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Asthma and risk of appendicitis in children: a population-based case-control study

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Abstract

Objective—To assess whether asthma is associated with risk of appendicitis in children.

Methods—We used a population-based case-control study design utilizing a comprehensive medical record review and predetermined criteria for appendicitis and asthma. All children (age<18 years) who resided in Olmsted County, Minnesota, and developed appendicitis between 2006 and 2012 were matched to controls (1:1) with regard to birthday, gender, registration date, and index date. Asthma status was ascertained using predetermined criteria. Active (current) asthma was defined as the presence of asthma symptoms or asthma-related events (eg, medication use, clinic visits, emergency department, or hospitalization) within one year prior to the index date. Inactive asthma was defined as subjects without these events. A conditional logistic regression model was used.

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Results—Among the 309 appendicitis cases identified, when stratified by asthma status, active asthma was associated with significantly increased risk of appendicitis when compared to inactive asthma (OR=2.48; 95% CI, 1.22–5.03) and to no asthma (OR=1.88; 95% CI, 1.07–3.27) (overall p-value=0.035). When controlling for potential confounders such as gender, age, and smoking status, active asthma was associated with a higher odds of developing appendicitis compared to non-asthmatics (adjusted OR=1.75, 95% CI 0.99–3.11) whereas inactive asthma was not (overall p-value=0.049). Tobacco smoke exposure within three months was associated with an increased risk of appendicitis (adjusted OR=1.66; 95% CI, 1.02, 2.69). Among asthma medications, leukotriene receptor antagonists reduced the risk of appendicitis (OR=0.18; 95% CI, 0.04–0.74).

Conclusions—Active asthma may be an unrecognized risk factor for appendicitis in children while a history of inactive asthma does not pose such risk. Further investigation exploring the underlying mechanisms is warranted.

Keywords

Appendicitis; asthma; control; risk; atopy; gastrointestinal inflammation; and epidemiology

INTRODUCTION

Asthma is the most common chronic childhood illness in the United States, causing significant morbidity and mortality. Prevalence of asthma in the United States (US) in 2010 was 9.8% for women and 7.0% for men, affecting 25.7 million Americans, of which 7.0 million (9.3%) were children aged 0–17 years.¹ Globally, nearly 300 million people are affected by asthma.² Previous studies have shown that individuals with asthma have an increased risk of serious and common infections of the respiratory tract, such as invasive pneumococcal diseases,^{3,4} *Streptococcus pyogenes*,⁵ *Bordetella pertussis*,⁶ *Staphylococcus aureus*,⁷ otitis media,⁷ otitis media,⁸ and *Mycoplasma pneumoniae*.⁹ and adaptive immunity,¹⁰ which may partly explain this increased propensity for infection. A recent review has posited that asthma may be more than a just a chronic airway disease as asthma also appears to possess features characteristic of systemic immune dysfunction.¹¹

In addition, recent studies have shown that asthma is associated with an increased risk of infection beyond the respiratory tract. For example, asthma has been reported to be associated with an increased risk of community-acquired *E. coli* bacteremia.¹² In addition, asthma was found to be significantly associated with herpes zoster reactivation causing shingles, a latent viral infection involving neural tissue.¹³ However, no previous study has looked at whether asthma is associated with gastrointestinal infections/inflammation such as appendicitis. Both asthma and appendicitis share similar epidemiological trends, such as the rising incidence in the US, higher rates in children, and seasonal variation with higher incidence of asthma attacks and appendicitis in the summer and fall seasons, suggesting potential common underlying pathway.¹⁴ The overall incidence of appendicitis in children age 0–19 was 119.7 per 100,000 with a cumulative incidence of 3.2% by age 20.¹⁵

Investigating the relationship between asthma and appendicitis will provide insights into the nature of the impact of asthma on the risk of infection because 1) appendicitis is not an airway-related infection but gastrointestinal in origin, 2) infection or inflammation is

involved in the pathophysiology, and 3) appendicitis is the most common cause for emergency abdominal surgery in children worldwide without known risk factors (suggesting unrecognized risk factors).¹⁶ We hypothesize that individuals with asthma have an increased risk of appendicitis as compared to those without asthma. To test this hypothesis, we conducted a retrospective population-based case-control study.

