



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

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3 1 TITLE PAGE

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7 3 **Asthma and Risk of Non-Respiratory Tract Infection: A Population-Based Case Control**

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9 4 **Study**

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26 36 interest.

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30 38 We reviewed the STROBE statement and addressed all items in that checklist and are
31 39 submitting the STROBE statement with the revised manuscript.

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35 41 Key Words: Asthma, Risk, Epidemiology, Community-acquired infections, *Escherichia Coli*,
36 42 Blood stream infection, genitourinary, and gastrointestinal tract

37 43 Abbreviations: BSI: blood stream infection, *E.Coli*: *Escherichia Coli*, TLR : Toll-like Receptor,

38 44 ICS : inhaled corticosteroid, PPV23: 23-valent pneumococcal polysaccharide vaccine

39 45 Word count: 2993

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46 Article summary

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

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

50 2. Key messages

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

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

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

56 3. Strength and limitations

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

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

62 Contributors

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

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3 69 participated in the study design, performed data analysis, interpreted the results, and drafted the
4
5 70 manuscript. BDW, ER, and YJJ had full access to data. All authors reviewed and approved the
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8 71 paper.
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10 72 There will be no additional data available.
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92 **Abstract:**

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

97 Methods: The study was designed as a population-based retrospective case-control study, which
98 included 259 eligible community-acquired *E. coli* BSI cases in Olmsted County, MN between
99 1998 and 2007 and 259 birthday-, gender-, and residency-matched controls. Only community-
100 acquired *E. coli* BSI cases were included. Asthma status was ascertained by predetermined
101 criteria. An adjusted odds ratio (OR) and 95% confidence interval (CI) for the association
102 between asthma and risk of community-acquired *E. coli* BSI was calculated using conditional
103 logistic regression.

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

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

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114 **Abstract Word Count:** 246

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115 INTRODUCTION

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

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

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

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

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3 138 microbial infections and whether asthma could be an unrecognized risk factor for non-airway-
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5 139 related bacterial infections.
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8 140 We hypothesize that individuals with asthma have an increased risk of community-
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10 141 acquired *E. coli* BSI, as compared to those without asthma. To test this hypothesis, we conducted
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12 142 a population-based retrospective case-control study.
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3 161 **METHODS**
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5 162 The study was approved by the Institutional Review Boards of both Mayo Clinic and
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7 163 Olmsted Medical Center. This study was designed as a population-based case-control study.
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10 164 **Study population and setting**
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12 165 Olmsted County, Minnesota is an excellent setting to conduct a population-based
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14 166 epidemiologic study such as this because medical care is virtually self-contained within the
15
16 167 community (nearly all Olmsted County residents receive medical cares from two medical centers
17
18 168 in the community). The population characteristics of Olmsted County residents are similar to
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20 169 those of non-Hispanic white.(21) If one grants the authorization for using medical record for
21
22 170 research (almost 95% of Olmsted County residents), each patient is assigned a unique identifier
23
24 171 under the auspices of the Rochester Epidemiology Project (REP).(22) Using REP resources, we
25
26 172 previously demonstrated that incidence rates of asthma for this community are similar to other
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28 173 communities. The annual incidence rate of asthma in Rochester was 238 cases per 100,000
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30 174 persons, which is comparable to those in other communities such as Tecumseh, Michigan
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32 175 (250/100,000).(23)
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39 176 **Study subjects: Case ascertainment**
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41 177 To test our study hypothesis, we utilized a population-based incidence parent study,
42
43 178 which previously identified the community-acquired cases to study antimicrobial resistance
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45 179 trends of *E. coli* BSI in the community. Details of the case ascertainment have been described
46
47 180 previously.(19) Briefly, using the microbiology databases at Mayo Clinic Rochester and Olmsted
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49 181 Medical Center, all eligible children and adults with monomicrobial *E. coli* BSI (n=274) among
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51 182 Olmsted County residents from January 1, 1998 to December 31, 2007 (i.e., a population-based
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53 183 all incident cases of *E. coli* BSI) were identified based on the criteria suggested by Freidman et
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3 184 al.(24) As *E. coli* BSI is required for inpatient parental treatment, community-acquired *E. coli*
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5 185 BSI was defined by isolation of *E. coli* from blood cultures at the time of hospital admission or
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8 186 within 48 hours after hospital admission for patients who did not fit criteria for health care–
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10 187 associated infection according to the Freidman’s criteria.(24) Medical records of all subjects
11
12 188 were reviewed by investigators of the previous study (MNA) to confirm the diagnosis of
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14 189 community-acquired *E. coli* BSI, assess clinical features, and determine the eligibility. Only
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16 190 community-acquired *E. coli* BSI was included because nosocomial and health care-associated *E.*
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18 191 *coli* BSI are unsuitable to address the aim of the present study (clinically, they are a high-risk
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20 192 population for *E. coli* BSI and not representative of the study population). The index date of BSI
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22 193 was defined as the date when blood cultures that eventually grew *E. coli* were obtained.
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25 194 Exclusion criteria for cases (and controls) included: 1) polymicrobial BSI caused by more than
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27 195 one microorganism, 2) blood cultures acquired at autopsy, 3) nosocomial and health care-
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29 196 associated *E. coli* BSI, 4) non-Olmsted County residency at the time of index date of BSI, 5) no
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31 197 research authorization for using medical record for research, and 6) health conditions making
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33 198 ascertainment of asthma difficult listed in Table 1.

