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Asthma and risk of non-respiratory tract infection: a population-based case–control study

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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* bloodstream 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-matched, gender-matched 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 OR and 95% 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 women and mean age was 61±22 years. Of the 259 cases 37 (14%) and 16 (6%) of 259 controls had a prior history of asthma (adjusted OR 2.74; 95% CI 1.11 to 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 to 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.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first population-based case–control study using predetermined criteria for asthma status and community-acquired *Escherichia coli* bloodstream infection. Also, our study setting has the epidemiologic merits of self-contained healthcare environment with comprehensive medical record system for research.
- The study has inherent limitations as a retrospective study. The study participants were predominantly white and were a relatively older population.

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 USA.[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 the risk of non-airway-related bacterial infections such as community-acquired *Escherichia coli* bloodstream 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 unrecognised 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 unrecognised risk factor for non-airway-related bacterial infections.

We hypothesise 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

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 epidemiological study such as this because medical care is virtually self-contained within the community (nearly all Olmsted County residents receive medical care from two medical centres in the community). The population characteristics of Olmsted County residents are similar to those of non-Hispanic white.[21] If one grants the authorisation 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/100 000 persons, which is comparable to those in other communities such as Tecumseh, Michigan (250/100 000).[23]

Study participants: case ascertainment

To test our study hypothesis, we utilised 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 1 January 1998 to 31 December 2007 (ie, a population-based all incident cases of *E coli* BSI) were identified based on the criteria suggested by Friedman *et al*.[24] As *E coli* BSI is required for inpatient parental treatment, community-acquired *E coli* BSI was defined by the isolation of *E coli* from blood cultures at the time of hospital admission or within 48 h after hospital admission for patients who did not fit the criteria for healthcare-associated infection according to the Friedman's criteria.[24] Medical records of all participants were reviewed by investigators of the previous study (MNA-H) 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 healthcare-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 healthcare-associated *E coli* BSI, (4) non-Olmsted County residency at the time of index date of BSI, (5) no research authorisation for using medical record for research and (6) health conditions making ascertainment of asthma difficult listed in box 1.

Selection of control participants

Control participants 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 participants 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 6 months for those <18 years of age and within 1 year for those >18 years of age), (3) the same clinic registration year as matched case (within 1 year) and (4) closest clinic visit to index date of matched case within 1 year. The index date for control participants was defined as the closest (within 1 year) clinic visit date to index date of BSI for their corresponding matched case. Based on the number of cases and controls enroled 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 OR (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 box 1. These criteria have been extensively used in research for asthma epidemiology and were found to have high reliability.[25–30] We included definite as well as probable asthma according to the criteria prior to the index date of BSI cases because most probable asthmatics

Box 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 dyspnoea, or history of cough and/or dyspnoea 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
   - Non-smoker (14 years or older)
   - Nasal polyps
   - Blood eosinophilia higher than 300/μL
   - Positive wheal and flare skin tests or elevated serum IgE
   - History of hay fever or infantile eczema or cough, dyspnoea 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 (eg, documented improvement of respiratory symptoms or FEV_1 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
- Hypogammaglobulinaemia (IgG less than 2.0 mg/mL) or other immunodeficiency disorder
- Wheezing occurring only in response to anaesthesia or medications
- Bullous emphysema or pulmonary fibrosis on chest radiograph
- PiZZ α_1-antitrypsin
- Cystic fibrosis
- Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis FVC forced vital capacity; FEV_1, forced expiratory volume in 1 s
- Pulmonary function tests that showed FEV_1 to be consistently below 50% predicted or diminished diffusion capacity

become definite over time.[6 31] The incidence dates (the first date when one met the criteria for asthma) for all patients with asthma 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 3 years prior to index date); active or current asthma (presence of clinical symptoms, asthma-related visits or asthma medications within 1 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 sensitisation against aeroallergens and food allergens, smoking status (either active or passive exposure to tobacco smoke), vaccination status and comorbid conditions at the time of index date as listed in table 1. The period of data collection was from 1 October 2011 to 30 May 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 analysed 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] ORs 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 α error of 0.05. All analyses were carried out with the statistical software package SAS, V.9.2 (SAS Institute, Cary, North Carolina, 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 FEV_1 <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 women, 249 (96%) were 18 years of age or older (age mean±SD, 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 summarised in table 1. There were only 10 asthmatics on moderate-dose or high-dose inhaled corticosteroid (ICS) and two asthmatics on systemic corticosteroid at the time of the index date. Comparing participants 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 23-valent pneumococcal polysaccharide vaccine (PPV23; 49% vs 44%, p=0.49) within 1 year prior to index date.

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

Of the 259 cases, 37 (14%) had a history of asthma prior to the index date of community-acquired *E coli* BSI, compared with 16 of 259 (6%) controls

Table 1 Sociodemographic and clinical characteristics of patients with *Escherichia coli* blood stream infection and their matched control participants