METHODS

Study setting

Rochester, Minnesota, is located in Southeast Minnesota and centrally within Olmsted County. During the study period, characteristics of the Rochester and Olmsted County populations were similar to those of the U.S. Caucasian population, with the exception of a higher proportion of the working population employed in the health care industry.^{17–19} Olmsted County, Minnesota, is an excellent setting to conduct a population-based epidemiologic study because medical care is virtually self-contained within the community. Authorization to use medical records for research is granted by over 95% of all individuals.²⁰ Medical records research using the geographically-defined population of Olmsted County is possible through the Rochester Epidemiology Project (REP) which has been continuously funded by NIH and maintained since 1966.²¹ The REP database consists of all inpatient and outpatient medical records from two major medical centers and numerous physician practices located in Olmsted County, Minnesota. Only those individuals with current, written research authorization were included in this study. The population demographics of Olmsted County and of those included the REP database have been previously described.²²

Study design

A retrospective population-based case-control design was employed. Children with appendicitis (cases) and their matched controls were identified from the REP database. Asthma status was assessed in both cases and controls. The Olmsted County Medical Center and Mayo Clinic Institutional Review Boards approved this study.

Identification of Appendicitis Cases

All individuals less than 18 years of age who had developed potential appendicitis (International Classification of Diseases, Ninth Revision (ICD-9) codes 540, 541, and 542) during the study period of 2006 to 2012 were identified. The entire medical record of each case was reviewed to determine if appendicitis identified by ICD-9 codes met the inclusion criteria outlined in Table 1. We included both definite and probable diagnoses as cases. Definite appendicitis required the presence of all three criteria: 1) a physician diagnosis of appendicitis, 2) confirmed surgeon's diagnosis OR evidence of periappendiceal abscess or ruptured appendicitis OR imaging study suggestive of appendicitis, 3) histopathological evidence of appendicitis (i.e., surgical pathology report demonstrating appendiceal transmural inflammation, necrosis and/or perforation) Probable appendicitis required the first two criteria when histopathological report was not available. The index date was defined as the date of appendectomy or date of probable or definite appendicitis diagnosis whichever came first (i.e., the time when one meets the criteria for case ascertainment).

The exclusion criteria included: 1) an appendectomy for an indication other than appendicitis (i.e., an incidental appendectomy, no appendicitis upon histopathological examination); 2) a gastrointestinal tract disorder that predisposed to appendicitis and/or appendectomy was present at or before the index date (e.g., celiac disease, Crohn's disease, ulcerative colitis); 3) clinical conditions making asthma ascertainment difficult (pulmonary function tests showed an FEV1 to be consistently below 50% predicted or evidence of diminished diffusion capacity, a tracheobronchial foreign body, wheezing occurred only in response to anesthesia or medications, bullous emphysema or pulmonary fibrosis was present on chest radiograph, or if PiZZ alpha1-antitrypsin, cystic fibrosis, or other major chest disease such as severe kyphoscoliosis or bronchiectasis) and could have a different underlying pathophysiology from asthma; 4) insufficient medical records to determine exposure (asthma) and outcome events (appendicitis); and 5) non-Olmsted County residency at index date or 12 months prior to the index date.

Selection of Controls

Controls were identified in the REP database as those who did not have ICD-9 codes for appendicitis (540, 541, and 542) and were matched to cases based upon date of birth (within one year), gender, clinic registration year (beginning of ascertained medical record), and clinic visit within the same year (end of ascertained medical record) to ensure similar exposure length (follow-up duration) and therefore detection rates between cases and controls. The index date for controls was defined as the closest clinic visit date (within one year) to the index date of their corresponding case. If multiple controls were identified, the list of controls in a random order was generated and then, abstractor applied the inclusion/exclusion criteria from control listed on the top until abstractor found the first control who met inclusion criteria. Controls were held to the same exclusion criteria as cases.