199 **Selection of control subjects**

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41 200 Control subjects were randomly selected with 1:1 matching from Olmsted County
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43 201 residents who had not had a history of *E. coli* BSI at the end of the study period. Briefly, a list of
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45 202 potential control subjects who had received medical care from either Mayo Clinic or Olmsted
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47 203 Medical Center and who met the matching criteria was generated and randomly selected from the
48
49 204 REP database for the present study. The matching criteria included: 1) gender, 2) birth date
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51 205 (within six months for those <18 years of age and within one year for those > 18 years of age), 3)
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53 206 the same clinic registration year as matched case (within one year), and 4) closest clinic visit to
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3 207 index date of matched case within one year. The index date for control subjects was defined as
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5 208 the closest (within one year) clinic visit date to index date of BSI for their corresponding
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8 209 matched case. Based on the number of cases and controls enrolled in this present study (259
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10 210 pair), assuming 8% of asthma prevalence among controls, this present study had 80% power to
11
12 211 detect an effect size of 2.27 of odds ratio (16.5% of asthma in cases). This effect size was
13
14 212 smaller than the reported effect sizes for the association between asthma and risk of microbial
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16 213 infection (OR: 2.4-6.7) suggesting adequate statistical power to address the study aim.(6, 10)
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20 214 **Exposure ascertainment (asthma status)**

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22 215 For determining asthma status of all cases and controls, we conducted comprehensive
23
24 216 medical record reviews to apply predetermined criteria for asthma as performed in our previous
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26 217 work.(5, 6) The criteria are delineated in Table 1. These criteria have been extensively used in
27
28 218 research for asthma epidemiology and were found to have high reliability.(25-30) We included
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30 219 both definite and probable asthma according to the criteria prior to the index date of BSI cases
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32 220 because most probable asthmatics become definite over time.(6, 31) The incidence dates (the
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34 221 first date when one met the criteria for asthma) for all asthmatic patients were determined; thus,
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36 222 we were able to discern the temporal relationship between asthma status (exposure) and *E coli*
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38 223 BSI (outcome). The risk of *E. coli* BSI was assessed in relation to the current asthma status(32):
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40 224 remission (no asthma symptoms, no asthma-related visits, or no asthma medications for at least
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42 225 three years prior to index date); active or current asthma (presence of clinical symptoms, asthma-
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44 226 related visits, or asthma medications within one year prior to index date); and inactive (not
45
46 227 current) asthma (presence of asthma symptoms, asthma-related visits, or asthma medications
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48 228 within 1-3 years prior to index date).
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55 229 **Other variables**

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3 230 Pertinent covariates and confounders were collected from medical records:
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5 231 sociodemographic variables (age, gender, ethnicity, and educational status), asthma medications
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7 232 including inhaled and systemic corticosteroids, family history of asthma, atopic status based on
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9 233 sensitization against aeroallergens and food allergens, smoking status (either active or passive
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11 234 exposure to tobacco smoke), vaccination status, and co-morbid conditions at the time of index
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13 235 date as listed in Table 2. The period of data collection was from October 1, 2011 to May 30,
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15 236 2012.

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20 237 **Statistical analysis**

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22 238 Formal comparison of asthma and other suspected risk factors between matched cases
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24 239 and controls was performed using conditional logistic regression, with community-acquired *E.*
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26 240 *coli* BSI as the target of prediction. All factors were analyzed for a univariate association with
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28 241 BSI, and any variables meeting the Greenland entry criteria ($P < 0.2$) were carried forward into a
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30 242 final multivariable model.(33)] Odds ratios (OR) from univariate (unadjusted) and multivariable
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32 243 (adjusted) models are reported to express the magnitude of association in terms of the likelihood
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34 244 of being a case. We calculated the population attributable risk percentage (PAR%) of asthma for
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36 245 community-acquired *E. coli* BSI using the formula established by Miettinen.(34) Statistical
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38 246 significance was tested at a two-sided alpha error of 0.05. All analyses were carried out with the
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40 247 statistical software package SAS, version 9.2 (SAS Institute, Cary, NC, USA).
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253 RESULTS

254 Study subjects

255 Of the 274 patients who were identified in the original study, 259 were eligible for the present
256 study. Fifteen patients were excluded; five for consistent FEV1 < 50%, two for restrictive lung
257 disease, two for significant kyphoscoliosis, two for bronchiectasis, one for cystic fibrosis, one for
258 pulmonary fibrosis, and two due to non-Olmsted County residency. Of the eligible 259 cases,
259 179 (69%) were female, 249 (96%) were 18 years of age or older (age mean±standard deviation,
260 61±22 years), and 222 (86%) were Caucasian. The characteristics of the cases and their matched
261 controls, and the individual associations with community-acquired *E. coli* BSI, are summarized
262 in Table 2. There were only 10 asthmatics on moderate- or high-dose inhaled corticosteroid (ICS)
263 and two asthmatics on systemic corticosteroid at the time of the index date. Comparing subjects
264 with asthma versus those without, there was no significant difference in the proportions, who had
265 received influenza vaccine (40% vs. 40%, p=0.99) or PPV23 (49% vs. 44%, p=0.49) within one
266 year prior to index date.

