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TITLE PAGE

Original Article

Asthma and Risk of Non-Respiratory Tract Infection: A Population-Based Case Control Study

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Conflict of interest: The study investigators have nothing to disclose that poses a conflict of interest.

We reviewed the STROBE statement and addressed all items in that checklist and are submitting the STROBE statement with the revised manuscript.

Key Words: Asthma, Risk, Epidemiology, Community-acquired infections, *Escherichia Coli*, Blood stream infection, genitourinary, and gastrointestinal tract

Abbreviations: BSI: blood stream infection, *E.Coli*: *Escherichia Coli*, TLR : Toll-like Receptor, ICS : inhaled corticosteroid, PPV23: 23-valent pneumococcal polysaccharide vaccine

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Article summary

1. Article focus: We addressed the following question in this study.

- Given the association between asthma and airway-related infection, is asthma also associated with non-airway-related serious infections such as *Escherichia coli* blood stream infection?

2. Key messages

- Individuals with asthma are at a significantly increased risk of non-airway-related infection, including community-acquired *E. coli* blood stream infection.

- The impact of asthma on risks of microbial infections may go beyond airways.

- Clinicians and patients should be aware of the association and recognize the risk of subsequent infection.

3. Strength and limitations

- This is the first population-based case-control study using predetermined criteria for asthma status and community-acquired *Escherichia coli* blood stream infection.

- The main limitation of the study is inherent limitations as a retrospective study and the study subjects were predominantly white.

Contributors

BDW collected data, interpreted the results, and drafted the manuscript; HJY participated in the study design, interpreted the results and reviewed the manuscript; ER collected data, interpreted the results, and reviewed manuscript; MNA assembled the original dataset for the E. coli BSI study, collected the original data, interpreted the results, and reviewed the manuscript; LMB participated in the study design, interpreted the results, and reviewed the manuscript; BPY participated in the study design, interpreted the results, and reviewed manuscript; and YJJ

participated in the study design, performed data analysis, interpreted the results, and drafted the manuscript. BDW, ER, and YJJ had full access to data. All authors reviewed and approved the paper.

There will be no additional data available.

Abstract:

Background: Asthmatics have increased risks of airway-related infections. Little is known about whether this is true for non-airway-related serious infections such as *Escherichia coli* blood stream infection (BSI). We assessed whether asthma is associated with a risk of developing community-acquired *E. coli* BSI.

Methods: The study was designed as a population-based retrospective case-control study, which included 259 eligible community-acquired *E. coli* BSI cases in Olmsted County, MN between 1998 and 2007 and 259 birthday-, gender-, and residency-matched controls. Only community-acquired *E. coli* BSI cases were included. Asthma status was ascertained by predetermined criteria. An adjusted odds ratio (OR) and 95% confidence interval (CI) for the association between asthma and risk of community-acquired *E. coli* BSI was calculated using conditional logistic regression.

Results: Of 259 eligible cases, 179 (69 %) were female and mean age was 61±22 years. Thirty-seven of 259 cases (14%) and 16 of 259 controls (6%) had a prior history of asthma (adjusted OR: 2.74; 95% CI: 1.11-6.76; p=0.029). The population attributable risk of asthma for community-acquired *E. coli* BSI was 9%. Although not statistically significant, there was a borderline association between having a history of food allergy and increased risk of community-acquired *E. coli* BSI (6% vs 2%; adjusted OR: 3.51; 95% CI: 0.94-13.11, p=0.062).

Conclusions: Based on the findings of the current population-based, case-control investigation, a history of asthma may be associated with risk of community-acquired *E. coli* BSI. The impact of asthma on risk of microbial infections may go beyond airways.

Abstract Word Count: 246

INTRODUCTION

Asthma is the most common chronic illness in childhood and is a major cause of morbidity in adults, affecting 4-17% of children and 7.7% of adults in the US.(1-3)] About 300 million people globally are estimated to be affected by asthma.(4)

Previous studies showed increased risks of microbial infections among individuals with asthma(5-10) and the population attributable risk for asthma of serious pneumococcal disease was 11-17%.(6, 10) Impaired innate and adaptive immune functions among asthmatics have been suggested for potential underlying mechanisms.(11-18) These study results are based on microbial infections of the airways. However, little is known about whether asthma status is associated with risk of non-airway-related bacterial infections such as community-acquired *Escherichia coli* blood stream infection (BSI).

Addressing this question should provide an important insight into the nature of the impact of asthma status on susceptibility to microbial infection. Specifically, it will improve our understanding on whether the impact of asthma status on susceptibility to infection goes beyond airways. In investigating this question, community-acquired *E. coli* BSI is suitable because it is not an airway-related infection but genitourinary tract/gastrointestinal origin, *E. coli* is a gram-negative bacterium with Toll-like Receptor (TLR)-4-mediated signal transduction for innate immunity, and *E. coli* is the most common cause of community-acquired BSI.(19) Up to 30% of individuals who developed community-acquired *E. coli* BSI did not have known risk factors,[(20)] suggesting that unrecognized risk factors exist that are associated with the development of community-acquired *E. coli* BSI.

Investigating the relationship between asthma and non-airway-related serious bacterial infections will advance our understanding on the extent to which asthma impacts susceptibility to

microbial infections and whether asthma could be an unrecognized risk factor for non-airway-related bacterial infections.

We hypothesize that individuals with asthma have an increased risk of community-acquired *E. coli* BSI, as compared to those without asthma. To test this hypothesis, we conducted a population-based retrospective case-control study.

METHODS

The study was approved by the Institutional Review Boards of both Mayo Clinic and Olmsted Medical Center. This study was designed as a population-based case-control study.

Study population and setting

Olmsted County, Minnesota is an excellent setting to conduct a population-based epidemiologic study such as this because medical care is virtually self-contained within the community (nearly all Olmsted County residents receive medical cares from two medical centers in the community). The population characteristics of Olmsted County residents are similar to those of non-Hispanic white.(21) If one grants the authorization for using medical record for research (almost 95% of Olmsted County residents), each patient is assigned a unique identifier under the auspices of the Rochester Epidemiology Project (REP).(22) Using REP resources, we previously demonstrated that incidence rates of asthma for this community are similar to other communities. The annual incidence rate of asthma in Rochester was 238 cases per 100,000 persons, which is comparable to those in other communities such as Tecumseh, Michigan (250/100,000).(23)

Study subjects: Case ascertainment

To test our study hypothesis, we utilized a population-based incidence parent study, which previously identified the community-acquired cases to study antimicrobial resistance trends of *E. coli* BSI in the community. Details of the case ascertainment have been described previously.(19) Briefly, using the microbiology databases at Mayo Clinic Rochester and Olmsted Medical Center, all eligible children and adults with monomicrobial *E. coli* BSI (n=274) among Olmsted County residents from January 1, 1998 to December 31, 2007 (i.e., a population-based all incident cases of *E. coli* BSI) were identified based on the criteria suggested by Freidman et

al.(24) As *E. coli* BSI is required for inpatient parental treatment, community-acquired *E. coli* BSI was defined by isolation of *E. coli* from blood cultures at the time of hospital admission or within 48 hours after hospital admission for patients who did not fit criteria for health care–associated infection according to the Freidman's criteria.(24) Medical records of all subjects were reviewed by investigators of the previous study (MNA) to confirm the diagnosis of community-acquired *E. coli* BSI, assess clinical features, and determine the eligibility. Only community-acquired *E. coli* BSI was included because nosocomial and health care-associated *E. coli* BSI are unsuitable to address the aim of the present study (clinically, they are a high-risk population for *E. coli* BSI and not representative of the study population). The index date of BSI was defined as the date when blood cultures that eventually grew *E. coli* were obtained. Exclusion criteria for cases (and controls) included: 1) polymicrobial BSI caused by more than one microorganism, 2) blood cultures acquired at autopsy, 3) nosocomial and health care-associated *E. coli* BSI, 4) non-Olmsted County residency at the time of index date of BSI, 5) no research authorization for using medical record for research, and 6) health conditions making ascertainment of asthma difficult listed in Table 1.

Selection of control subjects

Control subjects were randomly selected with 1:1 matching from Olmsted County residents who had not had a history of *E. coli* BSI at the end of the study period. Briefly, a list of potential control subjects who had received medical care from either Mayo Clinic or Olmsted Medical Center and who met the matching criteria was generated and randomly selected from the REP database for the present study. The matching criteria included: 1) gender, 2) birth date (within six months for those <18 years of age and within one year for those > 18 years of age), 3) the same clinic registration year as matched case (within one year), and 4) closest clinic visit to

index date of matched case within one year. The index date for control subjects was defined as the closest (within one year) clinic visit date to index date of BSI for their corresponding matched case. Based on the number of cases and controls enrolled in this present study (259 pair), assuming 8% of asthma prevalence among controls, this present study had 80% power to detect an effect size of 2.27 of odds ratio (16.5% of asthma in cases). This effect size was smaller than the reported effect sizes for the association between asthma and risk of microbial infection (OR: 2.4-6.7) suggesting adequate statistical power to address the study aim.(6, 10)

Exposure ascertainment (asthma status)

For determining asthma status of all cases and controls, we conducted comprehensive medical record reviews to apply predetermined criteria for asthma as performed in our previous work.(5, 6) The criteria are delineated in Table 1. These criteria have been extensively used in research for asthma epidemiology and were found to have high reliability.(25-30) We included both definite and probable asthma according to the criteria prior to the index date of BSI cases because most probable asthmatics become definite over time.(6, 31) The incidence dates (the first date when one met the criteria for asthma) for all asthmatic patients were determined; thus, we were able to discern the temporal relationship between asthma status (exposure) and *E coli* BSI (outcome). The risk of *E. coli* BSI was assessed in relation to the current asthma status(32): remission (no asthma symptoms, no asthma-related visits, or no asthma medications for at least three years prior to index date); active or current asthma (presence of clinical symptoms, asthma-related visits, or asthma medications within one year prior to index date); and inactive (not current) asthma (presence of asthma symptoms, asthma-related visits, or asthma medications within 1-3 years prior to index date).

Other variables

Pertinent covariates and confounders were collected from medical records: sociodemographic variables (age, gender, ethnicity, and educational status), asthma medications including inhaled and systemic corticosteroids, family history of asthma, atopic status based on sensitization against aeroallergens and food allergens, smoking status (either active or passive exposure to tobacco smoke), vaccination status, and co-morbid conditions at the time of index date as listed in Table 2. The period of data collection was from October 1, 2011 to May 30, 2012.

