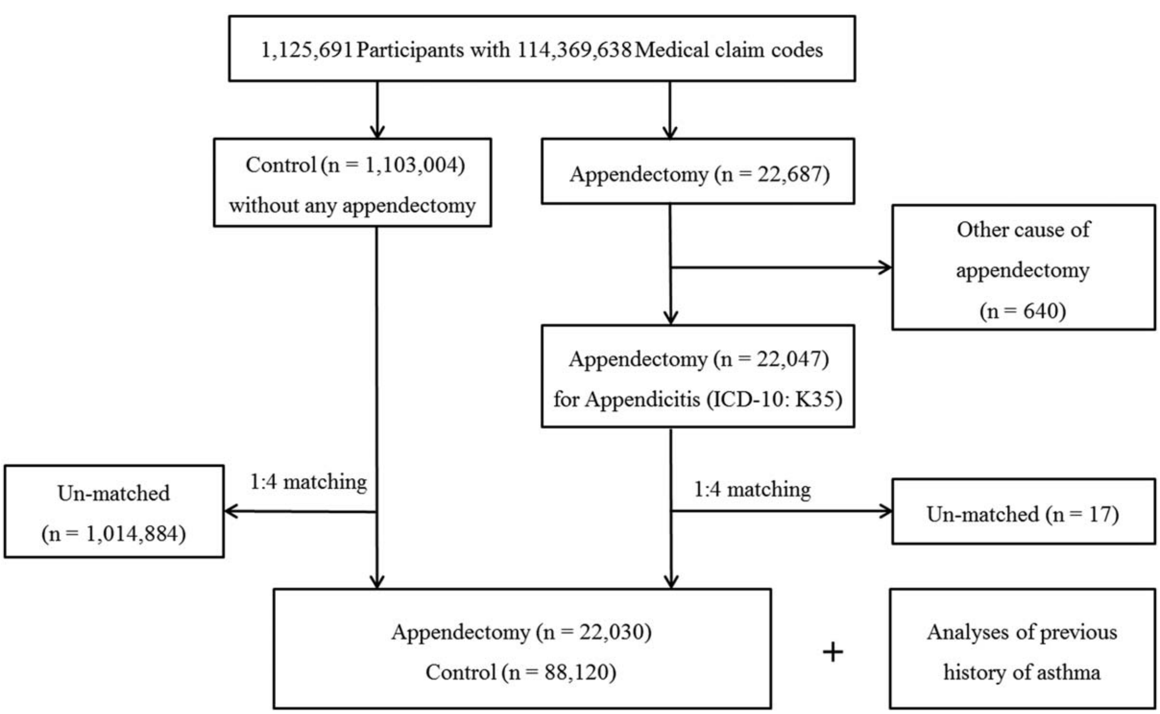

Figure 1. Schematic illustration of the participant selection process that was used in the present study. Of a total of 1,125,691 participants, 22,030 appendectomy participants were matched with 88,120 control participants by age, group, sex, income, region of residence, and past medical history.

strict matching increased the number of excluded study participants due to a lack of control participants. After matching, we analyzed the previous history of asthma in both the appendectomy and control groups.

2.3. Variables

The age groups were classified using 5-year intervals as follows: 0 to 4, 5 to 9, 10 to 14 . . . , and 85+ years old. A total of 18 age groups were designated. The income groups were initially divided into 41 classes (1 health aid class, 20 self-employed health insurance classes, and 20 employed health insurance classes). These groups were recategorized into 5 classes (class 1 [lowest income] to class 5 [highest income]). Region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

Participants' past medical history was evaluated using ICD-10 codes. For the accuracy of diagnosis, participants were considered to have hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) if they were treated ≥2 times. Participants were considered to have ischemic heart disease (I24 and I25) and cerebral stroke (I60-I66) if they were treated ≥1 time. Depression was defined using the ICD-10 codes F31 (bipolar affective disorder) through F39 (unspecified mood disorder) as recorded by a psychiatrist ≥2 times. COPD was determined by J43 (Emphysema) through J44 (other chronic obstructive pulmonary disease) who were treated with short-acting beta agonist, long-acting beta agonist, LAMA, and corticosteroid

2.4. Statistical analyses

Chi-square tests were used to compare the general characteristics between the appendectomy and control groups.

To analyze the odds ratio (OR) of asthma on appendectomy, a conditional logistic regression analysis was used. In this analysis, crude (simple) and adjusted (ischemic heart disease, cerebral stroke, depression, COPD) models were used, and 95% confidence intervals (CIs) were calculated. Age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia were stratified.