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

268 Thirty-seven of 259 (14%) cases had a history of asthma prior to the index date of community-
269 acquired *E. coli* BSI, compared with 16 of 259 (6%) controls (unadjusted OR: 2.75; 95% CI:
270 1.42-5.32; p=0.003). Of the 37 case subjects with asthma, 33 (89%) had definite asthma and 4
271 (11%) had probable asthma. Of the 16 controls with asthma, 12 (75%) had definite asthma and 4
272 (25%) had probable asthma. Among all 53 asthmatics, 18 were on ICS therapy at the index date
273 (8 on low-dose ICS and 10 on moderate to high-dose ICS therapy). The effect of asthma on risk
274 of community-acquired *E. coli* BSI, independent of other risk factors, is summarized in Table 3.
275 Subjects with a history of asthma by predetermined criteria for asthma in Table 1 had a nearly 3-

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3 276 fold higher risk of developing community-acquired *E. coli* BSI compared to those without
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6 277 asthma, controlling for all potential confounding factors (adjusted OR: 2.74; 95% CI: 1.11-6.76;
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8 278 $p=0.029$). The PAR% of asthma by predetermined criteria for asthma in Table 1 for the risk of *E.*
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10 279 *coli* BSI was 9%. The p -values for testing a significant interaction between asthma and
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12 280 categorized age were as follows: $p=0.285$ for age cutoff of 65 years (i.e., ≥ 65 vs. <65 years),
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14 281 $p=0.958$ for age cutoff of 40 years (i.e., ≥ 40 vs. <40 years), and $p=0.417$ for age cutoffs of 40
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17 282 years and 65 years (i.e., <40 , 40-65, vs. >65 years). As a result, we have no evidence of a
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20 283 differential asthma effect across age strata. Additional characteristics of asthma were also
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22 284 evaluated for an association with risk of community-acquired *E. coli* BSI (see Table 4). Adjusted
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24 285 for other factors, active asthma was associated with increased risk of *E. coli* BSI but for
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27 286 asthmatics on ICS therapy compared to non-asthmatics, but the overall 3-level effect was not
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29 287 statistically significant ($p=0.079$).

288 **Other variables and *E. coli* BSI**

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34 289 Several of the high-risk conditions, as well as non-Caucasian ethnicity, were independently
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36 290 associated with increased risk of community-acquired *E. coli* BSI (see Tables 2 and 3). A history
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38 291 of food allergy was found in 16 (6%) of 259 cases as compared with 6 (2%) of 259 controls
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41 292 (adjusted OR: 3.51; 95% CI: 0.94-13.11; $p=0.062$). Neither allergic rhinitis ($p=0.82$) nor atopic
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43 293 dermatitis ($p=0.87$) was found to be significantly associated with community-acquired *E. coli*
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45 294 BSI.

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300 DISCUSSION

301 To our knowledge, this is the first population-based, case-control study that demonstrated an
302 association between asthma and risk of non-respiratory bacterial infection such as community-
303 acquired *E. coli* BSI. This association was independent of other risk factors including age,
304 gender, follow-up duration, ethnicity, educational level, and comorbid conditions (adjusted OR:
305 2.74; 95% CI: 1.11-6.76; $p=0.029$). Analyses by different age cut-offs showed that the results
306 were not affected by age effect (e.g., younger vs. older than 40 years of age). Given either the
307 previously-reported non association (hazard ratio, HR: 1.29, 95%CI: 0.53-3.12) or a protective
308 effect (HR: 0.52, 95%CI:0.36-0.76) of ICS therapy on risk of pneumonia in asthmatics(35) and a
309 small number of asthmatics with moderate or high-dose ICS in our study (10 of 53, 19%), we
310 suspect that active or current asthma (or collectively those given ICS therapy) might be related to
311 risk of community-acquired *E. coli* BSI instead of ICS alone. There were only 2 asthmatics on
312 systemic corticosteroid therapy at the time of the index date; therefore, exposure to systemic
313 corticosteroid therapy was unlikely to account for the observed association. We believe that
314 susceptibility bias (e.g., covariate imbalance at baseline) is unlikely to account for the association
315 found in our study given the full adjustment for potential confounders. One concern could be
316 detection bias stemming from a situation where exposure status (asthma status) systematically
317 affects detection of outcomes. However, given *E. coli* BSI as a life-threatening condition, this is
318 unlikely and also there was no significant difference in symptom duration from BSI-related
319 symptom to index date between asthma and non-asthma in cases (4.7 ± 5.5 vs 5.2 ± 5.5 days,
320 $p=0.61$). Since detection of asthma depends on follow-up duration from registration to index
321 date of community-acquired *E. coli* BSI, we designed our study to ensure that duration was

