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 using a comprehensive medical record review and predetermined criteria for appendicitis and asthma. All children (age younger than 18 years of age) 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 1 year before the index date. Inactive asthma was defined as subjects without these events. A conditional logistic regression model was used.

Results: Among the 309 appendicitis cases identified, when stratified according to asthma status, active asthma was associated with significantly increased risk of appendicitis compared with inactive asthma (odds ratio [OR] = 2.48; 95% confidence interval [CI], 1.22–5.03) and to no asthma (OR = 1.88; 95% CI, 1.07–3.27; overall $P = .035$). When controlling for potential confounders such as gender, age, and smoking status, active asthma was associated with a higher odds of developing appendicitis compared with nonasthmatic patients (adjusted OR = 1.75; 95% CI, 0.99–3.11) whereas inactive asthma was not (overall $P = .049$). Tobacco smoke exposure within 3 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 might be an unrecognized risk factor for appendicitis in children whereas a history of inactive asthma does not pose such risk. Further investigation exploring the underlying mechanisms is warranted.

Keywords: appendicitis; asthma; atopy; control; epidemiology; gastrointestinal inflammation; risk

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What's New

Active asthma is associated with an 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 nonrespiratory morbidity such as appendicitis associated with active asthma status.

ASTHMA IS THE most common chronic childhood illness in the United States, causing significant morbidity and mortality. Prevalence of asthma in the United States 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 to 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,[7,8] *Mycoplasma pneumoniae*,[9] and adaptive immunity,[10] which might in part explain this increased propensity for infection. A recent review has posited that asthma might be more than just a chronic airway disease because 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 *Escherichia 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 investigated whether asthma is associated with gastrointestinal infections/inflammation such as appendicitis. Asthma and appendicitis share similar epidemiological trends, such as the rising incidence in the United States, higher rates in children, and seasonal variation with higher incidence of asthma attacks and appendicitis in the summer and fall seasons, suggesting a potential common underlying pathway.[14] The overall incidence of appendicitis in children age 0 to 19 years was 119.7 per 100,000 with a cumulative incidence of 3.2% by age 20 years.[15]

Investigating the relationship between asthma and appendicitis will provide insights into the nature of the effect 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 compared with 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 US 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 >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 the National Institutes of Health and maintained since 1966.[21] The REP database consists of all inpatient and outpatient medical records from 2 major medical centers and numerous physician practices located in Olmsted County, Minnesota. Only individuals with current, written research authorization were included in this study. The population demographic characteristics 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 used. Children with appendicitis (cases) and their matched control subjects were identified from the REP database. Asthma status was assessed in cases and control subjects. The Olmsted County Medical Center and Mayo Clinic institutional review boards approved this study.

IDENTIFICATION OF APPENDICITIS CASES

All individuals younger 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 definite and probable diagnoses as cases. Definite appendicitis required the presence of all 3 of the following 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 (ie, surgical pathology report demonstrating appendiceal transmural inflammation, necrosis and/or perforation). Probable appendicitis required the first 2 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 (ie, the time when one meets the criteria for case ascertainment).

The exclusion criteria included: 1) an appendectomy for an indication other than appendicitis (ie, 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 (eg, celiac disease, Crohn disease, ulcerative colitis), 3) clinical conditions making asthma ascertainment difficult (pulmonary function tests showed a forced expiratory volume in the first second to be consistently <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 α1-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 before the index date.

Table 1. The Criteria for Appendicitis Cases

Definite appendicitis = meets all 3 criteria listed below
Probable appendicitis = meets only criteria number 1 and/or number 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 showing appendiceal transmural inflammation, necrosis, and/or perforation)

Patients were excluded from the study if any of the following conditions were present:

- Incidental appendectomy (eg, pathology did not show evidence of appendicitis, appendectomy occurred during other surgery)
- Evidence of a known gastrointestinal tract disorder that might have predisposition toward appendectomy, including Celiac disease, Crohn disease, and ulcerative colitis.