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Increased risk of appendectomy in patients with gastroesophageal reflux disease

A nested case-control study using a national sample cohort

So Young Kim, MD[a], Hyung-Jong Kim, MD[b], Hyun Lim, MD[c], Man Sup Lim, MD[d], Miyoung Kim, MD[e], Hyo Geun Choi, MD[b,*]

Abstract

The purpose of this study is to confirm and complement previous data regarding an association between gastroesophageal reflux disease and appendectomy.

The Korean National Health Insurance Service-National Sample Cohort includes data from people ≥ 20 years old collected from 2002 to 2013. A total of 13,484 participants who received an appendectomy were matched with 53,936 controls at a 1:4 ratio. We analyzed the previous histories of gastroesophageal reflux disease (GERD) in the appendectomy and control groups. Appendectomies were identified using operation codes (Q2860-Q2863) exclusive for appendicitis (International Classification of Disease-10 (ICD-10): K35). GERD was defined using the ICD-10 (K21), and patients who were treated ≥ 2 times and were prescribed a proton pump inhibitor (PPI) for ≥ 2 weeks were included. Crude (simple) and adjusted odds ratios (ORs) for GERD and appendectomy were analyzed using conditional logistic regression analyses.

A higher GERD rate was detected in the appendectomy group (11.4% [1,713/15,062]) than in the control group (8.2% [4,947/60,248], $P<.001$). Adjusted ORs for GERD were 1.37 (95% confidence interval [CI] = 1.30–1.45) ($P<.001$). Subgroup analyses stratified according to age and sex revealed consistent findings. The adjusted OR for GERD in participants prescribed PPIs for ≥ 30 days was 1.31 (95% CI = 1.20–1.43), and the adjusted OR for GERD in participants prescribed PPIs for ≥ 60 days was 1.30 (95% CI = 1.15–1.48).

The Odds for GERD were higher in the appendectomy group than in the control group.

Abbreviations: CI = Confidence interval, GERD = Gastroesophageal reflux disease, HIRA = Health Insurance Review & Assessment, ICD-10 = International Classification of Disease-10, NHIS = Korean National Health Insurance Service, NSC = National Sample Cohort, OR = Odd ratio, PPIs = Proton pump inhibitors.

Keywords: appendectomy, appendicitis, cohort studies, epidemiology, gastroesophageal reflux, nested case-control studies, proton pump inhibitors

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[a] Department of Otorhinolaryngology-Head & Neck Surgery, CHA Bundang Medical Center, CHA University, Seongnam, [b] Department of Otorhinolaryngology-Head & Neck Surgery, Hallym University College of Medicine, [c] Department of Internal Medicine, Hallym University College of Medicine, Anyang, [d] Department of General Surgery, Hallym University College of Medicine, Chuncheon, [e] Department of Laboratory Medicine, 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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1. Introduction

Gastroesophageal reflux disease (GERD) is a condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications.[1] The prevalence of GERD is 18.1% to 27.8% in North America, 8.8% to 25.9% in Europe, 2.5% to 7.8% in East Asia,[2] and 4.6% to 7.3% in Korea.[3] The pathogenesis of GERD is multifactorial. Hypotension of the lower esophageal sphincter, delayed acid clearance in the esophagus, and increased esophagogastric junction compliance are possible factors contributing to pathogenesis.[4] It could be aggravated by obesity, diet, and neuromuscular dysfunction.[4] Comorbidities, such as diabetes or Parkinson disease, may cause gastric paresis[5,6] and induce GERD.[7]

Appendicitis is one of the most common emergencies, and it requires an appendectomy.[8] The annual incidence of appendicitis or appendectomy is 100 in Northern America, 151 in Western Europe, and 206 in Korea (per 100,000).[9] The incidence of appendicitis and appendectomy in Korea is reported to be 227.1 and 135.6 (per 100,000), respectively.[10] Direct luminal obstruction, infectious agents (adenovirus, cytomegalovirus, and fusobacteria), genetic factors (family histories), and environmental factors (seasonal presentation and ozone exposure) are suggested causes of appendicitis.[11] Excessive proliferation of nerve fiber into appendix with neuropeptide could cause appendicitis.[11]