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3 322 similar between cases and controls. Asthma prevalence in controls in our study was 6%, which is
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5 323 similar to that in adults (7%) in the United States (5.5% for males and 9.7% for females).(36)
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8 324 Also, the prevalence of other common chronic condition such as coronary heart disease in our
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10 325 study (15%) was similar to the national average (7.1% for adults aged 45-64 years and 19.8% for
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12 326 adults aged ≥ 65 years) suggesting that our control group may reasonably represent a general
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14 327 population of adults in the United States.(3) There were no significant differences in influenza
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16 328 and PPV23 vaccination rates between cases and controls, which may imply similar access to
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18 329 health care services. Also, food allergy approached to statistical significant association with risk
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20 330 of *E. coli* BSI but other atopic conditions were not. This is probably due to greater
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22 331 misclassification bias of ascertainment of allergic rhinitis and atopic dermatitis by ICD-9 code
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24 332 compared to asthma status and food allergy by predetermined criteria in our study. Taken
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26 333 together, our study results suggest that asthma status is independently associated with risk of
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28 334 community-acquired *E. coli* BSI.
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34 335 There are only a few previous studies, which assessed the incidence of *E. coli* BSI and
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36 336 risk factors associated with its development, including asthma. One study showed a higher risk
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38 337 of community-acquired *E. coli* BSI in asthmatics compared to non-asthmatics among those over
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40 338 65 years of age (5.5% vs. 1%).(37) However, another study showed reduced risk of *E. coli* BSI
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42 339 in asthmatics (rate ratio: 0.3; 95% CI: 0.2-0.4) compared to that in total regional population.(38)
43
44 340 These studies have significant limitations including no *a priori* hypothesis testing on the
45
46 341 relationship between asthma and risk of community-acquired *E. coli* BSI, utilization of
47
48 342 administrative data from health care organizations or case reports, ascertainment of *E. coli* BSI
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50 343 cases and asthma based on ICD-9 code, inclusion of only elderly patients aged over 65 years,(37)
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52 344 and no concurrent control group.(38) Thus, our study is the first population-based case-control
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3 345 study that demonstrated a relationship between asthma and risk of community-acquired *E. coli*
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5 346 BSI. Several studies showed increased risks of microbial infections in asthmatics[(5-7, 10, 11)
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8 347 but these studies only addressed the relationship between asthma and airway infections.
9

10 348 The mechanisms underlying the apparent association between asthma and risk of
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12 349 community-acquired *E. coli* BSI are unknown. Whether previously reported impaired innate
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14 350 immune factors that may predispose to infections due to viruses(13, 39, 40) and other bacteria
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16 351 are operative in community-acquired *E. coli* BSI is undefined. Recently, Habibzay et al reported
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18 352 impaired innate immunity against pneumococci through impaired TLR-receptor signal
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20 353 transduction by house dust mite allergic sensitization resulting in reduced neutrophil recruitment
21
22 354 and increased risk of pneumococcal infection in the airways.(11) It is worth investigating
23
24 355 whether allergic sensitization can induce similar impairment of innate immunity through TLR-4
25
26 356 for gram-negative bacteria in genitourinary or gastrointestinal tracts in asthmatics. Also, an
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28 357 adaptive immune response to gram-negative bacteria might be altered in asthmatics,(41) which
29
30 358 may affect susceptibility to gram-negative bacterial infection. For example, Koch et al reported
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32 359 impaired Type 1 helper T cell (Th1) response (interleukin-12-induced interferon- γ release from T
33
34 360 lymphocytes) to endotoxin from *Salmonella enteritidis* in asthmatics.(42) Further studies are
35
36 361 needed to address our study findings.
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43 362 The main strengths of our study are a population-based study design and include the
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45 363 epidemiologic merits of self-contained health care environment with comprehensive medical
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47 364 record system for research. We identified population-based all incident community-acquired *E.*
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49 365 *coli* BSI cases based on the Freidman criteria. We ascertained asthma status by applying
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51 366 predetermined criteria independent of a physician diagnosis of asthma or ICD-9 code. Also, our
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53 367 study has inherent limitations as a retrospective study. We could not obtain detail information on
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3 368 certain variables such as atopic sensitization data or smoking history (e.g., duration or the
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5 369 number of cigarettes a day) but we assumed this data to be missing at random (i.e., it is subject to
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8 370 non-differential misclassification bias for comparison groups of interest). Although our criteria
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10 371 for asthma was based on medical record review, given the absence of gold standard for asthma,
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12 372 the retrospective investigation for feasibility (due to infrequent *E coli* BSI), and the extensive use
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14 373 of the criteria in previous asthma research, we believe the criteria is unlikely to result in a
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16 374 significant bias affecting interpretation of the results. Our study finding that asthma prevalence
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18 375 among controls was similar to that at the national level should mitigate this concern. Our study
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20 376 subjects were predominantly white which might limit generalizability of our results to other
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22 377 ethnic groups. Our study subjects were relatively a older population affected by many comorbid
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24 378 conditions which might confound the study results. However, when we examined the effect of
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26 379 the interaction between age and asthma, we found that the main results on the association
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28 380 between asthma and risk of *E coli* BSI did not appear to be significantly affected by various
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30 381 cutoffs of age suggesting the results did not differ by age group (younger vs. older group).
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36 382 In conclusion, asthmatics might be at an increased risk of non-respiratory tract bacterial
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38 383 infections, including community-acquired *E. coli* BSI. The mechanisms responsible for this
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40 384 association are yet to be defined while additional investigations replicate our study findings.
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49
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391 study had no role in study design, data collection, data analysis, data interpretation, or writing of
392 the report.