Statistical analysis

Formal comparison of asthma and other suspected risk factors between matched cases and controls was performed using conditional logistic regression, with community-acquired *E. coli* BSI as the target of prediction. All factors were analyzed for a univariate association with BSI, and any variables meeting the Greenland entry criteria ($P< 0.2$) were carried forward into a final multivariable model.(33)] Odds ratios (OR) from univariate (unadjusted) and multivariable (adjusted) models are reported to express the magnitude of association in terms of the likelihood of being a case. We calculated the population attributable risk percentage (PAR%) of asthma for community-acquired *E. coli* BSI using the formula established by Miettinen.(34) Statistical significance was tested at a two-sided alpha error of 0.05. All analyses were carried out with the statistical software package SAS, version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Study subjects

Of the 274 patients who were identified in the original study, 259 were eligible for the present study. Fifteen patients were excluded; five for consistent FEV1 < 50%, two for restrictive lung disease, two for significant kyphoscoliosis, two for bronchiectasis, one for cystic fibrosis, one for pulmonary fibrosis, and two due to non-Olmsted County residency. Of the eligible 259 cases, 179 (69%) were female, 249 (96%) were 18 years of age or older (age mean±standard deviation, 61±22 years), and 222 (86%) were Caucasian. The characteristics of the cases and their matched controls, and the individual associations with community-acquired *E. coli* BSI, are summarized in Table 2. There were only 10 asthmatics on moderate- or high-dose inhaled corticosteroid (ICS) and two asthmatics on systemic corticosteroid at the time of the index date. Comparing subjects with asthma versus those without, there was no significant difference in the proportions, who had received influenza vaccine (40% vs. 40%, p=0.99) or PPV23 (49% vs. 44%, p=0.49) within one year prior to index date.

Association between asthma and risk of community-acquired *E. coli* BSI

Thirty-seven of 259 (14%) cases had a history of asthma prior to the index date of community-acquired *E. coli* BSI, compared with 16 of 259 (6%) controls (unadjusted OR: 2.75; 95% CI: 1.42-5.32; p=0.003). Of the 37 case subjects with asthma, 33 (89%) had definite asthma and 4 (11%) had probable asthma. Of the 16 controls with asthma, 12 (75%) had definite asthma and 4 (25%) had probable asthma. Among all 53 asthmatics, 18 were on ICS therapy at the index date (8 on low-dose ICS and 10 on moderate to high-dose ICS therapy). The effect of asthma on risk of community-acquired *E. coli* BSI, independent of other risk factors, is summarized in Table 3. Subjects with a history of asthma by predetermined criteria for asthma in Table 1 had a nearly 3-

fold higher risk of developing community-acquired *E. coli* BSI compared to those without asthma, controlling for all potential confounding factors (adjusted OR: 2.74; 95% CI: 1.11-6.76; p=0.029). The PAR% of asthma by predetermined criteria for asthma in Table 1 for the risk of *E. coli* BSI was 9%. The *p*-values for testing a significant interaction between asthma and categorized age were as follows: p=0.285 for age cutoff of 65 years (i.e., ≥65 vs. <65 years), p=0.958 for age cutoff of 40 years (i.e., ≥40 vs. <40 years), and p=0.417 for age cutoffs of 40 years and 65 years (i.e., <40, 40-65, vs. >65 years). As a result, we have no evidence of a differential asthma effect across age strata. Additional characteristics of asthma were also evaluated for an association with risk of community-acquired *E. coli* BSI (see Table 4). Adjusted for other factors, active asthma was associated with increased risk of *E. coli* BSI but for asthmatics on ICS therapy compared to non-asthmatics, but the overall 3-level effect was not statistically significant (p=0.079).

Other variables and *E. coli* BSI

Several of the high-risk conditions, as well as non-Caucasian ethnicity, were independently associated with increased risk of community-acquired *E. coli* BSI (see Tables 2 and 3). A history of food allergy was found in 16 (6%) of 259 cases as compared with 6 (2%) of 259 controls (adjusted OR: 3.51; 95% CI: 0.94-13.11; p=0.062). Neither allergic rhinitis (p=0.82) nor atopic dermatitis (p=0.87) was found to be significantly associated with community-acquired *E. coli* BSI.

DISCUSSION

To our knowledge, this is the first population-based, case-control study that demonstrated an association between asthma and risk of non-respiratory bacterial infection such as community-acquired *E. coli* BSI. This association was independent of other risk factors including age, gender, follow-up duration, ethnicity, educational level, and comorbid conditions (adjusted OR: 2.74; 95% CI: 1.11-6.76; p=0.029). Analyses by different age cut-offs showed that the results were not affected by age effect (e.g., younger vs. older than 40 years of age). Given either the previously-reported non association (hazard ratio, HR: 1.29, 95%CI: 0.53-3.12) or a protective effect (HR: 0.52, 95%CI:0.36-0.76) of ICS therapy on risk of pneumonia in asthmatics(35) and a small number of asthmatics with moderate or high-dose ICS in our study (10 of 53, 19%), we suspect that active or current asthma (or collectively those given ICS therapy) might be related to risk of community-acquired *E. coli* BSI instead of ICS alone. There were only 2 asthmatics on systemic corticosteroid therapy at the time of the index date; therefore, exposure to systemic corticosteroid therapy was unlikely to account for the observed association. We believe that susceptibility bias (e.g., covariate imbalance at baseline) is unlikely to account for the association found in our study given the full adjustment for potential confounders. One concern could be detection bias stemming from a situation where exposure status (asthma status) systematically affects detection of outcomes. However, given *E. coli* BSI as a life-threatening condition, this is unlikely and also there was no significant difference in symptom duration from BSI-related symptom to index date between asthma and non-asthma in cases (4.7±5.5 vs 5.2±5.5 days, p=0.61). Since detection of asthma depends on follow-up duration from registration to index date of community-acquired *E. coli* BSI, we designed our study to ensure that duration was

similar between cases and controls. Asthma prevalence in controls in our study was 6%, which is similar to that in adults (7%) in the United States (5.5% for males and 9.7% for females).(36) Also, the prevalence of other common chronic condition such as coronary heart disease in our study (15%) was similar to the national average (7.1% for adults aged 45-64 years and 19.8% for adults aged ≥ 65 years) suggesting that our control group may reasonably represent a general population of adults in the United States.(3) There were no significant differences in influenza and PPV23 vaccination rates between cases and controls, which may imply similar access to health care services. Also, food allergy approached to statistical significant association with risk of E coli BSI but other atopic conditions were not. This is probably due to greater misclassification bias of ascertainment of allergic rhinitis and atopic dermatitis by ICD-9 code compared to asthma status and food allergy by predetermined criteria in our study. Taken together, our study results suggest that asthma status is independently associated with risk of community-acquired *E. coli* BSI.

There are only a few previous studies, which assessed the incidence of *E. coli* BSI and risk factors associated with its development, including asthma. One study showed a higher risk of community-acquired *E. coli* BSI in asthmatics compared to non-asthmatics among those over 65 years of age (5.5% vs. 1%).(37) However, another study showed reduced risk of *E. coli* BSI in asthmatics (rate ratio: 0.3; 95% CI: 0.2-0.4) compared to that in total regional population.(38) These studies have significant limitations including no *a priori* hypothesis testing on the relationship between asthma and risk of community-acquired *E. coli* BSI, utilization of administrative data from health care organizations or case reports, ascertainment of *E. coli* BSI cases and asthma based on ICD-9 code, inclusion of only elderly patients aged over 65 years,(37) and no concurrent control group.(38) Thus, our study is the first population-based case-control

study that demonstrated a relationship between asthma and risk of community-acquired *E. coli* BSI. Several studies showed increased risks of microbial infections in asthmatics[(5-7, 10, 11) but these studies only addressed the relationship between asthma and airway infections.

The mechanisms underlying the apparent association between asthma and risk of community-acquired *E. coli* BSI are unknown. Whether previously reported impaired innate immune factors that may predispose to infections due to viruses(13, 39, 40) and other bacteria are operative in community-acquired *E. coli* BSI is undefined. Recently, Habibzay et al reported impaired innate immunity against pneumococci through impaired TLR-receptor signal transduction by house dust mite allergic sensitization resulting in reduced neutrophil recruitment and increased risk of pneumococcal infection in the airways.(11) It is worth investigating whether allergic sensitization can induce similar impairment of innate immunity through TLR-4 for gram-negative bacteria in genitourinary or gastrointestinal tracts in asthmatics. Also, an adaptive immune response to gram-negative bacteria might be altered in asthmatics,(41) which may affect susceptibility to gram-negative bacterial infection. For example, Koch et al reported impaired Type 1 helper T cell (Th1) response (interleukin-12-induced interferon-γ release from T lymphocytes) to endotoxin from *Salmonella enteritidis* in asthmatics.(42) Further studies are needed to address our study findings.

The main strengths of our study are a population-based study design and include the epidemiologic merits of self-contained health care environment with comprehensive medical record system for research. We identified population-based all incident community-acquired *E. coli* BSI cases based on the Freidman criteria. We ascertained asthma status by applying predetermined criteria independent of a physician diagnosis of asthma or ICD-9 code. Also, our study has inherent limitations as a retrospective study. We could not obtain detail information on

certain variables such as atopic sensitization data or smoking history (e.g., duration or the number of cigarettes a day) but we assumed this data to be missing at random (i.e., it is subject to non-differential misclassification bias for comparison groups of interest). Although our criteria for asthma was based on medical record review, given the absence of gold standard for asthma, the retrospective investigation for feasibility (due to infrequent *E coli* BSI), and the extensive use of the criteria in previous asthma research, we believe the criteria is unlikely to result in a significant bias affecting interpretation of the results. Our study finding that asthma prevalence among controls was similar to that at the national level should mitigate this concern. Our study subjects were predominantly white which might limit generalizability of our results to other ethnic groups. Our study subjects were relatively a older population affected by many comorbid conditions which might confound the study results. However, when we examined the effect of the interaction between age and asthma, we found that the main results on the association between asthma and risk of E colli BSI did not appear to be significantly affected by various cutoffs of age suggesting the results did not differ by age group (younger vs. older group).

In conclusion, asthmatics might be at an increased risk of non-respiratory tract bacterial infections, including community-acquired *E. coli* BSI. The mechanisms responsible for this association are yet to be defined while additional investigations replicate our study findings.