Based on these finding, it could be possible that appendicitis is related with GERD, as both gastrointestinal track disease might be affected by diet and autonomic imbalance. We hypothesized that appendicitis might be more prevalent in the patient with GERD. To complement our hypothesis, we reviewed the PubMed and Embase databases for studies using the keywords '(gastroesophageal reflux) AND ([appendicitis] OR [appendectomy] OR [appendix])' and limited the results to human-based studies published in English before Dec. 2017. Only one study reported an association between GERD and appendicitis.[12] These researchers suggested that proton pump inhibitors (PPIs) are a possible factor underlying the etiology between GERD and appendicitis, but they did not confirm their hypothesis. The purpose of this study is to evaluate the risk of appendectomy in patients with GERD using a national sample cohort of the Korean population. The results of this study extend previous findings on PPI use.

2. Materials and methods

2.1. Study population and data collection

The ethics committee of Hallym University (2014-I148) approved the use of these data. The Institutional Review Board exempted the requirement for written informed consent.

This national cohort study used data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The Korean NHIS selects samples directly from the entire population database to prevent non-sampling errors. Approximately 2% of the samples (1 million) were selected from the entire Korean population (50 million). The selected data were classified into 1476 levels (age [18 categories], sex [2 categories], and income level [41 categories]) using randomized stratified systematic sampling methods via proportional allocation to represent the entire population. A previous study verified the appropriateness of the sample after data selection.[13] The National Health Insurance Sharing Service provides a detailed description of the methods used to perform these procedures.[14] This cohort database included

1. personal information,
2. health insurance claim codes (procedures and prescriptions),
3. diagnostic codes using the International Classification of Disease-10 (ICD-10),
4. death records from the Korean National Statistical Office (using the Korean Standard Classification of disease),
5. socio-economic data (residence and income), and
6. medical examination data for each participant from 2002 to 2013.

All Korean citizens are recognized by a 13-digit resident registration number from birth to death. Therefore, exact population statistics have been determined using this database. All Koreans are required to enroll in the NHIS. All Korean hospitals and clinics use the 13-digit resident registration number to register individual patients in the medical insurance system. Therefore, the risk of overlapping medical records is minimal, even if a patient moves from one place to another. All medical treatments in Korea are tracked without exception using the Health Insurance Review & Assessment (HIRA) system. In Korea, the law states that a notice of death must be provided to an administrative entity before a funeral can be held. Medical doctors record the date and cause of death on a death certificate.

2.2. Participant selection

Out of 1,125,691 cases with 114,369,638 medical claim codes, we only included participants who had received an appendectomy, as identified using operation codes (Q2860-Q2863). Among appendectomy cases, we included appendectomies performed solely for appendicitis (ICD-10: K35) (n=22,047).

GERD was defined using the ICD-10 code K21 from 2002 through 2013. We identified participants who were treated for GERD ≥ 2 times and were prescribed PPIs for ≥ 2 weeks (n=137,807).

Participants who received an appendectomy were matched at a 1:4 ratio with participants in the control group, who did not undergo an appendectomy from 2002 through 2013 among this cohort. Participants in the control group were selected among total participants who were not categorized as appendectomy group (n=1,103,644). Subject were matched on age group, sex, income group, region of residence, and medical histories (eg, hypertension, diabetes, and dyslipidemia). Participants in the control group were sorted using a random number order and selected from top to bottom to prevent selection bias when selecting the matched participants. The matched control participants were presumed to have been treated at the same time as each matched participant who received an appendectomy based on the index date. Therefore, subjects in the control group who died before the index date were excluded. Participants who received an appendectomy were excluded (n=58) if we could not identify a sufficient number of matching participants. We excluded participants aged less than 20 years (n=6927). The 1:4 matching resulted in the inclusion of 15,602 participants who had received an appendectomy and 60,248 control participants. However, subjects were not matched for ischemic heart disease, cerebral stroke, or depression histories because strict matching increased the exclusion of participants due to the lack of control participants. We analyzed previous histories of GERD before the index date in the appendectomy and control groups after matching (Fig. 1).