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541 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 FEV₁ or FVC less than 70% predicted and another with at least 20% improvement to an FEV₁ of higher 70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV₁
 - 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 alpha₁-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 FEV₁ to be consistently below 50% predicted or diminished diffusion capacity

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550 Table 2. Sociodemographic, and clinical characteristics of patients with *Escherichia coli* blood
 551 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

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Other condition ^c	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

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604 Table 3. A multivariable conditional logistic regression model for the association between
 605 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.

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611 Table 4. Association of asthma control status and therapy with risk of community-acquired
 612 *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)

613 ^a Adjusted variables included all factors reported in the multivariable model (see Table 3) except for dichotomous asthma status

614 ^b P-value for overall comparison

615 ^c Active or current asthma was defined as the presence of asthma-related events including asthma symptoms, or use of asthma
 616 medications, and outpatient/emergency department/hospitalization for asthma within one year prior to index date of E coli BSI;
 617 Remission of asthma was defined as the absence of asthma-related events > 3 years prior to index date; Inactive (not current)
 618 asthma was defined as the presence of asthma-related events within 1-3 years prior to index date.
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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) (b) Indicate number of participants with missing data for each variable of interest(Table 2 &3)
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
			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
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**

Journal:	<i>BMJ Open</i>
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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Respiratory medicine
Keywords:	Asthma < THORACIC MEDICINE, EPIDEMIOLOGY, Gastrointestinal infections < GASTROENTEROLOGY

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Manuscripts

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) (b) Indicate number of participants with missing data for each variable of interest(Table 2 &3)
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
			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
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>.

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3 1 TITLE PAGE

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5 2 Original Article

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7 3 **Asthma and Risk of Non-Respiratory Tract Infection: A Population-Based Case Control**

8
9 4 **Study**

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13 6 Duk Won Bang, MD^{a,b}, Hyeon J. Yang, MD^c, Eell Ryoo, MD^{a,d}, Majdi N. Al-Hasan, MD^e,

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19 32 was also supported by the Rochester Epidemiology Project (R01-AG34676) from the National
20 33 Institute on Aging.

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27 35 Conflict of interest: The study investigators have nothing to disclose that poses a conflict of
28 36 interest.

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35 38 We reviewed the STROBE statement and addressed all items in that checklist and are
36 39 submitting the STROBE statement with the revised manuscript.

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42 41 Key Words: Asthma, Risk, Epidemiology, Community-acquired infections, *Escherichia Coli*,
43 42 Blood stream infection, genitourinary, and gastrointestinal tract

44
45 43 Abbreviations: BSI: blood stream infection, *E.Coli*: *Escherichia Coli*, TLR : Toll-like Receptor,

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47 44 ICS : inhaled corticosteroid, PPV23: 23-valent pneumococcal polysaccharide vaccine

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49 45 Word count: 2993

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46 Article summary

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

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

50 2. Key messages

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

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

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

56 3. Strength and limitations

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

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

62 Contributors

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

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2
3 69 participated in the study design, performed data analysis, interpreted the results, and drafted the
4
5 70 manuscript. BDW, ER, and YJJ had full access to data. All authors reviewed and approved the
6
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8 71 paper.
9

10 72 There will be no additional data available.
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For peer review only

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92 **Abstract:**

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

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

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

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

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

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

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

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115 asthma on risk of microbial infections may go beyond airways.

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117 **Abstract Word Count:** 246

118 INTRODUCTION

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

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

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

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

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

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

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164 **METHODS**

165 The study was approved by the Institutional Review Boards of both Mayo Clinic and

166 Olmsted Medical Center. This study was designed as a population-based case-control study.

167 **Study population and setting**

168 Olmsted County, Minnesota is an excellent setting to conduct a population-based

169 epidemiologic study such as this because medical care is virtually self-contained within the

170 community (nearly all Olmsted County residents receive medical cares from two medical centers

171 in the community). The population characteristics of Olmsted County residents are similar to

172 those of non-Hispanic white.(21) If one grants the authorization for using medical record for

173 research (almost 95% of Olmsted County residents), each patient is assigned a unique identifier

174 under the auspices of the Rochester Epidemiology Project (REP).(22) Using REP resources, we

175 previously demonstrated that incidence rates of asthma for this community are similar to other

176 communities. The annual incidence rate of asthma in Rochester was 238 cases per 100,000

177 persons, which is comparable to those in other communities such as Tecumseh, Michigan

178 (250/100,000).(23)

179 **Study subjects: Case ascertainment**

180 To test our study hypothesis, we utilized a population-based incidence parent study,

181 which previously identified the community-acquired cases to study antimicrobial resistance

182 trends of *E. coli* BSI in the community. Details of the case ascertainment have been described