For the subgroup analyses, we divided the participants by age and sex (<20 years old, 20–39 years old, 40–59 years old, and 60 + years; men and women). According to the number of asthma treatment histories, asthma patients who were treated ≥3, 4, and 5 times with asthmatic medications were analyzed for the OR for appendectomy.

Two-tailed analyses were conducted, and *P* values <.05 were considered to indicate significance. The results were analyzed using SPSS v. 22.0 (IBM, Armonk, NY).

3. Results

The rate of asthma was higher in the appendectomy group (15.2% [3358/22,030]) than in the control group (13.3% [11,749/88,120]; *P* < .001; Table 1). The general characteristics (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia) of the participants were exactly the same due to matching (*P* = 1.000). The rates of ischemic heart disease, cerebral stroke, and depression were higher in the appendectomy group than in the control group (all *P* < .05).

Table 1

General characteristics of participants.

	Total participants		
Characteristics	Appendectomy (n, %)	Control group (n, %)	*P*
Age (y)			1.000
0–4	124 (0.6)	496 (0.6)	
5–9	1344 (6.1)	5376 (6.1)	
10–14	2819 (12.8)	11,276 (12.8)	
15–19	2656 (12.1)	10,624 (12.1)	
20–24	1817 (8.2)	7268 (8.2)	
25–29	2021 (9.2)	8084 (9.2)	
30–34	2056 (9.3)	8224 (9.3)	
35–39	1837 (8.3)	7348 (8.3)	
40–44	1627 (7.4)	6508 (7.4)	
45–49	1331 (6.0)	5324 (6.0)	
50–54	1191 (5.4)	4764 (5.4)	
55–59	901 (4.1)	3604 (4.1)	
60–64	710 (3.2)	2840 (3.2)	
65–69	608 (2.8)	2432 (2.8)	
70–74	464 (2.1)	1856 (2.1)	
75–79	289 (1.3)	1156 (1.3)	
80–84	172 (0.8)	688 (0.8)	
85+	63 (0.3)	252 (0.3)	
Sex			1.000
Male	11,765 (53.4)	47,060 (53.4)	
Female	10,265 (46.6)	41,060 (46.6)	
Income		1.000	
1 (lowest)	3070 (13.9)	12,280 (13.9)	
2	3445 (15.6)	13,780 (15.6)	
3	4314 (19.6)	17,256 (19.6)	
4	5102 (23.2)	20,408 (23.2)	
5 (highest)	6099 (27.7)	24,396 (27.7)	
Region of residence			1.000
Urban	9788 (44.4)	39,152 (44.4)	
Rural	12,242 (55.6)	48,968 (55.6)	
Hypertension	3289 (14.9)	13,156 (14.9)	1.000
Diabetes	1690 (7.7)	6760 (7.7)	1.000
Dyslipidemia	2883 (13.1)	11,532 (13.1)	1.000
Ischemic heart disease	626 (2.8)	2125 (2.4)	<.001*
Cerebral stroke	945 (4.3)	3370 (3.8)	.001*
Depression	1582 (7.2)	5245 (6.0)	<.001*
COPD	861 (3.9)	2859 (3.2)	<.001*
Asthma	3358 (15.2)	11,749 (13.3)	<.001*

COPD = chronic obstructive pulmonary disease.

* Chi-square test; significance at *P* < .05.

The adjusted ORs of asthma was 1.18 in the appendectomy group (95% CI 1.13–1.23, *P* < .001; Table 2).

In the subgroup analyses, all of the crude and adjusted ORs of asthma were higher in the appendectomy group, except for in the subgroup of men who were 60+ years old (each *P* < .05; Table 3). The adjusted ORs were 1.10 (95% CI 1.01–1.19) in men <20 years old, 1.14 (95% CI 1.03–1.26) in women <20 years old, 1.24 (95% CI 1.04–1.47) in men who were 20 to 39 years old, 1.26 (95% CI 1.11–1.44) in women who were 20 to 39 years old women, 1.27 (95% CI 1.07–1.50) in men who were 40 to –59 years old, 1.20 (95% CI 1.05–1.37) in women who were 40 to 59 years old, and 1.36 (95% CI 1.17–1.58) in women who were 60+ years old. According to the number of asthma treatment histories, asthma patients who were treated ≥ 3, 4, and 5 times with asthmatic medications showed high ORs of appendectomy (Table 4 and see Table, Supplemental Content, http://links.lww.com/MD/D244, which illustrates the distributions of asthma according the number of clinic visits of asthma). The adjusted OR

Table 2

Crude and adjusted odd ratios (95% confidence interval) of appendectomy for asthma.