Characteristics	Case (n=259)	Control (n=259)	Unadjusted OR* (95% CI)	p Value
Age (years)	61±22	61±22	1.14 (0.78 to 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 to 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 to 0.93)	
Some college or more	110 (42%)	143 (55%)	0.33 (0.18 to 0.62)	
Unknown	9 (3%)	8 (3%)	–	
Influenza vaccination 1 year prior to index date	95 (37%)	110 (42%)	0.75 (0.51 to 1.10)	0.145
PPV23 prior to index date	117 (45%)	114 (44%)	1.08 (0.69 to 1.68)	0.736
Food allergy	16 (6%)	6 (2%)	2.67 (1.04 to 6.81)	0.040
Asthma	37 (14%)	16 (6%)	2.75 (1.42 to 5.32)	0.003
High-risk conditions				
Alcohol addiction	17 (7%)	1 (0%)	17.00 (2.26 to 127.75)	0.006
Autoimmune disease‡	9 (3%)	3 (1%)	3.00 (0.81 to 11.08)	0.099
Chronic obstructive lung disease	12 (5%)	9 (3%)	1.37 (0.55 to 3.42)	0.493
Chronic renal insufficiency	30 (12%)	4 (2%)	9.67 (2.94 to 31.73)	<0.001
Congestive heart failure	19 (7%)	2 (1%)	18.00 (2.40 to 134.84)	0.005
Coronary artery disease	52 (20%)	40 (15%)	1.46 (0.89 to 2.41)	0.136
Dementia	16 (6%)	7 (3%)	3.25 (1.06 to 9.97)	0.039
Diabetes mellitus	50 (19%)	24 (9%)	2.53 (1.44 to 4.43)	0.001
History of stroke	15 (6%)	10 (4%)	1.71 (0.67 to 4.35)	0.257
Immobilisation§	10 (4%)	1 (0%)	10.00 (1.28 to 78.12)	0.028
Immunosuppressive therapy	25 (10%)	4 (2%)	8.00 (2.41 to 26.57)	0.001
Malignancy	21 (8%)	12 (5%)	2.00 (0.90 to 4.45)	0.090
Recurrent urinary tract infection	29 (11%)	2 (1%)	14.50 (3.46 to 60.77)	<0.001
Transplant recipients	8 (3%)	0 (0%)	–	
Urinary incontinence	46 (18%)	20 (8%)	2.86 (1.55 to 5.25)	0.001
Other condition¶	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 to 2.58)	

*OR based on matched analysis taking into account gender, birthday, residency and follow-up duration
†Comorbidity conditions are not mutually exclusive.
‡Autoimmune disease includes systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease and other autoimmune diseases.
§Immobilisation includes hemi/para/quadri-plegia.
¶Other conditions include use of urinary catheter, device, genitourinary procedures (eg, prostate biopsy), and congenital anomaly.
PPV23, 23-valent pneumococcal polysaccharide vaccine.

(unadjusted OR 2.75; 95% CI 1.42 to 5.32; p=0.003). Of the 37 case participants 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 summarised in table 2. Participants with a history of asthma by predetermined criteria for asthma in box 1 had a nearly threefold 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 to 6.76; p=0.029). The PAR% of asthma by predetermined criteria for asthma in box 1 for the risk of *E coli* BSI was 9%. The p values for testing a significant interaction between asthma and categorised age were as follows: p=0.285 for age cut-off of 65 years (ie, ≥65 vs <65 years), p=0.958 for age cut-off of 40 years (ie, ≥40 vs <40 years) and p=0.417 for age cut-offs of 40 years and 65 years (ie, <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 3). 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; however, the

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

*Adjusted variables included all variables included in this table.

overall three-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 1 and 2). 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 to 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

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

*Adjusted variables included all factors reported in the multivariable model (see table 2) except for dichotomous asthma status.
†p Value for overall comparison.
‡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/hospitalisation for asthma within 1 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.

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 to6.76; p=0.029). Analyses by different age cut-offs showed that the results were not affected by age (eg, younger vs older than 40 years of age). Given either the previously reported non-association (HR 1.29, 95% CI 0.53 to 3.12) or a protective effect (HR 0.52, 95% CI 0.36 to 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 two patients with asthma 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 (eg, 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 that *E coli* BSI is 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 USA (5.5% for men and 9.7% for women).[36] Also, the prevalence of other common chronic conditions 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 USA.[3] There were no significant differences in influenza and PPV23 vaccination rates between cases and controls, which may imply similar access to healthcare services. Also, food allergy approached a statistically significant association with the risk of *E coli* BSI but other atopic conditions did not. This is probably due to greater misclassification bias of ascertainment of allergic rhinitis and atopic dermatitis by International Classification of Diseases (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 to 0.4) compared to that in the 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, utilisation of administrative data from healthcare organisations 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*[11] reported impaired innate immunity against pneumococci through impaired TLR-receptor signal transduction by house dust mite allergic sensitisation resulting in reduced neutrophil recruitment and increased risk of pneumococcal infection in the airways. It is worth investigating whether allergic sensitisation 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 epidemiological merits of self-contained healthcare environment with comprehensive medical record system for research. We identified population-based all incident community-acquired *E coli* BSI cases based on the Friedman 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 detailed information on certain variables such as atopic sensitisation data or smoking history (eg, duration or the number of cigarettes a day) but we assumed these data to be missing at random (ie, 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 a gold standard for asthma, the retrospective investigation for feasibility (due to infrequent *E coli* BSI) and the extensive use of the criterion in

previous asthma research, we believe the criterion 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 participants were predominantly white which might limit generalisability of our results to other ethnic groups. Our study participants 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 cut-offs 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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Contributors DWB 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 the manuscript; MNA-H assembled the original dataset for the *E coli* BSI study, collected the original data, interpreted the results and reviewed the manuscript; LMB and BPY participated in the study design, interpreted the results and reviewed the manuscript; and YJJ participated in the study design, performed data analysis, interpreted the results and drafted the manuscript. DWB, ER and YJJ had full access to data. All authors reviewed and approved the paper.

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