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3 183 previously.(19) Briefly, using the microbiology databases at Mayo Clinic Rochester and Olmsted
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5 184 Medical Center, all eligible children and adults with monomicrobial *E. coli* BSI (n=274) among
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7
8 185 Olmsted County residents from January 1, 1998 to December 31, 2007 (i.e., a population-based
9
10 186 all incident cases of *E. coli* BSI) were identified based on the criteria suggested by Freidman et
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12 187 al.(24) As *E. coli* BSI is required for inpatient parental treatment, community-acquired *E. coli*
13
14 188 BSI was defined by isolation of *E. coli* from blood cultures at the time of hospital admission or
15
16 189 within 48 hours after hospital admission for patients who did not fit criteria for health care–
17
18 190 associated infection according to the Freidman’s criteria.(24) Medical records of all subjects
19
20 191 were reviewed by investigators of the previous study (MNA) to confirm the diagnosis of
21
22 192 community-acquired *E. coli* BSI, assess clinical features, and determine the eligibility. Only
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24 193 community-acquired *E. coli* BSI was included because nosocomial and health care-associated *E.*
25
26 194 *coli* BSI are unsuitable to address the aim of the present study (clinically, they are a high-risk
27
28 195 population for *E. coli* BSI and not representative of the study population). The index date of BSI
29
30 196 was defined as the date when blood cultures that eventually grew *E. coli* were obtained.
31
32 197 Exclusion criteria for cases (and controls) included: 1) polymicrobial BSI caused by more than
33
34 198 one microorganism, 2) blood cultures acquired at autopsy, 3) nosocomial and health care-
35
36 199 associated *E. coli* BSI, 4) non-Olmsted County residency at the time of index date of BSI, 5) no
37
38 200 research authorization for using medical record for research, and 6) health conditions making
39
40 201 ascertainment of asthma difficult listed in Table 1.

202 **Selection of control subjects**

41
42 203 Control subjects were randomly selected with 1:1 matching from Olmsted County
43
44 204 residents who had not had a history of *E. coli* BSI at the end of the study period. Briefly, a list of
45
46 205 potential control subjects who had received medical care from either Mayo Clinic or Olmsted
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3 206 Medical Center and who met the matching criteria was generated and randomly selected from the
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5 207 REP database for the present study. The matching criteria included: 1) gender, 2) birth date
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8 208 (within six months for those <18 years of age and within one year for those > 18 years of age), 3)
9
10 209 the same clinic registration year as matched case (within one year), and 4) closest clinic visit to
11
12 210 index date of matched case within one year. The index date for control subjects was defined as
13
14 211 the closest (within one year) clinic visit date to index date of BSI for their corresponding
15
16 212 matched case. Based on the number of cases and controls enrolled in this present study (259
17
18 213 pair), assuming 8% of asthma prevalence among controls, this present study had 80% power to
19
20 214 detect an effect size of 2.27 of odds ratio (16.5% of asthma in cases). This effect size was
21
22 215 smaller than the reported effect sizes for the association between asthma and risk of microbial
23
24 216 infection (OR: 2.4-6.7) suggesting adequate statistical power to address the study aim.(6, 10)

29 217 **Exposure ascertainment (asthma status)**

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31 218 For determining asthma status of all cases and controls, we conducted comprehensive
32
33 219 medical record reviews to apply predetermined criteria for asthma as performed in our previous
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35 220 work.(5, 6) The criteria are delineated in Table 1. These criteria have been extensively used in
36
37 221 research for asthma epidemiology and were found to have high reliability.(25-30) We included
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39 222 both definite and probable asthma according to the criteria prior to the index date of BSI cases
40
41 223 because most probable asthmatics become definite over time.(6, 31) The incidence dates (the
42
43 224 first date when one met the criteria for asthma) for all asthmatic patients were determined; thus,
44
45 225 we were able to discern the temporal relationship between asthma status (exposure) and *E coli*
46
47 226 BSI (outcome). The risk of *E. coli* BSI was assessed in relation to the current asthma status(32):
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49 227 remission (no asthma symptoms, no asthma-related visits, or no asthma medications for at least
50
51 228 three years prior to index date); active or current asthma (presence of clinical symptoms, asthma-
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229 related visits, or asthma medications within one year prior to index date); and inactive (not
230 current) asthma (presence of asthma symptoms, asthma-related visits, or asthma medications
231 within 1-3 years prior to index date).

232 **Other variables**

233 Pertinent covariates and confounders were collected from medical records:
234 sociodemographic variables (age, gender, ethnicity, and educational status), asthma medications
235 including inhaled and systemic corticosteroids, family history of asthma, atopic status based on
236 sensitization against aeroallergens and food allergens, smoking status (either active or passive
237 exposure to tobacco smoke), vaccination status, and co-morbid conditions at the time of index
238 date as listed in Table 2. The period of data collection was from October 1, 2011 to May 30,
239 2012.