Asthma Ascertainment

Each case and control underwent a comprehensive medical record review. We determined asthma status prior to the index date for both cases and controls according to predetermined criteria outlined in Table 2. Both definite and probable asthma statuses were defined as asthma because probable asthma mostly became definite asthma over time.^{19,23}

We also classified asthma status as active vs. inactive asthma. Active or current asthma was defined as either the presence of asthma symptoms (e.g. wheezing, night cough, dyspnea), use of asthma control medications (e.g. short-acting beta agonists, inhaled corticosteroids, leukotriene inhibitors), and/or outpatient, inpatient or emergency department visits for asthma within 12 months of the index date. Inactive asthma was defined as the absence of asthma-related events within 12 months of the index date among children with asthma. The medication data was collected from medical records which are documented by nurses based on patient's (or parents'/guardians') report during the time of the office visit (i.e., not prescription data). This medication list is reviewed with the patient and updated accordingly during each visit to the physician.

Other variables

Other pertinent variables were collected. Atopic conditions other than asthma including atopic dermatitis (eczema) and allergic rhinitis; family history of asthma and other atopic conditions; household smoking status; pneumococcal and influenza vaccine status (as a proxy of access to health care); common co-morbid conditions such as drug allergy or mental illness (migraines and attention deficit hyperactivity disorder); recent gastrointestinal infection; and medication use were collected.

Statistical Analysis

We summarized characteristics of appendicitis cases and matched controls using descriptive statistics. Association of each characteristic, including history of asthma and asthma status based on current symptoms (i.e., no asthma, inactive asthma, and active asthma), with risk of appendicitis was tested using conditional logistic regression models. Additional multivariable conditional analysis was performed to further assess the association of asthma, controlling for pertinent covariates and confounders having association p-values less than 0.2 from univariate analysis (Greenland criteria).⁴² Odds ratio (OR) and its 95% confidence interval (CI) were presented for all analysis. All analyses were performed using JMP statistical software package (Ver 10.0.0; SAS Institute, Inc, Cary, NC).

RESULTS

Study Subjects

Of the total 378 potential appendicitis cases identified between 2006 and 2012, 69 were excluded. The reasons for exclusion included: no research authorization (n=18), incorrect ICD-9 code assignment for appendicitis (n=16), non-Olmsted County residency (n=13), incidental appendectomy performed during an unrelated procedure (n=7), gastrointestinal comorbidity that have predisposition to appendectomy (n=6), insufficient measurement data in medical record (n=6), respiratory comorbidity (n=2), and medical record unavailable (n=1). Summary of the characteristics of the cases (n=309) and controls (n=309) are summarized in Table 3.

Asthma and risk of appendicitis

No significant difference in a history of asthma (both inactive and active asthma) at time of index date between cases and controls was noted (24.5% in cases vs. 22.3% in controls; OR=1.15; 95% CI, 0.78–1.69). However, when stratified by asthma status, active asthma was associated with a significantly increased risk of appendicitis compared to those with either inactive asthma (unadjusted OR=2.48; 95% CI, 1.22–5.03) or no prior history of asthma (unadjusted OR=1.88; 95% CI, 1.07–3.27). This association persisted after controlling for other pertinent factors such as smoke exposure and migraines using a multivariate model for active asthma compared to no asthma (adjusted OR: 1.75, 95%CI: 0.99–3.11) as seen in Table 4 (overall p-value=0.049). To discern the potential associations between asthma medications used by patients with active asthma and the risk of appendicitis, we examined the frequency of individual asthma medication use between cases and controls. As summarized in Table 5, none of the asthma medications were associated

with the risk of appendicitis except leukotriene receptor antagonist (unadjusted OR=0.18; 95% CI, 0.04–0.74).