2.3. Variables

Fourteen age groups were designated and classified by 5-year intervals as follows: 20–24, 25–29, 30–34 . . . and 85+ years old. Income groups were initially divided into 41 classes (one health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 11 classes 1 (lowest income) -11 (highest income). They included one class of the lowest income group (heath aid) and other 10 classes by insurance premium. The 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' medical histories were evaluated using ICD-10 codes. Hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were examined for diagnostic accuracy if the participants were treated ≥ 2 times. Ischemic heart disease (I24 and I25) and cerebral stroke (I60-I66) were examined if the participants were treated ≥ 1 time. Depression was defined using

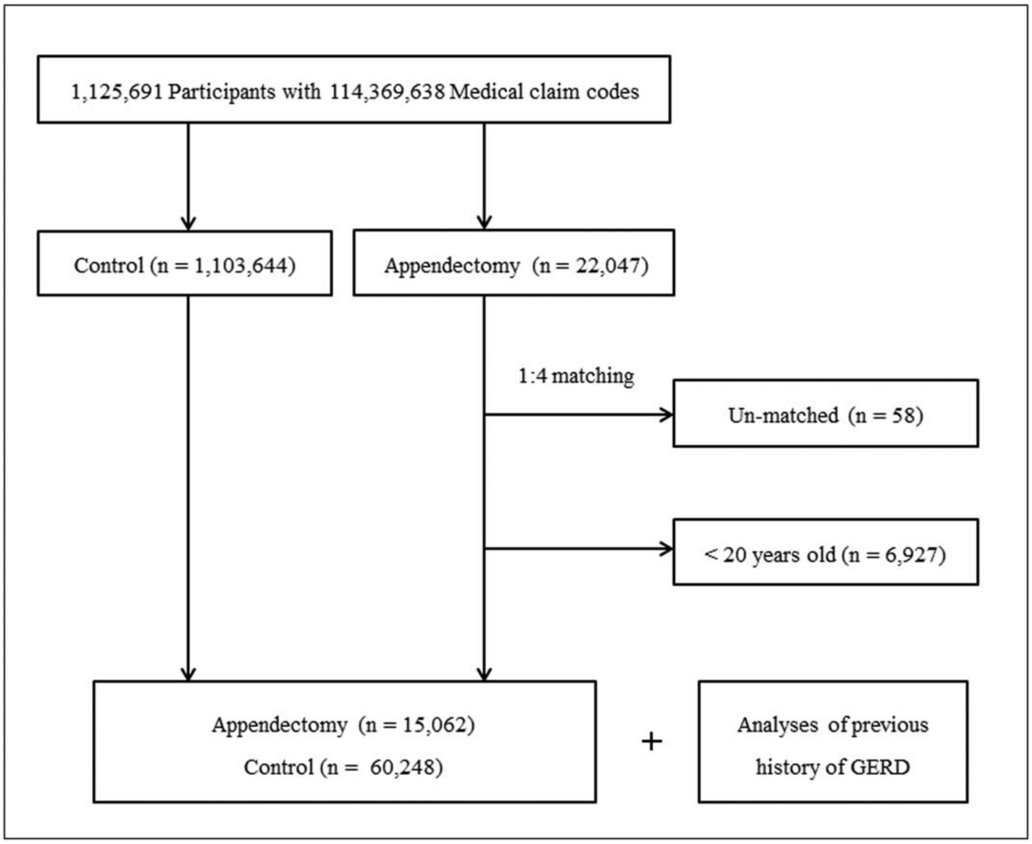

Figure 1. Schematic illustration of the participant selection process used in the present study. Of 1,125,691 participants, 15,062 participants who received an appendectomy were matched with 60,248 control participants for age group, sex, income group, region of residence, and medical histories.

the ICD-10 codes F31 (bipolar affective disorder) through F39 (unspecified mood disorder) assigned by a psychiatrist from 2002 through 2013. We selected participants who were treated for depression ≥ 2 times. We selected these variables as confounders in that these diseases are relatively common, and we think that they could reflect the general health status of participants.

2.4. Statistical analyses

An conditional logistic regression analysis was used to analyze the odd ratio (OR) of GERD in appendectomy patients. Crude (simple) and adjusted (age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, and depression histories) models were used in this analysis, and a 95% confidence interval (CI) was calculated.