240 **Statistical analysis**

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

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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

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3 275 (25%) had probable asthma. Among all 53 asthmatics, 18 were on ICS therapy at the index date
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6 276 (8 on low-dose ICS and 10 on moderate to high-dose ICS therapy). The effect of asthma on risk
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8 277 of community-acquired *E. coli* BSI, independent of other risk factors, is summarized in Table 3.
9
10 278 Subjects with a history of asthma by predetermined criteria for asthma in Table 1 had a nearly 3-
11
12 279 fold higher risk of developing community-acquired *E. coli* BSI compared to those without
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14 280 asthma, controlling for all potential confounding factors (adjusted OR: 2.74; 95% CI: 1.11-6.76;
15
16 281 $p=0.029$). The PAR% of asthma by predetermined criteria for asthma in Table 1 for the risk of *E.*
17
18 282 *coli* BSI was 9%. The p -values for testing a significant interaction between asthma and
19
20 283 categorized age were as follows: $p=0.285$ for age cutoff of 65 years (i.e., ≥ 65 vs. <65 years),
21
22 284 $p=0.958$ for age cutoff of 40 years (i.e., ≥ 40 vs. <40 years), and $p=0.417$ for age cutoffs of 40
23
24 285 years and 65 years (i.e., <40 , 40-65, vs. >65 years). As a result, we have no evidence of a
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26 286 differential asthma effect across age strata. Additional characteristics of asthma were also
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28 287 evaluated for an association with risk of community-acquired *E. coli* BSI (see Table 4). Adjusted
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30 288 for other factors, active asthma was associated with increased risk of *E. coli* BSI but for
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32 289 asthmatics on ICS therapy compared to non-asthmatics, but the overall 3-level effect was not
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34 290 statistically significant ($p=0.079$).

291 **Other variables and *E. coli* BSI**

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

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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

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3 321 unlikely and also there was no significant difference in symptom duration from BSI-related
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5 322 symptom to index date between asthma and non-asthma in cases (4.7 ± 5.5 vs 5.2 ± 5.5 days,
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8 323 $p=0.61$). Since detection of asthma depends on follow-up duration from registration to index
9
10 324 date of community-acquired *E. coli* BSI, we designed our study to ensure that duration was
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12 325 similar between cases and controls. Asthma prevalence in controls in our study was 6%, which is
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14 326 similar to that in adults (7%) in the United States (5.5% for males and 9.7% for females).(36)
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16 327 Also, the prevalence of other common chronic condition such as coronary heart disease in our
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18 328 study (15%) was similar to the national average (7.1% for adults aged 45-64 years and 19.8% for
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20 329 adults aged ≥ 65 years) suggesting that our control group may reasonably represent a general
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22 330 population of adults in the United States.(3) There were no significant differences in influenza
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24 331 and PPV23 vaccination rates between cases and controls, which may imply similar access to
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26 332 health care services. Also, food allergy approached to statistical significant association with risk
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28 333 of *E coli* BSI but other atopic conditions were not. This is probably due to greater
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30 334 misclassification bias of ascertainment of allergic rhinitis and atopic dermatitis by ICD-9 code
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32 335 compared to asthma status and food allergy by predetermined criteria in our study. Taken
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34 336 together, our study results suggest that asthma status is independently associated with risk of
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36 337 community-acquired *E. coli* BSI.
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44 338 There are only a few previous studies, which assessed the incidence of *E. coli* BSI and
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46 339 risk factors associated with its development, including asthma. One study showed a higher risk
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48 340 of community-acquired *E. coli* BSI in asthmatics compared to non-asthmatics among those over
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50 341 65 years of age (5.5% vs. 1%).(37) However, another study showed reduced risk of *E. coli* BSI
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52 342 in asthmatics (rate ratio: 0.3; 95% CI: 0.2-0.4) compared to that in total regional population.(38)
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54 343 These studies have significant limitations including no *a priori* hypothesis testing on the
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3 344 relationship between asthma and risk of community-acquired *E. coli* BSI, utilization of
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5 345 administrative data from health care organizations or case reports, ascertainment of *E. coli* BSI
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8 346 cases and asthma based on ICD-9 code, inclusion of only elderly patients aged over 65 years,(37)
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10 347 and no concurrent control group.(38) Thus, our study is the first population-based case-control
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12 348 study that demonstrated a relationship between asthma and risk of community-acquired *E. coli*
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14 349 BSI. Several studies showed increased risks of microbial infections in asthmatics[(5-7, 10, 11)
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16 350 but these studies only addressed the relationship between asthma and airway infections.
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20 351 The mechanisms underlying the apparent association between asthma and risk of
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22 352 community-acquired *E. coli* BSI are unknown. Whether previously reported impaired innate
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24 353 immune factors that may predispose to infections due to viruses(13, 39, 40) and other bacteria
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26 354 are operative in community-acquired *E. coli* BSI is undefined. Recently, Habibzay et al reported
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28 355 impaired innate immunity against pneumococci through impaired TLR-receptor signal
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30 356 transduction by house dust mite allergic sensitization resulting in reduced neutrophil recruitment
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32 357 and increased risk of pneumococcal infection in the airways.(11) It is worth investigating
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34 358 whether allergic sensitization can induce similar impairment of innate immunity through TLR-4
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36 359 for gram-negative bacteria in genitourinary or gastrointestinal tracts in asthmatics. Also, an
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38 360 adaptive immune response to gram-negative bacteria might be altered in asthmatics,(41) which
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40 361 may affect susceptibility to gram-negative bacterial infection. For example, Koch et al reported
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42 362 impaired Type 1 helper T cell (Th1) response (interleukin-12-induced interferon- γ release from T
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44 363 lymphocytes) to endotoxin from *Salmonella enteritidis* in asthmatics.(42) Further studies are
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46 364 needed to address our study findings.
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53 365 The main strengths of our study are a population-based study design and include the
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55 366 epidemiologic merits of self-contained health care environment with comprehensive medical
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3 367 record system for research. We identified population-based all incident community-acquired *E.*
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5 368 *coli* BSI cases based on the Freidman criteria. We ascertained asthma status by applying
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8 369 predetermined criteria independent of a physician diagnosis of asthma or ICD-9 code. Also, our
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10 370 study has inherent limitations as a retrospective study. We could not obtain detail information on
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12 371 certain variables such as atopic sensitization data or smoking history (e.g., duration or the
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14 372 number of cigarettes a day) but we assumed this data to be missing at random (i.e., it is subject to
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16 373 non-differential misclassification bias for comparison groups of interest). Although our criteria
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18 374 for asthma was based on medical record review, given the absence of gold standard for asthma,
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20 375 the retrospective investigation for feasibility (due to infrequent *E coli* BSI), and the extensive use
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22 376 of the criteria in previous asthma research, we believe the criteria is unlikely to result in a
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24 377 significant bias affecting interpretation of the results. Our study finding that asthma prevalence
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26 378 among controls was similar to that at the national level should mitigate this concern. Our study
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28 379 subjects were predominantly white which might limit generalizability of our results to other
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30 380 ethnic groups. Our study subjects were relatively an older population affected by many
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32 381 comorbid conditions, which might confound the study results. Therefore, we adjusted the
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34 382 association between asthma and risk of *E coli* BSI for each comorbid condition individually in
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36 383 our multivariate model. Since the prevalence of comorbid conditions is related to age, we
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38 384 examined the effect of the interaction between age and asthma. We found that the main results
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40 385 on the association between asthma and risk of *E coli* BSI did not appear to be significantly
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42 386 affected by various cutoffs of age suggesting the results did not differ by age group (younger vs.
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44 387 older group).
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3 388 In conclusion, asthmatics might be at an increased risk of non-respiratory tract bacterial
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5 389 infections, including community-acquired *E. coli* BSI. The mechanisms responsible for this
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8 390 association are yet to be defined while additional investigations replicate our study findings.
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13 392 **Acknowledgement**