Other variables and association with risk of appendicitis

Subjects who had atopic dermatitis, allergic rhinitis, or food allergies were not found to be at increased risk of appendicitis. Although atopic dermatitis met Greenland criteria ($P=0.18$), it was not included in the multivariate model given potential biological collinearity. A family history of asthma and other atopic conditions were not associated with risk of appendicitis. A history of migraines was not significantly associated with risk of appendicitis in univariate or multivariate analysis.

Although tobacco smoke exposure within three months of the index date failed to reach statistical significance with regard to the association with an increased risk of appendicitis in univariate analysis (unadjusted OR=1.57; 95% CI, 0.98–2.52), this association was statistically significant in a multivariate model adjusting for asthma status and migraines (adjusted OR=1.66; 95% CI, 1.02–2.69).

Subjects who were immunized with the influenza vaccine or pneumococcal vaccine showed no association with appendicitis. No associations were also found when looking at other comorbidities, such as migraines, attention deficit hyperactive disorder, and drug allergy, which were selected as the most common three comorbidities among cases in this study.

DISCUSSION

The association between asthma and the risk of appendicitis has not been previously studied. To our knowledge, this is the first population-based study that demonstrated an association between active asthma and an increased risk of appendicitis. While a history of inactive asthma was not associated with appendicitis, active asthma was associated with the risk of appendicitis compared to those with inactive or no asthma. This association was independent of age, gender, and smoking exposure.

We believe that susceptibility bias, such as covariate imbalance at baseline, is unlikely to account for the association found in our study because potential confounders were adjusted for in our analysis. However, there might be potential unmeasured confounders for our study. Since detection of asthma depends on follow-up duration from registration to index date of appendicitis, we designed our study to ensure that a follow-up duration was similar between cases and controls by matching registration date and index date to limit detection and lead time bias. There were no differences in rates of vaccination for influenza and PPV23 between cases and controls, which may imply similar access to healthcare services between the two groups. Atopic conditions such as atopic dermatitis, allergic rhinitis, and food allergies were not associated with increased risk of appendicitis. This may be due to the greater misclassification bias of ascertainment of allergic rhinitis, atopic dermatitis, and food allergy by ICD-9 code compared to asthma status by predetermined criteria in our study. Taken together, our study results suggest that active asthma status is independently associated with an increased risk of appendicitis.

Because no prior population-based studies exist, it is difficult to compare our results with those of previous studies. There is only one previous case-control study conducted in Turkey assessed the relationship between atopic sensitization status and the risk of appendicitis based on a convenience sample in a single institution.²⁴ The study reported that atopy status, determined by skin prick test (SPT) for inhalants or foods, was associated with an increased risk of appendicitis (34% in cases vs 8% in controls, $p < 0.001$). The study hypothesized that atopic sensitization, especially food allergy, might cause eosinophilic infiltration in appendix resulting mucosal swelling and narrowing of appendix leading to inflammation and infection. However, eosinophilic infiltration in appendectomy specimen, peripheral eosinophil count or the degree of inflammation in SPT was not associated with the risk of appendicitis.²⁴ As our study subjects did not have data on atopic sensitization, we could not address the relationship between atopic status and the risk of appendicitis in this manner. However, a history of food allergy in our study was not associated with the risk of appendicitis.