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Table 1. Definition of asthma

Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma with the first two conditions and/or if each of the following three conditions were present, and they were considered to have *probable* asthma if only the first two conditions were present:

1. History of cough with wheezing, and/or dyspnea, OR history of cough and/or dyspnea plus wheezing on examination,
2. Substantial variability in symptoms from time to time or periods of 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/uL
- 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 FEV_1 or FVC less than 70% predicted and another with at least 20% improvement to an FEV_1 of higher70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV_1
- Favorable clinical response to bronchodilator (e.g., documented improvement of respiratory symptoms or FEV1 in spirometry after bronchodilator therapy)

<u>Patients were excluded from the study if any of these conditions were present:</u>

- Tracheobronchial foreign body at or about the incidence date
- Hypogammaglobulinemia (IgG less than 2.0 mg/mL) or other immunodeficiency disorder
- Wheezing occurring only in response to anesthesia or medications
- Bullous emphysema or pulmonary fibrosis on chest radiograph
- PiZZ $alpha_1$-antitrypsin
- Cystic fibrosis
- Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis
  FVC forced vital capacity; FEV1, forced expiratory volume in 1 sec.
- Pulmonary function tests that showed FEV_1 to be consistently below 50% predicted or diminished diffusion capacity

Table 2. Sociodemographic, and clinical characteristics of patients with *Escherichia coli* blood stream infection and their matched control subjects

Characteristics	Case (n= 259)	Control (n= 259)	Unadjusted OR[a] (95% CI)	p value
Age (years)	61±22	61±22	1.14 (0.78, 1.67)	0.497
Female gender	179 (69%)	179 (69%)	-	
Ethnicity				<0.001
Caucasian (non-Hispanic)	222 (86%)	245 (95%)	Referent	
Other	37 (14%)	14 (5%)	4.83 (2.01, 11.64)	
Education status				0.004
Some high school or less	45 (17%)	21 (8%)	Referent	
High school graduate	95 (37%)	87 (34%)	0.50 (0.27, 0.93)	
Some college or more	110 (42%)	143 (55%)	0.33 (0.18, 0.62)	
Unknown	9 (3%)	8 (3%)	-	
Influenza vaccination 1 year prior to index date	95 (37%)	110 (42%)	0.75 (0.51, 1.10)	0.145
PPV23 prior to index date	117 (45%)	114 (44%)	1.08 (0.69, 1.68)	0.736
Food allergy	16 (6%)	6 (2%)	2.67 (1.04, 6.81)	0.040
Asthma	37 (14%)	16 (6%)	2.75 (1.42, 5.32)	0.003
High-risk conditions				
Alcohol addiction	17 (7%)	1 (0%)	17.00 (2.26, 127.75)	0.006
Autoimmune disease[c]	9 (3%)	3 (1%)	3.00 (0.81, 11.08)	0.099
Chronic obstructive lung disease	12 (5%)	9 (3%)	1.37 (0.55, 3.42)	0.493
Chronic renal insufficiency	30 (12%)	4 (2%)	9.67 (2.94, 31.73)	<0.001
Congestive heart failure	19 (7%)	2 (1%)	18.00 (2.40, 134.84)	0.005
Coronary artery disease	52 (20%)	40 (15%)	1.46 (0.89, 2.41)	0.136
Dementia	16 (6%)	7 (3%)	3.25 (1.06, 9.97)	0.039
Diabetes mellitus	50 (19%)	24 (9%)	2.53 (1.44, 4.43)	0.001
History of stroke	15 (6%)	10 (4%)	1.71 (0.67, 4.35)	0.257
Immobilization[d]	10 (4%)	1 (0%)	10.00 (1.28, 78.12)	0.028
Immunosuppressive therapy	25 (10%)	4 (2%)	8.00 (2.41, 26.57)	0.001
Malignancy	21 (8%)	12 (5%)	2.00 (0.90, 4.45)	0.090
Recurrent urinary tract infection	29 (11%)	2 (1%)	14.50 (3.46, 60.77)	<0.001
Transplant recipients	8(3%)	0 (0%)	-	
Urinary incontinence	46 (18%)	20 (8%)	2.86 (1.55, 5.25)	0.001

Other condition[e]	14 (5%)	0 (0%)	-	-
Smoke				0.058
No (including ex-smoker)	206 (80%)	222 (86%)	Referent	
Active	53 (20%)	37 (14%)	1·59 (0.98, 2.58)	

[a] Odds ratio based on matched analysis taking into account gender, birthday, residency, and follow-up duration
[b] Comorbidity conditions are not mutually exclusive
[c] Autoimmune disease includes SLE, rheumatoid arthritis, inflammatory bowel disease and other autoimmune diseases
[d] Immobilization includes hemi/para/quadri-plegia
[e] Other conditions include use of urinary catheter, device, genitourinary procedures (e.g., prostate biopsy), and congenital anomaly

Table 3. A multivariable conditional logistic regression model for the association between asthma and risk of community-acquired *Escherichia coli* bloodstream infection

Characteristics	Case (n= 259)	Control (n= 259)	Adjusted OR[a] (95% CI)	p value
Ethnicity				0.003
Caucasian (non-Hispanic)	222 (86%)	245 (95%)	Referent	
Other	37 (14%)	14 (5%)	5.90 (1.85, 18.84)	
Education status				0.646
Some high school or less	45 (17%)	21 (8%)	Referent	
High school graduate	95 (37%)	87 (34%)	0.89 (0.37, 2.14)	
Some college or more	110 (42%)	143 (55%)	0.65 (0.28, 1.50)	
Unknown	9 (3%)	8 (3%)	-	
Influenza vaccination 1 year prior to index date	95 (37%)	110 (42%)	0.58 (0.33, 1.02)	0.058
Food allergy	16 (6%)	6 (2%)	3.51 (0.94, 13.11)	0.062
Asthma	37 (14%)	16 (6%)	2.74 (1.11, 6.76)	0.029
Active smoking	53 (20%)	37 (14%)	1.31 (0.69, 2.47)	0.412
High-risk conditions				
Alcohol addiction	17 (7%)	1 (0%)	32.31 (1.91, 546.18)	0.016
Autoimmune diseases	9 (3%)	3 (1%)	1.79 (0.23, 13.72)	0.574
Chronic renal insufficiency	30 (12%)	4 (2%)	4.76 (1.16, 19.59)	0.030
Congestive heart failure	19 (7%)	2 (1%)	9.86 (0.93, 104.59)	0.058
Coronary artery disease	52 (20%)	40 (15%)	0.81 (0.37, 1.77)	0.593
Dementia	16 (6%)	7 (3%)	4.14 (0.96, 17.96)	0.057
Diabetes mellitus	50 (19%)	24 (9%)	2.39 (0.97, 5.87)	0.057
Immobilization	10 (4%)	1 (0%)	39.86 (2.30, 690.42)	0.011
Immunosuppressive therapy	25 (10%)	4 (2%)	8.51 (1.32, 54.96)	0.024
Malignancy	21 (8%)	12 (5%)	2.18 (0.59, 8.11)	0.243
Recurrent urinary tract infection	29 (11%)	2 (1%)	13.54 (2.42, 75.65)	0.003
Urinary incontinence	46 (18%)	20 (8%)	2.57 (1.05, 6.26)	0.038

[a] Adjusted variables included all variables included in this table.

Table 4. Association of asthma control status and therapy with risk of community-acquired *Escherichia coli* bloodstream infection

Asthma characteristics	Total (n=518)	Unadjusted OR (95% CI), p-value	Adjusted OR[a] (95% CI), p-value
Inhaled corticosteroid therapy (ICS)		*p=0.009*[b]	*p=0.079*[b]
No asthma	465 (90%)	Referent	Referent
Asthma without ICS	35 (7%)	1.90 (0.88, 4.09)	1.99 (0.67, 5.94)
Asthma with ICS	18 (3%)	7.00 (1.59, 30.80)	5.33 (0.90, 31.66)
Asthma status[c]		*p=0.005*[b]	*p=0.067*[b]
No asthma	465 (90%)	Referent	Referent
Remission or inactive asthma	17 (3%)	1.25 (0.45, 3.50)	1.25 (0.25, 6.30)
Active or current asthma	36 (7%)	4.37 (1.80, 10.62)	3.89 (1.23, 12.28)

[a] Adjusted variables included all factors reported in the multivariable model (see Table 3) except for dichotomous asthma status
[b] P-value for overall comparison
[c] 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 E coli BSI; Remission of asthma was defined as the absence of asthma-related events > 3 years prior to index date; Inactive (not current) asthma was defined as the presence of asthma-related events within 1-3 years prior to index date.

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract(title)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found(abstract)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported(lines 96-112)
Objectives	3	State specific objectives, including any prespecified hypotheses (lines 113-119)
Methods		
Study design	4	Present key elements of study design early in the paper(lines 139-140)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (lines 142-145/159/212-213)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (table 1, 153~)
		(*b*) For matched studies, give matching criteria and the number of controls per case (176~)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable(191-213)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group(177-186)
Bias	9	Describe any efforts to address potential sources of bias(289-306)
Study size	10	Explain how the study size was arrived at(186-190)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why(214-224)
Statistical methods (214-224)	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed(N/A)
		(*d*) If applicable, explain how matching of cases and controls was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (N/A)
		(b) Give reasons for non-participation at each stage(N/A)
		(c) Consider use of a flow diagram(N/A)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders(Table 2 &3)
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Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure(Table 2 &3)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and

(Table 2, 3 & 4)		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Table 2 &3)
Discussion		
Key results	18	Summarise key results with reference to study objectives (277-281)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias(338-346)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence(334-347)
Generalisability	21	Discuss the generalisability (external validity) of the study results(346-349)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based(356-360)

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Asthma and Risk of Non-Respiratory Tract Infection: A Population-Based Case Control Study

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Primary Subject Heading:	Epidemiology
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TITLE PAGE

Original Article

Asthma and Risk of Non-Respiratory Tract Infection: A Population-Based Case Control Study

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Conflict of interest: The study investigators have nothing to disclose that poses a conflict of interest.

We reviewed the STROBE statement and addressed all items in that checklist and are submitting the STROBE statement with the revised manuscript.

Key Words: Asthma, Risk, Epidemiology, Community-acquired infections, *Escherichia Coli*, Blood stream infection, genitourinary, and gastrointestinal tract

Abbreviations: BSI: blood stream infection, *E.Coli*: *Escherichia Coli*, TLR : Toll-like Receptor, ICS : inhaled corticosteroid, PPV23: 23-valent pneumococcal polysaccharide vaccine

Word count: 2993

Article summary

1. Article focus: We addressed the following question in this study.

- Given the association between asthma and airway-related infection, is asthma also associated with non-airway-related serious infections such as *Escherichia coli* blood stream infection?

2. Key messages

- Individuals with asthma are at a significantly increased risk of non-airway-related infection, including community-acquired *E. coli* blood stream infection.

- The impact of asthma on risks of microbial infections may go beyond airways.

- Clinicians and patients should be aware of the association and recognize the risk of subsequent infection.

3. Strength and limitations

- This is the first population-based case-control study using predetermined criteria for asthma status and community-acquired *Escherichia coli* blood stream infection.

- The main limitation of the study is inherent limitations as a retrospective study and the study subjects were predominantly white.

Contributors

BDW collected data, interpreted the results, and drafted the manuscript; HJY participated in the study design, interpreted the results and reviewed the manuscript; ER collected data, interpreted the results, and reviewed manuscript; MNA assembled the original dataset for the E. coli BSI study, collected the original data, interpreted the results, and reviewed the manuscript; LMB participated in the study design, interpreted the results, and reviewed the manuscript; BPY participated in the study design, interpreted the results, and reviewed manuscript; and YJJ

participated in the study design, performed data analysis, interpreted the results, and drafted the manuscript. BDW, ER, and YJJ had full access to data. All authors reviewed and approved the paper.

There will be no additional data available.

Abstract:

Objectives: Asthmatics have increased risks of airway-related infections. Little is known about whether this is true for non-airway-related serious infections such as *Escherichia coli* blood stream infection (BSI). We assessed whether asthma is associated with a risk of developing community-acquired *E. coli* BSI.

Design: The study was designed as a population-based retrospective case-control study.

Setting: This population-based study was conducted in Olmsted County, Minnesota.

Participants: The study included 259 all eligible community-acquired *E. coli* BSI cases in Olmsted County, MN between 1998 and 2007 and 259 birthday-, gender-, and residency-matched controls.

Primary and secondary outcome measures: Only community-acquired *E. coli* BSI cases as the primary outcome was included. Asthma status as an exposure was ascertained by predetermined criteria. An adjusted odds ratio (OR) and 95% confidence interval (CI) for the association between asthma and risk of community-acquired *E. coli* BSI was calculated using conditional logistic regression.