We stratified participants by age and sex for subgroup analyses (< 40 years old, ≥ 40 years old & < 60 years old, ≥ 60 years old; men and women).

In other analyses, we analyzed the ORs for GERD with of ≥ 30 days, and ≥ 60 days of PPI prescription before appendectomy

Two-tailed analyses were performed, and *P* values less than .05 were considered significant. The results were statistically analyzed using SPSS v. 22.0 (IBM, Armonk, NY, USA).

3. Results

A higher GERD rate was observed in the appendectomy group (11.4% [1,713/15,062]) than in the control group (8.2% [4,947/60,248], $P<.001$, Table 1). The general characteristics (age, sex, income, region of residence, and histories of hypertension, diabetes, and dyslipidemia) of participants were identical due to matching ($P=1.000$). Higher rates of histories of ischemic heart disease, cerebral stroke, and depression were observed in the appendectomy group (all *P* values < .05). The adjusted OR for GERD was 1.37 (95% CI = 1.30–1.45 (*P* values < .001, Table 2).

In the subgroup analyses, higher crude and adjusted Odds for GERD were observed in the appendectomy group (all *P* values < .05, Table 3). Adjusted ORs were 1.37 (95% CI = 1.18–1.61) in < 40-year-old men, 1.45 (95% CI = 1.26–1.67) in < 40-year-old women, 1.35 (95% CI = 1.20–1.52) in 40–59-year-old men, 1.36 (95% CI = 1.22–1.53) in 40 to 59-year-old women, 1.23 (95% CI = 1.08–1.42) in ≥ 60-year-old men, and 1.41 (95% CI = 1.25–1.59) in ≥ 60-year-old women.

In other analyses, the adjusted OR for GERD with prescription of PPIs for ≥ 30 days was 1.31 (95% CI = 1.20–1.43), and the adjusted OR for GERD with prescription of PPIs for ≥ 60 days was 1.30 (95% CI = 1.15–1.48) (all *P* values < .001, Table 4).

4. Discussion

In the present study, higher Odds for GERD were observed in participants who received an appendectomy than in the control group. We obtained consistent results from different age groups and both sexes. The ORs for GERD with longer administration of PPI prescriptions was not higher than ORs for GERD with shorter administration of PPI prescriptions. These findings confirm and complement the results of a previous study[12] that reported a higher adjusted OR of 2.05 (95% CI = 1.80–2.33).

Table 1

General characteristics of participants.

Characteristics	Total participants: Appendectomy (n, %)	Total participants: Control group (n, %)	*P* value
Age (years old)			1.000
20–24	1,811 (12.0)	7,244 (12.0)	
25–29	2,015 (13.4)	8,060 (13.4)	
30–34	2,054 (13.6)	8,216 (13.6)	
35–39	1,834 (12.2)	7,336 (12.2)	
40–44	1,627 (10.8)	6,508 (10.8)	
45–49	1,331 (8.8)	5,324 (8.8)	
50–54	1,191 (7.9)	4,764 (7.9)	
55–59	901 (6.0)	3,604 (6.0)	
60–64	710 (4.7)	2,840 (4.7)	
65–69	608 (4.0)	2,432 (4.0)	
70–74	464 (3.1)	1,856 (3.1)	
75–79	288 (1.9)	1,152 (1.9)	
80–84	168 (1.1)	672 (1.1)	
85+	60 (0.4)	240 (0.4)	
Sex			1.000
Male	7,605 (50.5)	30,420 (50.5)	
Female	7,457 (49.5)	29,828 (49.5)	
Income			1.000
1 (lowest)	142 (0.9)	568 (0.9)	
2	938 (6.2)	3,752 (6.2)	
3	1,112 (7.4)	4,448 (7.4)	
4	1,200 (8.0)	4,800 (8.0)	
5	1,338 (8.9)	5,352 (8.9)	
6	1,479 (9.8)	5,916 (9.8)	
7	1,561 (10.4)	6,244 (10.4)	
8	1,670 (11.1)	6,680 (11.1)	
9	1,766 (11.7)	7,064 (11.7)	
10	1,914 (12.7)	7,656 (12.7)	
11 (highest)	1,942 (12.9)	7,768 (12.9)	
Region of residence			1.000
Urban	6,773 (45.0)	27,092 (45.0)	
Rural	8,289 (55.0)	33,156 (55.0)	
Hypertension	3,246 (21.6)	12,984 (21.6)	1.000
Diabetes	1,647 (10.9)	6,588 (10.9)	1.000
Dyslipidemia	2,793 (18.5)	11,172 (18.5)	1.000
Ischemic heart disease	616 (4.1)	2,093 (3.5)	<.001*
Cerebral stroke	924 (6.1)	3,378 (5.6)	.013*
Depression	1,269 (8.4)	4,367 (7.2)	<.001*
GERD with PPI prescription ≥ 14 days	1,713 (11.4)	4,947 (8.2)	<.001*
GERD with PPI prescription ≥ 30 days	646 (4.3)	1,950 (3.2)	<.001*
GERD with PPI prescription ≥ 60 days	327 (2.2)	993 (1.6)	<.001*