Although overall incidence of appendicitis in the US since 1993 increased with the highest frequency in the 10 to 19 year age group, the etiology of appendicitis remains under investigation.¹⁴ The overall incidence of appendicitis in children age 0–19 was 119.7 per 100,000, which is slightly less when compared to incidence rate in our study of 132.7 per 100,000.¹⁵ The incidence rate was highest in our study among those between ages 14 and 17, which is consistent with the ages of peak incidence rates in previous studies.^{15,25}

The two most well validated criteria for diagnosing children with suspected appendicitis (Pediatric Appendicitis Score and Alvarado Score) failed to meet current performance benchmarks for clinical prediction rules, suggesting a lack of identifiable risk factors that can accurately predict appendicitis.²⁶ Appendicitis has been thought to be the result of obstruction of the appendicular lumen leading to increased luminal pressure and subsequent inflammation. However, a study measuring the intraluminal pressure in patients with appendicitis showed increased pressure in only 25% of the patients, suggesting that obstruction may develop as a result of the inflammatory process rather than being a causative agent.²⁷ Similarly, a more recent study showed that fecaliths were identified in only 18% of patients with appendicitis and in 29% of those without appendicitis.²⁸ In our study, fecaliths were present in 37.7% of the pathology reports, which suggests that another mechanism may have a more significant causative role. More recent work has suggested that appendicitis may be driven by inflammation, and may be mediated via immunologic mechanisms.^{29,30} Therefore, the inflammatory states of asthma and its underlying immunologic pathology may put individuals at an increased risk for appendicitis. In the early stages of appendicitis, mucosal epithelium disruption with invasive bacterial infection, ulceration, and inflammation before dilation of the appendix are characteristic pathologic findings.³¹ A recent clinical trial showed that antibiotic therapy alone for CT-proven, uncomplicated appendicitis was not inferior to appendectomy (difference: -27% , 95%CI: -31.6% to ∞) in the primary end point (discharge without need for surgery and no recurrence of appendicitis in one year for antibiotic therapy group and successful completion of appendectomy).³² Given the multiple potential causes for appendicitis, the large proportion of children affected by asthma, and the potential benefit for using antibiotic use

in a certain subset of patients, a history of active asthma might be an important unrecognized risk factor for appendicitis.

The main strengths of our study include the population-based study design, ascertainment of asthma by predetermined criteria independent of physician diagnosis of asthma or ICD-9 code. Second, epidemiologic advantages for our study setting include a self-contained healthcare environment with a comprehensive, unified medical record system for research. Finally, our previous study results, which showed the association between asthma and non-respiratory infections, were based on the same asthma criteria as this study.¹²

This study has the inherent limitations of a retrospective study. For example, we obtained medication data from parents'/caregivers' report on medication use at each visit but we could not ensure medication adherence. Although we adjusted the main results for age, sex, and smoking status, we did not adjust for potential cofounders such as body mass index as they were unavailable at index date. We did not obtain laboratory information, such as atopic sensitization data or inflammatory markers described above under the potential mechanisms. Generalization of our results to other ethnicities needs to be cautious because of a predominantly white population in our study.

In summary, active asthma may be an unrecognized risk factor for developing appendicitis in children. Further investigation exploring the potential benefit of leukotriene receptor antagonist among patients with asthma in reducing the risk of appendicitis is warranted. As asthma may increase the risk of gastrointestinal infection and inflammation as found in appendicitis, the impact of asthma seems to go beyond airway-related morbidity.

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Abbreviations

OR	odds ratios
CI	confidence intervals
REP	Rochester Epidemiology Project
ICD-9	International Classification of Disease
AD	allergic dermatitis
AR	allergic rhinitis
REP	Rochester Epidemiology Project
NIH	National Institutes of Health

ICD-9	International Classification of Disease
SPT	skin prick test

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WHAT'S NEW

Active asthma is associated with increased risk of appendicitis. Clinicians and parents whose children have asthma should make an effort to control asthma through preventive and therapeutic interventions to decrease the risk of non-respiratory morbidity such as appendicitis associated with active asthma status.