Results: Of 259 eligible cases, 179 (69 %) were female and mean age was 61±22 years. Thirty-seven of 259 cases (14%) and 16 of 259 controls (6%) had a prior history of asthma (adjusted OR: 2.74; 95% CI: 1.11-6.76; p=0.029). The population attributable risk of asthma for community-acquired *E. coli* BSI was 9%. Although not statistically significant, there was a borderline association between having a history of food allergy and increased risk of community-acquired *E. coli* BSI (6% vs 2%; adjusted OR: 3.51; 95% CI: 0.94-13.11, p=0.062).

Conclusions: Based on the findings of the current population-based, case-control investigation, a history of asthma may be associated with risk of community-acquired *E. coli* BSI. The impact of

asthma on risk of microbial infections may go beyond airways.

Abstract Word Count: 246

INTRODUCTION

Asthma is the most common chronic illness in childhood and is a major cause of morbidity in adults, affecting 4-17% of children and 7.7% of adults in the US.(1-3)] About 300 million people globally are estimated to be affected by asthma.(4)

Previous studies showed increased risks of microbial infections among individuals with asthma(5-10) and the population attributable risk for asthma of serious pneumococcal disease was 11-17%.(6, 10) Impaired innate and adaptive immune functions among asthmatics have been suggested for potential underlying mechanisms.(11-18) These study results are based on microbial infections of the airways. However, little is known about whether asthma status is associated with risk of non-airway-related bacterial infections such as community-acquired *Escherichia coli* blood stream infection (BSI).

Addressing this question should provide an important insight into the nature of the impact of asthma status on susceptibility to microbial infection. Specifically, it will improve our understanding on whether the impact of asthma status on susceptibility to infection goes beyond airways. In investigating this question, community-acquired *E. coli* BSI is suitable because it is not an airway-related infection but genitourinary tract/gastrointestinal origin, *E. coli* is a gram-negative bacterium with Toll-like Receptor (TLR)-4-mediated signal transduction for innate immunity, and *E. coli* is the most common cause of community-acquired BSI.(19) Up to 30% of individuals who developed community-acquired *E. coli* BSI did not have known risk

factors,[(20)] suggesting that unrecognized risk factors exist that are associated with the development of community-acquired *E. coli* BSI.

Investigating the relationship between asthma and non-airway-related serious bacterial infections will advance our understanding on the extent to which asthma impacts susceptibility to microbial infections and whether asthma could be an unrecognized risk factor for non-airway-related bacterial infections.

We hypothesize that individuals with asthma have an increased risk of community-acquired *E. coli* BSI, as compared to those without asthma. To test this hypothesis, we conducted a population-based retrospective case-control study.

METHODS

The study was approved by the Institutional Review Boards of both Mayo Clinic and Olmsted Medical Center. This study was designed as a population-based case-control study.

Study population and setting

Olmsted County, Minnesota is an excellent setting to conduct a population-based epidemiologic study such as this because medical care is virtually self-contained within the community (nearly all Olmsted County residents receive medical cares from two medical centers in the community). The population characteristics of Olmsted County residents are similar to those of non-Hispanic white.(21) If one grants the authorization for using medical record for research (almost 95% of Olmsted County residents), each patient is assigned a unique identifier under the auspices of the Rochester Epidemiology Project (REP).(22) Using REP resources, we previously demonstrated that incidence rates of asthma for this community are similar to other communities. The annual incidence rate of asthma in Rochester was 238 cases per 100,000 persons, which is comparable to those in other communities such as Tecumseh, Michigan (250/100,000).(23)

Study subjects: Case ascertainment

To test our study hypothesis, we utilized a population-based incidence parent study, which previously identified the community-acquired cases to study antimicrobial resistance trends of *E. coli* BSI in the community. Details of the case ascertainment have been described

previously.(19) Briefly, using the microbiology databases at Mayo Clinic Rochester and Olmsted Medical Center, all eligible children and adults with monomicrobial *E. coli* BSI (n=274) among Olmsted County residents from January 1, 1998 to December 31, 2007 (i.e., a population-based all incident cases of *E. coli* BSI) were identified based on the criteria suggested by Freidman et al.(24) As *E. coli* BSI is required for inpatient parental treatment, community-acquired *E. coli* BSI was defined by isolation of *E. coli* from blood cultures at the time of hospital admission or within 48 hours after hospital admission for patients who did not fit criteria for health care–associated infection according to the Freidman's criteria.(24) Medical records of all subjects were reviewed by investigators of the previous study (MNA) to confirm the diagnosis of community-acquired *E. coli* BSI, assess clinical features, and determine the eligibility. Only community-acquired *E. coli* BSI was included because nosocomial and health care-associated *E. coli* BSI are unsuitable to address the aim of the present study (clinically, they are a high-risk population for *E. coli* BSI and not representative of the study population). The index date of BSI was defined as the date when blood cultures that eventually grew *E. coli* were obtained. Exclusion criteria for cases (and controls) included: 1) polymicrobial BSI caused by more than one microorganism, 2) blood cultures acquired at autopsy, 3) nosocomial and health care-associated *E. coli* BSI, 4) non-Olmsted County residency at the time of index date of BSI, 5) no research authorization for using medical record for research, and 6) health conditions making ascertainment of asthma difficult listed in Table 1.

Selection of control subjects

Control subjects were randomly selected with 1:1 matching from Olmsted County residents who had not had a history of *E. coli* BSI at the end of the study period. Briefly, a list of potential control subjects who had received medical care from either Mayo Clinic or Olmsted

Medical Center and who met the matching criteria was generated and randomly selected from the REP database for the present study. The matching criteria included: 1) gender, 2) birth date (within six months for those <18 years of age and within one year for those > 18 years of age), 3) the same clinic registration year as matched case (within one year), and 4) closest clinic visit to index date of matched case within one year. The index date for control subjects was defined as the closest (within one year) clinic visit date to index date of BSI for their corresponding matched case. Based on the number of cases and controls enrolled in this present study (259 pair), assuming 8% of asthma prevalence among controls, this present study had 80% power to detect an effect size of 2.27 of odds ratio (16.5% of asthma in cases). This effect size was smaller than the reported effect sizes for the association between asthma and risk of microbial infection (OR: 2.4-6.7) suggesting adequate statistical power to address the study aim.(6, 10)

Exposure ascertainment (asthma status)

For determining asthma status of all cases and controls, we conducted comprehensive medical record reviews to apply predetermined criteria for asthma as performed in our previous work.(5, 6) The criteria are delineated in Table 1. These criteria have been extensively used in research for asthma epidemiology and were found to have high reliability.(25-30) We included both definite and probable asthma according to the criteria prior to the index date of BSI cases because most probable asthmatics become definite over time.(6, 31) The incidence dates (the first date when one met the criteria for asthma) for all asthmatic patients were determined; thus, we were able to discern the temporal relationship between asthma status (exposure) and *E coli* BSI (outcome). The risk of *E. coli* BSI was assessed in relation to the current asthma status(32): remission (no asthma symptoms, no asthma-related visits, or no asthma medications for at least three years prior to index date); active or current asthma (presence of clinical symptoms, asthma-

related visits, or asthma medications within one year prior to index date); and inactive (not current) asthma (presence of asthma symptoms, asthma-related visits, or asthma medications within 1-3 years prior to index date).

Other variables

Pertinent covariates and confounders were collected from medical records: sociodemographic variables (age, gender, ethnicity, and educational status), asthma medications including inhaled and systemic corticosteroids, family history of asthma, atopic status based on sensitization against aeroallergens and food allergens, smoking status (either active or passive exposure to tobacco smoke), vaccination status, and co-morbid conditions at the time of index date as listed in Table 2. The period of data collection was from October 1, 2011 to May 30, 2012.

Statistical analysis

Formal comparison of asthma and other suspected risk factors between matched cases and controls was performed using conditional logistic regression, with community-acquired *E. coli* BSI as the target of prediction. All factors were analyzed for a univariate association with BSI, and any variables meeting the Greenland entry criteria ($P< 0.2$) were carried forward into a final multivariable model.(33)] Odds ratios (OR) from univariate (unadjusted) and multivariable (adjusted) models are reported to express the magnitude of association in terms of the likelihood of being a case. We calculated the population attributable risk percentage (PAR%) of asthma for community-acquired *E. coli* BSI using the formula established by Miettinen.(34) Statistical significance was tested at a two-sided alpha error of 0.05. All analyses were carried out with the statistical software package SAS, version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Study subjects

Of the 274 patients who were identified in the original study, 259 were eligible for the present study. Fifteen patients were excluded; five for consistent FEV1 < 50%, two for restrictive lung disease, two for significant kyphoscoliosis, two for bronchiectasis, one for cystic fibrosis, one for pulmonary fibrosis, and two due to non-Olmsted County residency. Of the eligible 259 cases, 179 (69%) were female, 249 (96%) were 18 years of age or older (age mean±standard deviation, 61±22 years), and 222 (86%) were Caucasian. The characteristics of the cases and their matched controls, and the individual associations with community-acquired *E. coli* BSI, are summarized in Table 2. There were only 10 asthmatics on moderate- or high-dose inhaled corticosteroid (ICS) and two asthmatics on systemic corticosteroid at the time of the index date. Comparing subjects with asthma versus those without, there was no significant difference in the proportions, who had received influenza vaccine (40% vs. 40%, p=0.99) or PPV23 (49% vs. 44%, p=0.49) within one year prior to index date.

Association between asthma and risk of community-acquired *E. coli* BSI

Thirty-seven of 259 (14%) cases had a history of asthma prior to the index date of community-acquired *E. coli* BSI, compared with 16 of 259 (6%) controls (unadjusted OR: 2.75; 95% CI: 1.42-5.32; p=0.003). Of the 37 case subjects with asthma, 33 (89%) had definite asthma and 4 (11%) had probable asthma. Of the 16 controls with asthma, 12 (75%) had definite asthma and 4

(25%) had probable asthma. Among all 53 asthmatics, 18 were on ICS therapy at the index date (8 on low-dose ICS and 10 on moderate to high-dose ICS therapy). The effect of asthma on risk of community-acquired *E. coli* BSI, independent of other risk factors, is summarized in Table 3. Subjects with a history of asthma by predetermined criteria for asthma in Table 1 had a nearly 3-fold higher risk of developing community-acquired *E. coli* BSI compared to those without asthma, controlling for all potential confounding factors (adjusted OR: 2.74; 95% CI: 1.11-6.76; p=0.029). The PAR% of asthma by predetermined criteria for asthma in Table 1 for the risk of *E. coli* BSI was 9%. The *p*-values for testing a significant interaction between asthma and categorized age were as follows: p=0.285 for age cutoff of 65 years (i.e., ≥65 vs. <65 years), p=0.958 for age cutoff of 40 years (i.e., ≥40 vs. <40 years), and p=0.417 for age cutoffs of 40 years and 65 years (i.e., <40, 40-65, vs. >65 years). As a result, we have no evidence of a differential asthma effect across age strata. Additional characteristics of asthma were also evaluated for an association with risk of community-acquired *E. coli* BSI (see Table 4). Adjusted for other factors, active asthma was associated with increased risk of *E. coli* BSI but for asthmatics on ICS therapy compared to non-asthmatics, but the overall 3-level effect was not statistically significant (p=0.079).