* Chi-square test. Significance at $P<.05$.
GERD = gastro esophageal reflux diseases.

PPI is the most common treatment for GERD, but it might cause appendicitis. The shared pathogenesis between GERD and appendectomy is not clear. PPI may alter the microbiome in the gastrointestinal (GI) tract,[15] and bacterial growth, such as Fusobacterium, may cause appendicitis.[16] Prolonged use of PPIs increases the pH of gastric acid and decreases antibacterial activity, which may cause various infections, such as pneumonia or clostridium difficile infections.[17] In this study, we analyzed the ORs for GERD in participants with long-term PPI use (≥ 30 days and ≥ 60 days). We did not analyze intermittent times or PPI dose, but participants with GERD and long-term PPI use did not exhibit higher ORs than the total sample of participants with GERD.

Both GERD and appendicitis could be affected by autonomic imbalance. Low sphincter pressure, transient lower esophageal sphincter relaxation, problem of esophageal clearance could result in GERD.[4] Dysfunction of autonomic nervous system such as reduced parasympathetic activity, could result in GERD.[18] Abnormal proliferation of nerve fibers in the appendix could provoke appendicitis with increased levels of neuropeptides such as vasoactive intestinal peptide and substance P.[11,19]

Dietary factors may act as confounders between appendicitis and GERD. A low fiber and high carbohydrate diet may be responsible for appendicitis,[20] and these factors also increase the risk of GERD.[21] GI motility may affect appendicitis and GERD. Direct luminal obstruction may cause appendicitis.[11] Decreased gastric motility and esophageal clearance may cause GERD.[22] GERD is associated with sarcoidosis, amyloidosis, hypothyroidism,

Table 2

Crude and adjusted odd ratios (95% confidence interval) of GERD for appendectomy (n = 75,310).

Characteristics	GERD: Crude	*P* value	Adjusted†	*P* value
Appendectomy	1.38 (1.31–1.46)	<.001*	1.37 (1.30–1.45)	<.001*
Control	1.00		1.00	

GERD = gastro esophageal reflux diseases.
* Logistic regression analyses, Significance at $P<.05$.
† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, and depression histories.

Table 3

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

Characteristics	GERD: Crude	*P* value	Adjusted†	*P* value
Age < 40 years old, men (n = 19,870)				
Appendectomy	1.37 (1.18–1.61)	<.001*	1.37 (1.18–1.61)	<.001*
Control	1.00		1.00	
Age < 40 years old, women (n = 18,700)				
Appendectomy	1.47 (1.28–1.69)	<.001*	1.45 (1.26–1.67)	<.001*
Control	1.00		1.00	
Age ≥ 40 years old & < 60 years old, men (n = 12,910)				
Appendectomy	1.36 (1.21–1.53)	<.001*	1.35 (1.20–1.52)	<.001*
Control	1.00		1.00	
Age ≥ 40 years old & < 60 years old, women (n = 12,340)				
Appendectomy	1.37 (1.23–1.54)	<.001*	1.36 (1.22–1.53)	<.001*
Control	1.00		1.00	
Age ≥ 60 years old, men (n = 5,245)				
Appendectomy	1.24 (1.08–1.43)	.002*	1.23 (1.08–1.42)	.003*
Control	1.00		1.00	
Age ≥ 60 years old, women (n = 6,245)				
Appendectomy	1.43 (1.27–1.61)	<.001*	1.41 (1.25–1.59)	<.001*
Control	1.00		1.00	

GERD = gastro esophageal reflux diseases.
* Logistic regression analyses, Significance at $P<.05$.
† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, and depression histories.