Characteristics	Asthma			
	Crude*	P	Adjusted*,†	P
Appendectomy	1.19 (1.14–1.25)	<.001‡	1.18 (1.13–1.23)	<.001‡
Control	1.00		1.00	

* Stratified model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories.
† Adjusted model for ischemic heart disease, cerebral stroke, depression, and chronic obstructive pulmonary disease (COPD) histories.
‡ Conditional logistic regression analyses; significance at $P<.05$.

of appendectomy for asthma was 1.16 (95% CI 1.10–1.22), 1.14 (95% CI 1.08–1.20), and 1.13 (95% CI 1.06–1.20) in ≥ 3, 4, and 5 times of clinic visits of asthma.

4. Discussion

The appendectomy group demonstrated a higher odds of asthma than the control group in this study (adjusted OR 1.18, 95% CI 1.13–1.23, $P<.001$). The increased odds of asthma in appendectomy patients was consistent according to age and sex. This is not only the first study involving an adult population but also the largest population study to evaluate the association between asthma and appendectomy. Similar to the present results, a case-control study reported a 1.88-times higher risk of appendicitis in asthma patients than in a control group composed of individuals younger than 18 years old (95% CI 1.07–3.27, $P=.035$).[13] The higher odds of appendectomy for asthma patients were consistent according to the number of clinic visits of asthma.

Several plausible pathophysiologic mechanisms including allergy or atopy, lymphoid hyperplasia, and infectious causes might link asthma with appendectomy. Allergies or atopy in asthma patients could influence the intraluminal allergic response of the appendix. Previous studies have reported increased allergic reactions as assessed by a skin prick test positivity or eosinophil cationic protein levels in appendicitis patients.[16,17] A prospective study reported an increase in the skin prick test positivity rate in acute appendicitis patients compared with a control group (34.2% vs 8%; $P<.001$).[16] Similarly, acute appendicitis patients demonstrated higher levels of eosinophil cationic protein than a control group, suggesting local eosinophilic reaction and degranulation in these patients.[17] These allergic reactions could accelerate inflammation and obstruction of the appendix and lead to appendicitis.

Asthma might induce immune reactions and cause the consequent lymphoid hyperplasia and inflammation associated with appendicitis. A few studies have suggested that there is a relationship between asthma and lymphoid hyperplasia of nonrespiratory organs including the gastrointestinal tract.[18,19] For instance, as many as 85.7% of patients with lymphoid hyperplasia of the large intestine (cecum, colon, and rectum) have allergic airway diseases and positive reactions to inhalant allergens.[18,19] Because the appendix is an organ with a large number of lymphoid follicles, asthma-induced reactive lymphoid hyperplasia could manifest in the lumen of appendix to cause obstruction or inflammation in appendicitis.

Table 3

Subgroup analysis of crude and adjusted odd ratios (95% confidence interval) of appendectomy for asthma according to age and sex.

Characteristics	Asthma			
	Crude*	P	Adjusted*,†	P
Age <20 y, men (n=20,725)				
Appendectomy	1.09 (1.01–1.18)	.032‡	1.10 (1.01–1.19)	.027‡
Control	1.00		1.00	
Age <20 y, women (n=13,990)				
Appendectomy	1.14 (1.03–1.26)	.012‡	1.14 (1.03–1.26)	.011‡
Control	1.00		1.00	
Age 20–39 y, men (n=19,920)				
Appendectomy	1.24 (1.04–1.47)	.015‡	1.24 (1.04–1.47)	.016‡
Control	1.00		1.00	
Age 20–39 y, women (n=18,735)				
Appendectomy	1.29 (1.13–1.47)	<.001‡	1.26 (1.11–1.44)	<.001‡
Control	1.00		1.00	
Age 40–59 y, men (n=12,910)				
Appendectomy	1.30 (1.10–1.53)	.002‡	1.27 (1.07–1.50)	.006‡
Control	1.00		1.00	
Age 40–59 y, women (n=12,340)				
Appendectomy	1.23 (1.08–1.41)	.002‡	1.20 (1.05–1.37)	.007‡
Control	1.00		1.00	
Age 60+ y, men (n=5270)				
Appendectomy	1.22 (1.01–1.46)	.037‡	1.15 (0.95–1.40)	.154
Control	1.00		1.00	
Age 60+ y, women (n=6260)				
Appendectomy	1.38 (1.19–1.60)	<.001‡	1.36 (1.17–1.58)	<.001‡
Control	1.00		1.00	

* Stratified model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories.
† Adjusted model for ischemic heart disease, cerebral stroke, depression, and chronic obstructive pulmonary disease (COPD) histories.
‡ Conditional logistic regression analyses; significance at $P<.05$.

Table 4

Crude and adjusted odd ratios (95% confidence interval) of appendectomy for asthma according the number of clinic visits of asthma.