Other variables and *E. coli* BSI

Several of the high-risk conditions, as well as non-Caucasian ethnicity, were independently associated with increased risk of community-acquired *E. coli* BSI (see Tables 2 and 3). A history of food allergy was found in 16 (6%) of 259 cases as compared with 6 (2%) of 259 controls (adjusted OR: 3.51; 95% CI: 0.94-13.11; p=0.062). Neither allergic rhinitis (p=0.82) nor atopic dermatitis (p=0.87) was found to be significantly associated with community-acquired *E. coli* BSI.

DISCUSSION

To our knowledge, this is the first population-based, case-control study that demonstrated an association between asthma and risk of non-respiratory bacterial infection such as community-acquired *E. coli* BSI. This association was independent of other risk factors including age, gender, follow-up duration, ethnicity, educational level, and comorbid conditions (adjusted OR: 2.74; 95% CI: 1.11-6.76; p=0.029). Analyses by different age cut-offs showed that the results were not affected by age effect (e.g., younger vs. older than 40 years of age). Given either the previously-reported non association (hazard ratio, HR: 1.29, 95%CI: 0.53-3.12) or a protective effect (HR: 0.52, 95%CI:0.36-0.76) of ICS therapy on risk of pneumonia in asthmatics(35) and a small number of asthmatics with moderate or high-dose ICS in our study (10 of 53, 19%), we suspect that active or current asthma (or collectively those given ICS therapy) might be related to risk of community-acquired *E. coli* BSI instead of ICS alone. There were only 2 asthmatics on systemic corticosteroid therapy at the time of the index date; therefore, exposure to systemic corticosteroid therapy was unlikely to account for the observed association. We believe that susceptibility bias (e.g., covariate imbalance at baseline) is unlikely to account for the association found in our study given the full adjustment for potential confounders. One concern could be detection bias stemming from a situation where exposure status (asthma status) systematically affects detection of outcomes. However, given *E. coli* BSI as a life-threatening condition, this is

unlikely and also there was no significant difference in symptom duration from BSI-related symptom to index date between asthma and non-asthma in cases (4.7±5.5 vs 5.2±5.5 days, p=0.61). Since detection of asthma depends on follow-up duration from registration to index date of community-acquired *E. coli* BSI, we designed our study to ensure that duration was similar between cases and controls. Asthma prevalence in controls in our study was 6%, which is similar to that in adults (7%) in the United States (5.5% for males and 9.7% for females).(36) Also, the prevalence of other common chronic condition such as coronary heart disease in our study (15%) was similar to the national average (7.1% for adults aged 45-64 years and 19.8% for adults aged ≥ 65 years) suggesting that our control group may reasonably represent a general population of adults in the United States.(3) There were no significant differences in influenza and PPV23 vaccination rates between cases and controls, which may imply similar access to health care services. Also, food allergy approached to statistical significant association with risk of E coli BSI but other atopic conditions were not. This is probably due to greater misclassification bias of ascertainment of allergic rhinitis and atopic dermatitis by ICD-9 code compared to asthma status and food allergy by predetermined criteria in our study. Taken together, our study results suggest that asthma status is independently associated with risk of community-acquired *E. coli* BSI.

There are only a few previous studies, which assessed the incidence of *E. coli* BSI and risk factors associated with its development, including asthma. One study showed a higher risk of community-acquired *E. coli* BSI in asthmatics compared to non-asthmatics among those over 65 years of age (5.5% vs. 1%).(37) However, another study showed reduced risk of *E. coli* BSI in asthmatics (rate ratio: 0.3; 95% CI: 0.2-0.4) compared to that in total regional population.(38) These studies have significant limitations including no *a priori* hypothesis testing on the

relationship between asthma and risk of community-acquired *E. coli* BSI, utilization of administrative data from health care organizations or case reports, ascertainment of *E. coli* BSI cases and asthma based on ICD-9 code, inclusion of only elderly patients aged over 65 years,(37) and no concurrent control group.(38) Thus, our study is the first population-based case-control study that demonstrated a relationship between asthma and risk of community-acquired *E. coli* BSI. Several studies showed increased risks of microbial infections in asthmatics[(5-7, 10, 11) but these studies only addressed the relationship between asthma and airway infections.

The mechanisms underlying the apparent association between asthma and risk of community-acquired *E. coli* BSI are unknown. Whether previously reported impaired innate immune factors that may predispose to infections due to viruses(13, 39, 40) and other bacteria are operative in community-acquired *E. coli* BSI is undefined. Recently, Habibzay et al reported impaired innate immunity against pneumococci through impaired TLR-receptor signal transduction by house dust mite allergic sensitization resulting in reduced neutrophil recruitment and increased risk of pneumococcal infection in the airways.(11) It is worth investigating whether allergic sensitization can induce similar impairment of innate immunity through TLR-4 for gram-negative bacteria in genitourinary or gastrointestinal tracts in asthmatics. Also, an adaptive immune response to gram-negative bacteria might be altered in asthmatics,(41) which may affect susceptibility to gram-negative bacterial infection. For example, Koch et al reported impaired Type 1 helper T cell (Th1) response (interleukin-12-induced interferon-γ release from T lymphocytes) to endotoxin from *Salmonella enteritidis* in asthmatics.(42) Further studies are needed to address our study findings.

The main strengths of our study are a population-based study design and include the epidemiologic merits of self-contained health care environment with comprehensive medical

record system for research. We identified population-based all incident community-acquired *E. coli* BSI cases based on the Freidman criteria. We ascertained asthma status by applying predetermined criteria independent of a physician diagnosis of asthma or ICD-9 code. Also, our study has inherent limitations as a retrospective study. We could not obtain detail information on certain variables such as atopic sensitization data or smoking history (e.g., duration or the number of cigarettes a day) but we assumed this data to be missing at random (i.e., it is subject to non-differential misclassification bias for comparison groups of interest). Although our criteria for asthma was based on medical record review, given the absence of gold standard for asthma, the retrospective investigation for feasibility (due to infrequent *E coli* BSI), and the extensive use of the criteria in previous asthma research, we believe the criteria is unlikely to result in a significant bias affecting interpretation of the results. Our study finding that asthma prevalence among controls was similar to that at the national level should mitigate this concern. Our study subjects were predominantly white which might limit generalizability of our results to other ethnic groups. Our study subjects were relatively an older population affected by many comorbid conditions, which might confound the study results. Therefore, we adjusted the association between asthma and risk of E coli BSI for each comorbid condition individually in our multivariate model. Since the prevalence of comorbid conditions is related to age, we examined the effect of the interaction between age and asthma. We found that the main results on the association between asthma and risk of *E coli* BSI did not appear to be significantly affected by various cutoffs of age suggesting the results did not differ by age group (younger vs. older group).

In conclusion, asthmatics might be at an increased risk of non-respiratory tract bacterial infections, including community-acquired *E. coli* BSI. The mechanisms responsible for this association are yet to be defined while additional investigations replicate our study findings.

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Table 1. Definition of asthma

Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma with the first two conditions and/or if each of the following three conditions were present, and they were considered to have *probable* asthma if only the first two conditions were present:

1. History of cough with wheezing, and/or dyspnea, OR history of cough and/or dyspnea plus wheezing on examination,
2. Substantial variability in symptoms from time to time or periods of 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/uL
- 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 FEV_1 or FVC less than 70% predicted and another with at least 20% improvement to an FEV_1 of higher70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV_1
- Favorable clinical response to bronchodilator (e.g., documented improvement of respiratory symptoms or FEV1 in spirometry after bronchodilator therapy)

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

- Tracheobronchial foreign body at or about the incidence date
- Hypogammaglobulinemia (IgG less than 2.0 mg/mL) or other immunodeficiency disorder
- Wheezing occurring only in response to anesthesia or medications
- Bullous emphysema or pulmonary fibrosis on chest radiograph
- PiZZ $alpha_1$-antitrypsin
- Cystic fibrosis
- Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis

FVC forced vital capacity; FEV1, forced expiratory volume in 1 sec.

- Pulmonary function tests that showed FEV_1 to be consistently below 50% predicted or diminished diffusion capacity

Table 2. Sociodemographic, and clinical characteristics of patients with *Escherichia coli* blood stream infection and their matched control subjects

Characteristics	Case (n= 259)	Control (n= 259)	Unadjusted OR[a] (95% CI)	p value
Age (years)	61±22	61±22	1.14 (0.78, 1.67)	0.497
Female gender	179 (69%)	179 (69%)	-	
Ethnicity				<0.001
Caucasian (non-Hispanic)	222 (86%)	245 (95%)	Referent	
Other	37 (14%)	14 (5%)	4.83 (2.01, 11.64)	
Education status				0.004
Some high school or less	45 (17%)	21 (8%)	Referent	
High school graduate	95 (37%)	87 (34%)	0.50 (0.27, 0.93)	
Some college or more	110 (42%)	143 (55%)	0.33 (0.18, 0.62)	
Unknown	9 (3%)	8 (3%)	-	
Influenza vaccination 1 year prior to index date	95 (37%)	110 (42%)	0.75 (0.51, 1.10)	0.145
PPV23 prior to index date	117 (45%)	114 (44%)	1.08 (0.69, 1.68)	0.736
Food allergy	16 (6%)	6 (2%)	2.67 (1.04, 6.81)	0.040
Asthma	37 (14%)	16 (6%)	2.75 (1.42, 5.32)	0.003
High-risk conditions				
Alcohol addiction	17 (7%)	1 (0%)	17.00 (2.26, 127.75)	0.006
Autoimmune disease[c]	9 (3%)	3 (1%)	3.00 (0.81, 11.08)	0.099
Chronic obstructive lung disease	12 (5%)	9 (3%)	1.37 (0.55, 3.42)	0.493
Chronic renal insufficiency	30 (12%)	4 (2%)	9.67 (2.94, 31.73)	<0.001
Congestive heart failure	19 (7%)	2 (1%)	18.00 (2.40, 134.84)	0.005
Coronary artery disease	52 (20%)	40 (15%)	1.46 (0.89, 2.41)	0.136
Dementia	16 (6%)	7 (3%)	3.25 (1.06, 9.97)	0.039
Diabetes mellitus	50 (19%)	24 (9%)	2.53 (1.44, 4.43)	0.001
History of stroke	15 (6%)	10 (4%)	1.71 (0.67, 4.35)	0.257
Immobilization[d]	10 (4%)	1 (0%)	10.00 (1.28, 78.12)	0.028
Immunosuppressive therapy	25 (10%)	4 (2%)	8.00 (2.41, 26.57)	0.001
Malignancy	21 (8%)	12 (5%)	2.00 (0.90, 4.45)	0.090
Recurrent urinary tract infection	29 (11%)	2 (1%)	14.50 (3.46, 60.77)	<0.001
Transplant recipients	8(3%)	0 (0%)	-	
Urinary incontinence	46 (18%)	20 (8%)	2.86 (1.55, 5.25)	0.001
Other condition[e]	14 (5%)	0 (0%)	-	-
Smoke				0.058
No (including ex-smoker)	206 (80%)	222 (86%)	Referent	

Active	53 (20%)	37 (14%)	1·59 (0.98, 2.58)