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Table 1

The Criteria for Appendicitis Cases

Definite appendicitis = meets all 3 criteria listed below	
Probable appendicitis =meets only criteria #1 and/or #2 below	
1	Physician diagnosis of appendicitis
2	Confirmed surgeon's diagnosis of appendicitis OR evidence of periappendiceal abscess OR ruptured appendicitis after appendectomy OR imaging suggestive of appendicitis
3	Histopathologic evidence of appendicitis (surgical pathology report demonstrating appendiceal transmural inflammation, necrosis and/or perforation)
Patients were excluded from the study if any of these conditions were present:	
<ul style="list-style-type: none">• Incidental appendectomy (e.g., pathology did not show evidence of appendicitis, appendectomy occurred during other surgery)• Evidence of a known gastrointestinal tract disorder that may have predisposition towards appendectomy, including Celiac disease, Crohn's disease and ulcerative colitis.	

Table 2**Definition of Asthma**

Definite asthma = a physician had made a diagnosis of asthma and the presence of two of the following 3 conditions or if each of the following 3 conditions were present.

Probable asthma = only 2 of the following 3 conditions were present or a physician had made a diagnosis of asthma with either none or only one of the following three conditions:

- 1** History of cough with dyspnea and/or wheezing, OR history of cough and/or dyspnea plus wheezing on examination,
- 2** Substantial variability in symptoms from time to time or periods of three weeks or more when symptoms were absent, and
- 3** Two or more of the following:
 - Sleep disturbance by nocturnal cough and wheeze
 - Nonsmoker (14 years or older)
 - Nasal polyps
 - Blood eosinophilia higher than 300/ μ L
 - Positive wheal and flare skin tests OR elevated serum IgE
 - History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen
 - Pulmonary function tests showing one FEV₁ or FVC < 70% predicted and another with at least 12% improvement to an FEV₁ of higher than 70% predicted OR methacholine challenge test showing 20% decline in FEV₁
 - Favorable clinical response to bronchodilator (e.g., documented 12% improvement of FEV₁ on spirometry after bronchodilator therapy)

Table 3

Sociodemographic and Clinical Characteristics of Cases and Matched Controls, Olmsted County, Minnesota, 2006–2012

Characteristics	Controls (N=309)	Cases (N=309)	Odds ratio	95% CI
<i>Sociodemographic factors</i>				
Age at case's index date (year)				
Mean (SD)	12.4 (3.9)	12.2 (3.9)		
Median (IQR)	12.7 (9.4, 15.8)	12.6 (9.3, 15.5)		
Gender: n (%)				
Male	185 (60%)	185 (60%)		
Female	124 (40%)	124 (40%)		
Ethnicity: n (%)				
Caucasian	246 (80%)	244 (79%)	Referent	Referent
Non-Caucasian	59 (19%)	61 (20%)	1.05	0.67, 1.64
Unknown	4 (1%)	4 (1%)	1.01	0.25, 4.07
<i>Asthma and other atopic conditions</i>				
Family History of atopic conditions: n (%)				
Asthma	61 (20%)	62 (20%)	1.02	0.69, 1.50
Atopic Dermatitis (AD) and/or Allergic Rhinitis (AR)	67 (22%)	70 (23%)	1.06	0.72, 1.55
History of asthma: n (%)				
No	240 (78%)	233 (75%)	Referent	Referent
Yes	69 (22%)	76 (25%)	1.15	0.78, 1.69
Asthma status: n (%)				
No asthma	240 (78%)	233 (75%)	Referent	Referent
Inactive asthma ^b	46 (15%)	35 (11%)	0.76	0.46, 1.26
Active asthma ^a	23 (7%)	41 (13%)	1.88	1.07, 3.27
Other atopic conditions: n (%)				
Atopic dermatitis (AD)	40 (13%)	52 (17%)	1.36	0.87, 2.14
Allergic rhinitis (AR)	84 (27%)	81 (26%)	0.95	0.66, 1.37
AD and/or AR	99 (32%)	107 (35%)	1.13	0.80, 1.60
Food allergy: n (%)				
No food allergy	297 (96%)	301 (97%)	Referent	Referent
History of food allergy	12 (4%)	8 (3%)	0.66	0.27, 1.63
<i>Other variables</i>				
Smoking status: n (%)				
Never exposed to smoke	229 (74%)	231 (75%)	Referent	Referent
Past exposure to smoke	15 (5%)	8 (3%)	0.56	0.24, 1.33
Current exposure to smoke	32 (10%)	51 (17%)	1.57	0.98, 2.52
No Documentation	33 (11%)	19 (6%)	0.55	0.29, 1.02
Vaccination Status: n (%)				
Influenza Vaccine	119 (39%)	126 (41%)	1.11	0.79, 1.56
Pneumococcal Vaccine (PPV23)	4 (1%)	5 (2%)	1.33	0.30, 5.96