Characteristics	Odd ratios			
	Crude	*P*	Adjusted†,‡	*P*
Asthma ≥3 times of clinics visit with medication histories				
Appendectomy	1.18 (1.12–1.24)	<.001*	1.16 (1.10–1.22)	<.001*
Control	1.00		1.00	
Asthma ≥4 times of clinics visit with medication histories				
Appendectomy	1.16 (1.10–1.22)	<.001*	1.14 (1.08–1.20)	<.001*
Control	1.00		1.00	
Asthma ≥5 times of clinics visit with medication histories				
Appendectomy	1.15 (1.09–1.22)	<.001*	1.13 (1.06–1.20)	<.001*
Control	1.00		1.00	

* Conditional logistic regression analyses; significance at $P < .05$.
† Stratified model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories.
‡ Adjusted model for ischemic heart disease, cerebral stroke, depression, and chronic obstructive pulmonary disease (COPD) histories.

Asthma could increase the susceptibility to infection, which might increase the risk of acute appendicitis. Several clinical studies have reported an increased risk of infection in multiple nonrespiratory tract sites in asthma patients.[19–21] The odds of *Escherichia coli* bacteremia was 2.74 times higher in individuals with asthma than in those in a control group (95% CI 1.11–6.76, $P = .029$).[19] In addition, the incidence of latent nonrespiratory infections, such as herpes zoster, was 2.09 times higher in the asthma group than in an age and sex-matched control group (95% CI 1.24–3.52, $P = .006$).[21] Increased susceptibility to bacterial infection might increase the risk of acute appendicitis. Most of the luminal contents of acute appendicitis patients (98%) were incubated pathogens.[22] Common infectious causes of appendicitis have described including *Escherichia coli* and *Pseudomonas aeruginosa*.[22,23] In addition, a genome-wide expression analysis study delineated increased mRNA expression of genes associated with neutrophil innate defense systems in acute appendicitis patients.[6] Thus, the increased susceptibility to infection in asthma patients could increase the risk of the infection associated with acute appendicitis.

According to age and sex, all the age and sex subgroups except for men ≥60 years old demonstrated higher odds of asthma in the appendectomy group than in the control group in this study. The relatively low prevalence of appendectomy in the elderly population could alleviate the statistical power of the present results. Appendicitis mainly occurs in young populations with a peak incidence in individuals who are 20 to 30 years old.[1]

This study has several merits in terms of the matched control group, verified cohort population, and objective disease criteria. The control group was matched with the appendectomy group for socioeconomic status in the present study. On the contrary, a previous study did not match for the socioeconomic status between the study and control groups.[13] Because medical accessibility is a crucial factor for detecting appendicitis and recommending appendectomy, socioeconomic status should be considered to prevent selection bias. Moreover, this study used a control group that was matched for past medical history of hypertension, diabetes, and dyslipidemia and demographic factors, such as age, sex, income, and region of residence. The differences in comorbid conditions between the study and control groups could result in confounding effects, especially in this adult population. In addition to these advances, this study improved upon previous findings by using a large representative nationwide cohort. There were no missing participants in this study because all Korean citizens were enrolled in the NHIS without exception. The representativeness of this sample cohort was validated in a previous study.[24] For the accuracy of diagnosis, both asthma and appendectomy were defined according to previous studies.[3,8] In addition, multiple inclusion criteria including ICD-10 codes and treatment history or medication history enhanced the fidelity of diagnosis. Because surgeries such as appendectomy are covered by national health insurance in Korea, the accuracy of surgical codes is very strictly controlled.

However, several limitations should be considered to interpret the present results. The severity of both asthma and appendicitis could not be accessed from the NHIS data. Although prescriptions for asthma were included in this study, the detailed management and severity of asthma were not evaluated. For appendicitis, subclinical acute appendicitis may have been excluded in this study due to spontaneous recovery. Acute appendicitis patients who underwent appendectomy were included in this study to improve the fidelity of diagnosis. Thus, only patients with appendicitis requiring a surgical intervention were included in this study. However, appendectomy due to acute appendicitis could be a surrogate marker for acute appendicitis. In addition, although several confounders were matched and/or adjusted for, some lifestyle factors including obesity, smoking history, and alcohol consumption were not available in the NHIS data.

5. Conclusion

Asthma was associated with appendectomy due to appendicitis in both young and adult populations.

Author contributions

Formal analysis: Dong Jun Oh, Bumjung Park, Il-Seok Park, Hyo Geun Choi.
Writing – original draft: So Young Kim, Hyo Geun Choi.
Writing – review & editing: So Young Kim, Dong Jun Oh, Bumjung Park, Il-Seok Park, Hyo Geun Choi.
Hyo Geun Choi orcid: 0000-0003-1655-9549.

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