[a] Odds ratio based on matched analysis taking into account gender, birthday, residency, and follow-up duration
[b] Comorbidity conditions are not mutually exclusive
[c] Autoimmune disease includes SLE, rheumatoid arthritis, inflammatory bowel disease and other autoimmune diseases
[d] Immobilization includes hemi/para/quadri-plegia
[e] Other conditions include use of urinary catheter, device, genitourinary procedures (e.g., prostate biopsy), and congenital anomaly

Table 3. A multivariable conditional logistic regression model for the association between asthma and risk of community-acquired *Escherichia coli* bloodstream infection

Characteristics	Case (n= 259)	Control (n= 259)	Adjusted OR[a] (95% CI)	p value

Ethnicity				0.003
Caucasian (non-Hispanic)	222 (86%)	245 (95%)	Referent	
Other	37 (14%)	14 (5%)	5.90 (1.85, 18.84)	
Education status				0.646
Some high school or less	45 (17%)	21 (8%)	Referent	
High school graduate	95 (37%)	87 (34%)	0.89 (0.37, 2.14)	
Some college or more	110 (42%)	143 (55%)	0.65 (0.28, 1.50)	
Unknown	9 (3%)	8 (3%)	-	
Influenza vaccination 1 year prior to index date	95 (37%)	110 (42%)	0.58 (0.33, 1.02)	0.058
Food allergy	16 (6%)	6 (2%)	3.51 (0.94, 13.11)	0.062
Asthma	37 (14%)	16 (6%)	2.74 (1.11, 6.76)	0.029
Active smoking	53 (20%)	37 (14%)	1.31 (0.69, 2.47)	0.412
High-risk conditions				
Alcohol addiction	17 (7%)	1 (0%)	32.31 (1.91, 546.18)	0.016
Autoimmune diseases	9 (3%)	3 (1%)	1.79 (0.23, 13.72)	0.574
Chronic renal insufficiency	30 (12%)	4 (2%)	4.76 (1.16, 19.59)	0.030
Congestive heart failure	19 (7%)	2 (1%)	9.86 (0.93, 104.59)	0.058
Coronary artery disease	52 (20%)	40 (15%)	0.81 (0.37, 1.77)	0.593
Dementia	16 (6%)	7 (3%)	4.14 (0.96, 17.96)	0.057
Diabetes mellitus	50 (19%)	24 (9%)	2.39 (0.97, 5.87)	0.057
Immobilization	10 (4%)	1 (0%)	39.86 (2.30, 690.42)	0.011
Immunosuppressive therapy	25 (10%)	4 (2%)	8.51 (1.32, 54.96)	0.024
Malignancy	21 (8%)	12 (5%)	2.18 (0.59, 8.11)	0.243
Recurrent urinary tract infection	29 (11%)	2 (1%)	13.54 (2.42, 75.65)	0.003
Urinary incontinence	46 (18%)	20 (8%)	2.57 (1.05, 6.26)	0.038

[a] Adjusted variables included all variables included in this table.

Table 4. Association of asthma control status and therapy with risk of community-acquired *Escherichia coli* bloodstream infection

Asthma characteristics	Total	Unadjusted OR	Adjusted OR[a]

	(n=518)	(95% CI), p-value	(95% CI), p-value
Inhaled corticosteroid therapy (ICS)		*p=0.009*[b]	*p=0.079*[b]
No asthma	465 (90%)	Referent	Referent
Asthma without ICS	35 (7%)	1.90 (0.88, 4.09)	1.99 (0.67, 5.94)
Asthma with ICS	18 (3%)	7.00 (1.59, 30.80)	5.33 (0.90, 31.66)
Asthma status[c]		*p=0.005*[b]	*p=0.067*[b]
No asthma	465 (90%)	Referent	Referent
Remission or inactive asthma	17 (3%)	1.25 (0.45, 3.50)	1.25 (0.25, 6.30)
Active or current asthma	36 (7%)	4.37 (1.80, 10.62)	3.89 (1.23, 12.28)

[a] Adjusted variables included all factors reported in the multivariable model (see Table 3) except for dichotomous asthma status
[b] P-value for overall comparison
[c] 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 E coli BSI; Remission of asthma was defined as the absence of asthma-related events > 3 years prior to index date; Inactive (not current) asthma was defined as the presence of asthma-related events within 1-3 years prior to index date.

TITLE PAGE

Original Article

Asthma and Risk of Non-Respiratory Tract Infection: A Population-Based Case Control Study

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Conflict of interest: The study investigators have nothing to disclose that poses a conflict of interest.

We reviewed the STROBE statement and addressed all items in that checklist and are submitting the STROBE statement with the revised manuscript.

Key Words: Asthma, Risk, Epidemiology, Community-acquired infections, *Escherichia Coli*, Blood stream infection, genitourinary, and gastrointestinal tract

Abbreviations: BSI: blood stream infection, *E.Coli*: *Escherichia Coli*, TLR : Toll-like Receptor, ICS : inhaled corticosteroid, PPV23: 23-valent pneumococcal polysaccharide vaccine

Word count: 2993

Article summary

1. Article focus: We addressed the following question in this study.

- Given the association between asthma and airway-related infection, is asthma also associated with non-airway-related serious infections such as *Escherichia coli* blood stream infection?

2. Key messages

- Individuals with asthma are at a significantly increased risk of non-airway-related infection, including community-acquired *E. coli* blood stream infection.

- The impact of asthma on risks of microbial infections may go beyond airways.

- Clinicians and patients should be aware of the association and recognize the risk of subsequent infection.

3. Strength and limitations

- This is the first population-based case-control study using predetermined criteria for asthma status and community-acquired *Escherichia coli* blood stream infection.

- The main limitation of the study is inherent limitations as a retrospective study and the study subjects were predominantly white.

Contributors

BDW collected data, interpreted the results, and drafted the manuscript; HJY participated in the study design, interpreted the results and reviewed the manuscript; ER collected data, interpreted the results, and reviewed manuscript; MNA assembled the original dataset for the E. coli BSI study, collected the original data, interpreted the results, and reviewed the manuscript; LMB participated in the study design, interpreted the results, and reviewed the manuscript; BPY participated in the study design, interpreted the results, and reviewed manuscript; and YJJ

participated in the study design, performed data analysis, interpreted the results, and drafted the manuscript. BDW, ER, and YJJ had full access to data. All authors reviewed and approved the paper.

There will be no additional data available.

Abstract:

Objectives: Asthmatics have increased risks of airway-related infections. Little is known about whether this is true for non-airway-related serious infections such as *Escherichia coli* blood stream infection (BSI). We assessed whether asthma is associated with a risk of developing community-acquired *E. coli* BSI.

Design: The study was designed as a population-based retrospective case-control study.

Setting: This population-based study was conducted in Olmsted County, Minnesota.

Participants: The study included 259 all eligible community-acquired *E. coli* BSI cases in Olmsted County, MN between 1998 and 2007 and 259 birthday-, gender-, and residency-matched controls.

Primary and secondary outcome measures: Only community-acquired *E. coli* BSI cases as the primary outcome was included. Asthma status as an exposure was ascertained by predetermined criteria. An adjusted odds ratio (OR) and 95% confidence interval (CI) for the association between asthma and risk of community-acquired *E. coli* BSI was calculated using conditional logistic regression.

Results: Of 259 eligible cases, 179 (69 %) were female and mean age was 61±22 years. Thirty-seven of 259 cases (14%) and 16 of 259 controls (6%) had a prior history of asthma (adjusted OR: 2.74; 95% CI: 1.11-6.76; p=0.029). The population attributable risk of asthma for community-acquired *E. coli* BSI was 9%. Although not statistically significant, there was a borderline association between having a history of food allergy and increased risk of community-acquired *E. coli* BSI (6% vs 2%; adjusted OR: 3.51; 95% CI: 0.94-13.11, p=0.062).

Conclusions: Based on the findings of the current population-based, case-control investigation, a history of asthma may be associated with risk of community-acquired *E. coli* BSI. The impact of

asthma on risk of microbial infections may go beyond airways.

Abstract Word Count: 246

INTRODUCTION

Asthma is the most common chronic illness in childhood and is a major cause of morbidity in adults, affecting 4-17% of children and 7.7% of adults in the US.(1-3)] About 300 million people globally are estimated to be affected by asthma.(4)

Previous studies showed increased risks of microbial infections among individuals with asthma(5-10) and the population attributable risk for asthma of serious pneumococcal disease was 11-17%.(6, 10) Impaired innate and adaptive immune functions among asthmatics have been suggested for potential underlying mechanisms.(11-18) These study results are based on microbial infections of the airways. However, little is known about whether asthma status is associated with risk of non-airway-related bacterial infections such as community-acquired *Escherichia coli* blood stream infection (BSI).

Addressing this question should provide an important insight into the nature of the impact of asthma status on susceptibility to microbial infection. Specifically, it will improve our understanding on whether the impact of asthma status on susceptibility to infection goes beyond airways. In investigating this question, community-acquired *E. coli* BSI is suitable because it is not an airway-related infection but genitourinary tract/gastrointestinal origin, *E. coli* is a gram-negative bacterium with Toll-like Receptor (TLR)-4-mediated signal transduction for innate immunity, and *E. coli* is the most common cause of community-acquired BSI.(19) Up to 30% of individuals who developed community-acquired *E. coli* BSI did not have known risk

factors,[(20)] suggesting that unrecognized risk factors exist that are associated with the development of community-acquired *E. coli* BSI.

Investigating the relationship between asthma and non-airway-related serious bacterial infections will advance our understanding on the extent to which asthma impacts susceptibility to microbial infections and whether asthma could be an unrecognized risk factor for non-airway-related bacterial infections.

We hypothesize that individuals with asthma have an increased risk of community-acquired *E. coli* BSI, as compared to those without asthma. To test this hypothesis, we conducted a population-based retrospective case-control study.

METHODS

The study was approved by the Institutional Review Boards of both Mayo Clinic and Olmsted Medical Center. This study was designed as a population-based case-control study.

Study population and setting

Olmsted County, Minnesota is an excellent setting to conduct a population-based epidemiologic study such as this because medical care is virtually self-contained within the community (nearly all Olmsted County residents receive medical cares from two medical centers in the community). The population characteristics of Olmsted County residents are similar to those of non-Hispanic white.(21) If one grants the authorization for using medical record for research (almost 95% of Olmsted County residents), each patient is assigned a unique identifier under the auspices of the Rochester Epidemiology Project (REP).(22) Using REP resources, we previously demonstrated that incidence rates of asthma for this community are similar to other communities. The annual incidence rate of asthma in Rochester was 238 cases per 100,000 persons, which is comparable to those in other communities such as Tecumseh, Michigan (250/100,000).(23)

Study subjects: Case ascertainment

To test our study hypothesis, we utilized a population-based incidence parent study, which previously identified the community-acquired cases to study antimicrobial resistance trends of *E. coli* BSI in the community. Details of the case ascertainment have been described

previously.(19) Briefly, using the microbiology databases at Mayo Clinic Rochester and Olmsted Medical Center, all eligible children and adults with monomicrobial *E. coli* BSI (n=274) among Olmsted County residents from January 1, 1998 to December 31, 2007 (i.e., a population-based all incident cases of *E. coli* BSI) were identified based on the criteria suggested by Freidman et al.(24) As *E. coli* BSI is required for inpatient parental treatment, community-acquired *E. coli* BSI was defined by isolation of *E. coli* from blood cultures at the time of hospital admission or within 48 hours after hospital admission for patients who did not fit criteria for health care–associated infection according to the Freidman's criteria.(24) Medical records of all subjects were reviewed by investigators of the previous study (MNA) to confirm the diagnosis of community-acquired *E. coli* BSI, assess clinical features, and determine the eligibility. Only community-acquired *E. coli* BSI was included because nosocomial and health care-associated *E. coli* BSI are unsuitable to address the aim of the present study (clinically, they are a high-risk population for *E. coli* BSI and not representative of the study population). The index date of BSI was defined as the date when blood cultures that eventually grew *E. coli* were obtained. Exclusion criteria for cases (and controls) included: 1) polymicrobial BSI caused by more than one microorganism, 2) blood cultures acquired at autopsy, 3) nosocomial and health care-associated *E. coli* BSI, 4) non-Olmsted County residency at the time of index date of BSI, 5) no research authorization for using medical record for research, and 6) health conditions making ascertainment of asthma difficult listed in Table 1.