Table 4

Analyses of crude and adjusted odd ratios (95% confidence interval) of GERD for appendectomy according to the dates of PPI prescription (n=75,310).

Characteristics	GERD			
	Crude	*P* value	Adjusted†	*P* value
GERD with PPI prescription ≥ 30 days				
Appendectomy	1.33 (1.21–1.45)	<.001*	1.31 (1.20–1.43)	<.001*
Control	1.00		1.00	
GERD with PPI prescription ≥ 60 days				
Appendectomy	1.32 (1.16–1.49)	<.001*	1.30 (1.15–1.48)	<.001*
Control	1.00		1.00	

GERD=gastro esophageal reflux diseases, PPI=proton pump inhibitor.
* Logistic regression analyses, Significance at $P<.05$.
† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, cerebral stroke, and depression histories.

rheumatoid arthritis, mixed connective tissue disorders, Sjögren syndrome, systemic sclerosis, diabetes mellitus, cholecystectomy, and sleeve gastrectomy.[22] These diseases might affect the motility of the GI track and result in appendicitis.

The hygiene hypothesis may contribute to both GERD and appendicitis. The hygiene hypothesis was proposed as a trigger for appendicitis because epidemic appendicitis appears in development.[20] Increased hygiene decreases infections in infants, which subsequently decreases immunity[20] and may increase the risk of appendicitis. GERD is more common in developed countries,[23] thus appendicitis may also be increased in developments.[20] Therefore, the association between appendicitis and GERD might be confounded by the effects of development.

The advantages of this study are consistent with those of our previous studies using the national sample cohort.[24–26] We used a large representative nationwide population. No participants dropped out during the follow-up period because NHIS data include all Korean citizens without exception. Participants in the control group were randomly selected and matched for age, sex, income, region of residence, and medical histories to avoid confounding effects. An adjusted logistic regression model was used to minimize confounders. We maintained statistical power when participants were stratified into subgroups for further analyses because of the large number of participants. This study complements a previous study that did not analyze participants according to sex.[12] In this study, we found consistent results regardless of sex. We used patient claim codes in the HIRA data to identify GERD and appendectomy. These recorded data are not distorted by patient memory, which represents a common issue when using survey questionnaires. Surgical claim codes (appendectomy) are reviewed for accuracy by HIRA due to premium costs. The estimated prevalence of GERD was 5.24% (707,620/1,125,691 * 12 years) in this study, which is within the range of the known prevalence of GERD (4.6–7.3%) in Korea.[3]

This study has several limitations. We did not analyze the severity of GERD in participants. Patients with GERD might have been overlooked if these patients did not visit a clinic. We used appendectomy rather than appendicitis itself to obtain an accurate diagnosis. However, appendectomy may be a surrogate marker of appendicitis. We did not analyze the possible confounding factors, such as obesity, smoking, and dietary habits, between GERD and appendicitis. Microbiology, such as bacterial or viral infections of the GI tract, was not evaluated.

5. Conclusions

The Odds for GERD increased in participants who received an appendectomy. This relationship was consistent in all age groups and in both genders. Patients with GERD and long-term PPI use did not exhibit higher ORs than the total sample of participants with GERD.

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Author contributions

Conceptualization: Hyo Geun Choi.
Formal analysis: Hyung-Jong Kim, Hyun Lim, Man Sup Lim.
Supervision: Hyo Geun Choi.
Writing – original draft: So Young Kim, Hyo Geun Choi.
Writing – review & editing: So Young Kim, Hyung-Jong Kim, Man Sup Lim, Miyoung Kim, Hyo Geun Choi.
Hyo Geun Choi orcid: 0000-0003-1655-9549.

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