Characteristics	Controls (N=309)	Cases (N=309)	Odds ratio	95% CI
Comorbidities				
Migraine	11 (4%)	19 (6%)	1.73	0.82, 3.63
ADHD	44 (14%)	40 (13%)	0.90	0.56, 1.42
Drug Allergy	49 (16%)	57 (19%)	1.20	0.79, 1.83

^aActive (or current asthma) was defined as the presence of asthma-related events including asthma symptoms, or use of asthma medications, and outpatient/emergency department/hospitalization for asthma within one year prior to index date of appendicitis;

^bInactive asthma was defined as the presence of asthma-related events > 12 months prior to index date.

Table 4

Multivariate Analysis of the Association Between Asthma Status and Risk of Appendicitis Using

	Unadjusted OR	95% CI	Adjusted OR	95% CI
Asthma Status	<i>P</i> =0.035		<i>P</i> =0.049	
No asthma (n=473)	Referent	Referent	Referent	Referent
Inactive asthma ^b (n=81)	0.76	0.46, 1.26	0.70	0.42, 1.19
Active asthma ^a (n=64)	1.88	1.07, 3.27	1.75	0.99, 3.11
Smoke Exposure Status	<i>P</i> =0.021		<i>P</i> =0.028	
Never exposed to smoke (n=460)	Referent	Referent	Referent	Referent
Past exposure to smoke (n=23)	0.56	0.24, 1.33	0.60	0.25, 1.45
Current exposure to smoke (n=83)	1.57	0.98, 2.52	1.66	1.02, 2.69
No documentation to smoke (n=52)	0.55	0.29, 1.02	0.58	0.31, 1.10
Migraine Status	<i>P</i> =0.149		<i>P</i> =0.279	
No migraine (n=588)	Referent	Referent	Referent	Referent
Migraine (n=30)	1.73	0.82, 3.63	1.54	0.71, 3.37

^a Active (or current asthma) was defined as the presence of asthma-related events including asthma symptoms, or use of asthma medications, and outpatient/emergency department/hospitalization for asthma within one year prior to index date of appendicitis;

^b Inactive asthma was defined as the presence of asthma-related events > 12 months prior to index date.

Table 5

The association between asthma medications and the risk of appendicitis among patients with active asthma

Asthma therapy	Controls (N=23)	Cases (N=41)	Unadjusted OR	95% CI
Any asthma medication use vs. none	22 (96%)	38 (93%)	0.47	0.04, 4.91
Inhaled corticosteroid vs. without	10 (44%)	18 (44%)	0.87	0.29, 2.58
Oral systemic corticosteroid vs. without	4 (17%)	2 (5%)	0.23	0.04, 1.43
Short acting beta agonist vs. without	22 (96%)	38 (93%)	0.47	0.04, 4.91
Long acting beta agonist vs. without	2 (9%)	3 (7%)	0.94	0.14, 6.30
Leukotriene receptor antagonist vs. without	8 (35%)	5 (12%)	0.18	0.04, 0.74

^a Asthma medication use overall and specific medication use in active asthma subjects were compared between appendicitis cases vs. matched controls adjusted for age and sex.