Selection of control subjects

Control subjects were randomly selected with 1:1 matching from Olmsted County residents who had not had a history of *E. coli* BSI at the end of the study period. Briefly, a list of potential control subjects who had received medical care from either Mayo Clinic or Olmsted

Medical Center and who met the matching criteria was generated and randomly selected from the REP database for the present study. The matching criteria included: 1) gender, 2) birth date (within six months for those <18 years of age and within one year for those > 18 years of age), 3) the same clinic registration year as matched case (within one year), and 4) closest clinic visit to index date of matched case within one year. The index date for control subjects was defined as the closest (within one year) clinic visit date to index date of BSI for their corresponding matched case. Based on the number of cases and controls enrolled in this present study (259 pair), assuming 8% of asthma prevalence among controls, this present study had 80% power to detect an effect size of 2.27 of odds ratio (16.5% of asthma in cases). This effect size was smaller than the reported effect sizes for the association between asthma and risk of microbial infection (OR: 2.4-6.7) suggesting adequate statistical power to address the study aim.(6, 10)

Exposure ascertainment (asthma status)

For determining asthma status of all cases and controls, we conducted comprehensive medical record reviews to apply predetermined criteria for asthma as performed in our previous work.(5, 6) The criteria are delineated in Table 1. These criteria have been extensively used in research for asthma epidemiology and were found to have high reliability.(25-30) We included both definite and probable asthma according to the criteria prior to the index date of BSI cases because most probable asthmatics become definite over time.(6, 31) The incidence dates (the first date when one met the criteria for asthma) for all asthmatic patients were determined; thus, we were able to discern the temporal relationship between asthma status (exposure) and *E coli* BSI (outcome). The risk of *E. coli* BSI was assessed in relation to the current asthma status(32): remission (no asthma symptoms, no asthma-related visits, or no asthma medications for at least three years prior to index date); active or current asthma (presence of clinical symptoms, asthma-

related visits, or asthma medications within one year prior to index date); and inactive (not current) asthma (presence of asthma symptoms, asthma-related visits, or asthma medications within 1-3 years prior to index date).

Other variables

Pertinent covariates and confounders were collected from medical records: sociodemographic variables (age, gender, ethnicity, and educational status), asthma medications including inhaled and systemic corticosteroids, family history of asthma, atopic status based on sensitization against aeroallergens and food allergens, smoking status (either active or passive exposure to tobacco smoke), vaccination status, and co-morbid conditions at the time of index date as listed in Table 2. The period of data collection was from October 1, 2011 to May 30, 2012.

Statistical analysis

Formal comparison of asthma and other suspected risk factors between matched cases and controls was performed using conditional logistic regression, with community-acquired *E. coli* BSI as the target of prediction. All factors were analyzed for a univariate association with BSI, and any variables meeting the Greenland entry criteria ($P< 0.2$) were carried forward into a final multivariable model.(33)] Odds ratios (OR) from univariate (unadjusted) and multivariable (adjusted) models are reported to express the magnitude of association in terms of the likelihood of being a case. We calculated the population attributable risk percentage (PAR%) of asthma for community-acquired *E. coli* BSI using the formula established by Miettinen.(34) Statistical significance was tested at a two-sided alpha error of 0.05. All analyses were carried out with the statistical software package SAS, version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Study subjects

Of the 274 patients who were identified in the original study, 259 were eligible for the present study. Fifteen patients were excluded; five for consistent FEV1 < 50%, two for restrictive lung disease, two for significant kyphoscoliosis, two for bronchiectasis, one for cystic fibrosis, one for pulmonary fibrosis, and two due to non-Olmsted County residency. Of the eligible 259 cases, 179 (69%) were female, 249 (96%) were 18 years of age or older (age mean±standard deviation, 61±22 years), and 222 (86%) were Caucasian. The characteristics of the cases and their matched controls, and the individual associations with community-acquired *E. coli* BSI, are summarized in Table 2. There were only 10 asthmatics on moderate- or high-dose inhaled corticosteroid (ICS) and two asthmatics on systemic corticosteroid at the time of the index date. Comparing subjects with asthma versus those without, there was no significant difference in the proportions, who had received influenza vaccine (40% vs. 40%, p=0.99) or PPV23 (49% vs. 44%, p=0.49) within one year prior to index date.

Association between asthma and risk of community-acquired *E. coli* BSI

Thirty-seven of 259 (14%) cases had a history of asthma prior to the index date of community-acquired *E. coli* BSI, compared with 16 of 259 (6%) controls (unadjusted OR: 2.75; 95% CI: 1.42-5.32; p=0.003). Of the 37 case subjects with asthma, 33 (89%) had definite asthma and 4 (11%) had probable asthma. Of the 16 controls with asthma, 12 (75%) had definite asthma and 4

(25%) had probable asthma. Among all 53 asthmatics, 18 were on ICS therapy at the index date (8 on low-dose ICS and 10 on moderate to high-dose ICS therapy). The effect of asthma on risk of community-acquired *E. coli* BSI, independent of other risk factors, is summarized in Table 3. Subjects with a history of asthma by predetermined criteria for asthma in Table 1 had a nearly 3-fold higher risk of developing community-acquired *E. coli* BSI compared to those without asthma, controlling for all potential confounding factors (adjusted OR: 2.74; 95% CI: 1.11-6.76; p=0.029). The PAR% of asthma by predetermined criteria for asthma in Table 1 for the risk of *E. coli* BSI was 9%. The *p*-values for testing a significant interaction between asthma and categorized age were as follows: p=0.285 for age cutoff of 65 years (i.e., ≥65 vs. <65 years), p=0.958 for age cutoff of 40 years (i.e., ≥40 vs. <40 years), and p=0.417 for age cutoffs of 40 years and 65 years (i.e., <40, 40-65, vs. >65 years). As a result, we have no evidence of a differential asthma effect across age strata. Additional characteristics of asthma were also evaluated for an association with risk of community-acquired *E. coli* BSI (see Table 4). Adjusted for other factors, active asthma was associated with increased risk of *E. coli* BSI but for asthmatics on ICS therapy compared to non-asthmatics, but the overall 3-level effect was not statistically significant (p=0.079).

Other variables and *E. coli* BSI

Several of the high-risk conditions, as well as non-Caucasian ethnicity, were independently associated with increased risk of community-acquired *E. coli* BSI (see Tables 2 and 3). A history of food allergy was found in 16 (6%) of 259 cases as compared with 6 (2%) of 259 controls (adjusted OR: 3.51; 95% CI: 0.94-13.11; p=0.062). Neither allergic rhinitis (p=0.82) nor atopic dermatitis (p=0.87) was found to be significantly associated with community-acquired *E. coli* BSI.

DISCUSSION

To our knowledge, this is the first population-based, case-control study that demonstrated an association between asthma and risk of non-respiratory bacterial infection such as community-acquired *E. coli* BSI. This association was independent of other risk factors including age, gender, follow-up duration, ethnicity, educational level, and comorbid conditions (adjusted OR: 2.74; 95% CI: 1.11-6.76; p=0.029). Analyses by different age cut-offs showed that the results were not affected by age effect (e.g., younger vs. older than 40 years of age). Given either the previously-reported non association (hazard ratio, HR: 1.29, 95%CI: 0.53-3.12) or a protective effect (HR: 0.52, 95%CI:0.36-0.76) of ICS therapy on risk of pneumonia in asthmatics(35) and a small number of asthmatics with moderate or high-dose ICS in our study (10 of 53, 19%), we suspect that active or current asthma (or collectively those given ICS therapy) might be related to risk of community-acquired *E. coli* BSI instead of ICS alone. There were only 2 asthmatics on systemic corticosteroid therapy at the time of the index date; therefore, exposure to systemic corticosteroid therapy was unlikely to account for the observed association. We believe that susceptibility bias (e.g., covariate imbalance at baseline) is unlikely to account for the association found in our study given the full adjustment for potential confounders. One concern could be detection bias stemming from a situation where exposure status (asthma status) systematically affects detection of outcomes. However, given *E. coli* BSI as a life-threatening condition, this is

unlikely and also there was no significant difference in symptom duration from BSI-related symptom to index date between asthma and non-asthma in cases (4.7±5.5 vs 5.2±5.5 days, p=0.61). Since detection of asthma depends on follow-up duration from registration to index date of community-acquired *E. coli* BSI, we designed our study to ensure that duration was similar between cases and controls. Asthma prevalence in controls in our study was 6%, which is similar to that in adults (7%) in the United States (5.5% for males and 9.7% for females).(36) Also, the prevalence of other common chronic condition such as coronary heart disease in our study (15%) was similar to the national average (7.1% for adults aged 45-64 years and 19.8% for adults aged ≥ 65 years) suggesting that our control group may reasonably represent a general population of adults in the United States.(3) There were no significant differences in influenza and PPV23 vaccination rates between cases and controls, which may imply similar access to health care services. Also, food allergy approached to statistical significant association with risk of E coli BSI but other atopic conditions were not. This is probably due to greater misclassification bias of ascertainment of allergic rhinitis and atopic dermatitis by ICD-9 code compared to asthma status and food allergy by predetermined criteria in our study. Taken together, our study results suggest that asthma status is independently associated with risk of community-acquired *E. coli* BSI.

There are only a few previous studies, which assessed the incidence of *E. coli* BSI and risk factors associated with its development, including asthma. One study showed a higher risk of community-acquired *E. coli* BSI in asthmatics compared to non-asthmatics among those over 65 years of age (5.5% vs. 1%).(37) However, another study showed reduced risk of *E. coli* BSI in asthmatics (rate ratio: 0.3; 95% CI: 0.2-0.4) compared to that in total regional population.(38) These studies have significant limitations including no *a priori* hypothesis testing on the

relationship between asthma and risk of community-acquired *E. coli* BSI, utilization of administrative data from health care organizations or case reports, ascertainment of *E. coli* BSI cases and asthma based on ICD-9 code, inclusion of only elderly patients aged over 65 years,(37) and no concurrent control group.(38) Thus, our study is the first population-based case-control study that demonstrated a relationship between asthma and risk of community-acquired *E. coli* BSI. Several studies showed increased risks of microbial infections in asthmatics[(5-7, 10, 11) but these studies only addressed the relationship between asthma and airway infections.

The mechanisms underlying the apparent association between asthma and risk of community-acquired *E. coli* BSI are unknown. Whether previously reported impaired innate immune factors that may predispose to infections due to viruses(13, 39, 40) and other bacteria are operative in community-acquired *E. coli* BSI is undefined. Recently, Habibzay et al reported impaired innate immunity against pneumococci through impaired TLR-receptor signal transduction by house dust mite allergic sensitization resulting in reduced neutrophil recruitment and increased risk of pneumococcal infection in the airways.(11) It is worth investigating whether allergic sensitization can induce similar impairment of innate immunity through TLR-4 for gram-negative bacteria in genitourinary or gastrointestinal tracts in asthmatics. Also, an adaptive immune response to gram-negative bacteria might be altered in asthmatics,(41) which may affect susceptibility to gram-negative bacterial infection. For example, Koch et al reported impaired Type 1 helper T cell (Th1) response (interleukin-12-induced interferon-γ release from T lymphocytes) to endotoxin from *Salmonella enteritidis* in asthmatics.(42) Further studies are needed to address our study findings.

The main strengths of our study are a population-based study design and include the epidemiologic merits of self-contained health care environment with comprehensive medical

record system for research. We identified population-based all incident community-acquired *E. coli* BSI cases based on the Freidman criteria. We ascertained asthma status by applying predetermined criteria independent of a physician diagnosis of asthma or ICD-9 code. Also, our study has inherent limitations as a retrospective study. We could not obtain detail information on certain variables such as atopic sensitization data or smoking history (e.g., duration or the number of cigarettes a day) but we assumed this data to be missing at random (i.e., it is subject to non-differential misclassification bias for comparison groups of interest). Although our criteria for asthma was based on medical record review, given the absence of gold standard for asthma, the retrospective investigation for feasibility (due to infrequent *E coli* BSI), and the extensive use of the criteria in previous asthma research, we believe the criteria is unlikely to result in a significant bias affecting interpretation of the results. Our study finding that asthma prevalence among controls was similar to that at the national level should mitigate this concern. Our study subjects were predominantly white which might limit generalizability of our results to other ethnic groups. Our study subjects were relatively an older population affected by many comorbid conditions, which might confound the study results. Therefore, we adjusted the association between asthma and risk of E coli BSI for each comorbid condition individually in our multivariate model. Since the prevalence of comorbid conditions is related to age, we examined the effect of the interaction between age and asthma. We found that the main results on the association between asthma and risk of *E coli* BSI did not appear to be significantly affected by various cutoffs of age suggesting the results did not differ by age group (younger vs. older group).

In conclusion, asthmatics might be at an increased risk of non-respiratory tract bacterial infections, including community-acquired *E. coli* BSI. The mechanisms responsible for this association are yet to be defined while additional investigations replicate our study findings.

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Table 1. Definition of asthma

Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma with the first two conditions and/or if each of the following three conditions were present, and they were considered to have *probable* asthma if only the first two conditions were present:

1. History of cough with wheezing, and/or dyspnea, OR history of cough and/or dyspnea plus wheezing on examination,
2. Substantial variability in symptoms from time to time or periods of 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/uL
- 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 FEV_1 or FVC less than 70% predicted and another with at least 20% improvement to an FEV_1 of higher70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV_1
- Favorable clinical response to bronchodilator (e.g., documented improvement of respiratory symptoms or FEV1 in spirometry after bronchodilator therapy)

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

- Tracheobronchial foreign body at or about the incidence date
- Hypogammaglobulinemia (IgG less than 2.0 mg/mL) or other immunodeficiency disorder
- Wheezing occurring only in response to anesthesia or medications
- Bullous emphysema or pulmonary fibrosis on chest radiograph
- PiZZ $alpha_1$-antitrypsin
- Cystic fibrosis
- Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis

FVC forced vital capacity; FEV1, forced expiratory volume in 1 sec.

- Pulmonary function tests that showed FEV_1 to be consistently below 50% predicted or diminished diffusion capacity

Table 2. Sociodemographic, and clinical characteristics of patients with *Escherichia coli* blood stream infection and their matched control subjects

Characteristics	Case (n= 259)	Control (n= 259)	Unadjusted OR[a] (95% CI)	p value
Age (years)	61±22	61±22	1.14 (0.78, 1.67)	0.497
Female gender	179 (69%)	179 (69%)	-	
Ethnicity				<0.001
Caucasian (non-Hispanic)	222 (86%)	245 (95%)	Referent	
Other	37 (14%)	14 (5%)	4.83 (2.01, 11.64)	
Education status				0.004
Some high school or less	45 (17%)	21 (8%)	Referent	
High school graduate	95 (37%)	87 (34%)	0.50 (0.27, 0.93)	
Some college or more	110 (42%)	143 (55%)	0.33 (0.18, 0.62)	
Unknown	9 (3%)	8 (3%)	-	
Influenza vaccination 1 year prior to index date	95 (37%)	110 (42%)	0.75 (0.51, 1.10)	0.145
PPV23 prior to index date	117 (45%)	114 (44%)	1.08 (0.69, 1.68)	0.736
Food allergy	16 (6%)	6 (2%)	2.67 (1.04, 6.81)	0.040
Asthma	37 (14%)	16 (6%)	2.75 (1.42, 5.32)	0.003
High-risk conditions				
Alcohol addiction	17 (7%)	1 (0%)	17.00 (2.26, 127.75)	0.006
Autoimmune disease[c]	9 (3%)	3 (1%)	3.00 (0.81, 11.08)	0.099
Chronic obstructive lung disease	12 (5%)	9 (3%)	1.37 (0.55, 3.42)	0.493
Chronic renal insufficiency	30 (12%)	4 (2%)	9.67 (2.94, 31.73)	<0.001
Congestive heart failure	19 (7%)	2 (1%)	18.00 (2.40, 134.84)	0.005
Coronary artery disease	52 (20%)	40 (15%)	1.46 (0.89, 2.41)	0.136
Dementia	16 (6%)	7 (3%)	3.25 (1.06, 9.97)	0.039
Diabetes mellitus	50 (19%)	24 (9%)	2.53 (1.44, 4.43)	0.001
History of stroke	15 (6%)	10 (4%)	1.71 (0.67, 4.35)	0.257
Immobilization[d]	10 (4%)	1 (0%)	10.00 (1.28, 78.12)	0.028
Immunosuppressive therapy	25 (10%)	4 (2%)	8.00 (2.41, 26.57)	0.001
Malignancy	21 (8%)	12 (5%)	2.00 (0.90, 4.45)	0.090
Recurrent urinary tract infection	29 (11%)	2 (1%)	14.50 (3.46, 60.77)	<0.001
Transplant recipients	8(3%)	0 (0%)	-	
Urinary incontinence	46 (18%)	20 (8%)	2.86 (1.55, 5.25)	0.001
Other condition[e]	14 (5%)	0 (0%)	-	-
Smoke				0.058
No (including ex-smoker)	206 (80%)	222 (86%)	Referent	

Active	53 (20%)	37 (14%)	1·59 (0.98, 2.58)

[a] Odds ratio based on matched analysis taking into account gender, birthday, residency, and follow-up duration
[b] Comorbidity conditions are not mutually exclusive
[c] Autoimmune disease includes SLE, rheumatoid arthritis, inflammatory bowel disease and other autoimmune diseases
[d] Immobilization includes hemi/para/quadri-plegia
[e] Other conditions include use of urinary catheter, device, genitourinary procedures (e.g., prostate biopsy), and congenital anomaly

Table 3. A multivariable conditional logistic regression model for the association between asthma and risk of community-acquired *Escherichia coli* bloodstream infection

Characteristics	Case (n= 259)	Control (n= 259)	Adjusted OR[a] (95% CI)	p value

Ethnicity				0.003
Caucasian (non-Hispanic)	222 (86%)	245 (95%)	Referent	
Other	37 (14%)	14 (5%)	5.90 (1.85, 18.84)	
Education status				0.646
Some high school or less	45 (17%)	21 (8%)	Referent	
High school graduate	95 (37%)	87 (34%)	0.89 (0.37, 2.14)	
Some college or more	110 (42%)	143 (55%)	0.65 (0.28, 1.50)	
Unknown	9 (3%)	8 (3%)	-	
Influenza vaccination 1 year prior to index date	95 (37%)	110 (42%)	0.58 (0.33, 1.02)	0.058
Food allergy	16 (6%)	6 (2%)	3.51 (0.94, 13.11)	0.062
Asthma	37 (14%)	16 (6%)	2.74 (1.11, 6.76)	0.029
Active smoking	53 (20%)	37 (14%)	1.31 (0.69, 2.47)	0.412
High-risk conditions				
Alcohol addiction	17 (7%)	1 (0%)	32.31 (1.91, 546.18)	0.016
Autoimmune diseases	9 (3%)	3 (1%)	1.79 (0.23, 13.72)	0.574
Chronic renal insufficiency	30 (12%)	4 (2%)	4.76 (1.16, 19.59)	0.030
Congestive heart failure	19 (7%)	2 (1%)	9.86 (0.93, 104.59)	0.058
Coronary artery disease	52 (20%)	40 (15%)	0.81 (0.37, 1.77)	0.593
Dementia	16 (6%)	7 (3%)	4.14 (0.96, 17.96)	0.057
Diabetes mellitus	50 (19%)	24 (9%)	2.39 (0.97, 5.87)	0.057
Immobilization	10 (4%)	1 (0%)	39.86 (2.30, 690.42)	0.011
Immunosuppressive therapy	25 (10%)	4 (2%)	8.51 (1.32, 54.96)	0.024
Malignancy	21 (8%)	12 (5%)	2.18 (0.59, 8.11)	0.243
Recurrent urinary tract infection	29 (11%)	2 (1%)	13.54 (2.42, 75.65)	0.003
Urinary incontinence	46 (18%)	20 (8%)	2.57 (1.05, 6.26)	0.038

[a] Adjusted variables included all variables included in this table.

Table 4. Association of asthma control status and therapy with risk of community-acquired *Escherichia coli* bloodstream infection

Asthma characteristics	Total	Unadjusted OR	Adjusted OR[a]

	(n=518)	(95% CI), p-value	(95% CI), p-value
Inhaled corticosteroid therapy (ICS)		*p=0.009*[b]	*p=0.079*[b]
No asthma	465 (90%)	Referent	Referent
Asthma without ICS	35 (7%)	1.90 (0.88, 4.09)	1.99 (0.67, 5.94)
Asthma with ICS	18 (3%)	7.00 (1.59, 30.80)	5.33 (0.90, 31.66)
Asthma status[c]		*p=0.005*[b]	*p=0.067*[b]
No asthma	465 (90%)	Referent	Referent
Remission or inactive asthma	17 (3%)	1.25 (0.45, 3.50)	1.25 (0.25, 6.30)
Active or current asthma	36 (7%)	4.37 (1.80, 10.62)	3.89 (1.23, 12.28)

[a] Adjusted variables included all factors reported in the multivariable model (see Table 3) except for dichotomous asthma status
[b] P-value for overall comparison
[c] 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 E coli BSI; Remission of asthma was defined as the absence of asthma-related events > 3 years prior to index date; Inactive (not current) asthma was defined as the presence of asthma-related events within 1-3 years prior to index date.