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26 398 the report.
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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 FEV₁ or FVC less than 70% predicted and another with at least 20% improvement to an FEV₁ of higher 70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV₁
 - 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 alpha₁-antitrypsin
 - Cystic fibrosis
 - Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis
- FVC forced vital capacity; FEV₁, forced expiratory volume in 1 sec.
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- Pulmonary function tests that showed FEV₁ to be consistently below 50% predicted or diminished diffusion capacity

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

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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	

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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
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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
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	(n=518)	(95% CI), p-value	(95% CI), p-value
Inhaled corticosteroid therapy (ICS)		<i>p</i> =0.009 ^b	<i>p</i> =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		<i>p</i> =0.005 ^b	<i>p</i> =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.

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1 TITLE PAGE

2 Original Article

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

4 **Study**

5
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32 was also supported by the Rochester Epidemiology Project (R01-AG34676) from the National
33 Institute on Aging.

34

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

37

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

40

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

43 Abbreviations: BSI: blood stream infection, *E.Coli*: *Escherichia Coli*, TLR : Toll-like Receptor,

44 ICS : inhaled corticosteroid, PPV23: 23-valent pneumococcal polysaccharide vaccine

45 Word count: 2993

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46 Article summary

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

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

50 2. Key messages

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

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

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

56 3. Strength and limitations

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

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

61 Contributors

62 BDW collected data, interpreted the results, and drafted the manuscript; HJY participated in the
63 study design, interpreted the results and reviewed the manuscript; ER collected data, interpreted
64 the results, and reviewed manuscript; MNA assembled the original dataset for the *E. coli* BSI
65 study, collected the original data, interpreted the results, and reviewed the manuscript; LMB
66 participated in the study design, interpreted the results, and reviewed the manuscript; BPY
67 participated in the study design, interpreted the results, and reviewed manuscript; and YJJ
68 participated in the study design, interpreted the results, and reviewed manuscript; and YJJ

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

72 There will be no additional data available.

For peer review only

DW Bang et al

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2
3 **92 Abstract:**
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6 **93 Objectives:** Asthmatics have increased risks of airway-related infections. Little is known about
7
8 **94** whether this is true for non-airway-related serious infections such as *Escherichia coli* blood
9
10 **95** stream infection (BSI). We assessed whether asthma is associated with a risk of developing
11
12 **96** community-acquired *E. coli* BSI.
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15 **97 Design:** The study was designed as a population-based retrospective case-control study.
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18 **98 Setting:** This population-based study was conducted in Olmsted County, Minnesota.
19

20 **99 Participants:** The study included 259 all eligible community-acquired *E. coli* BSI cases in
21
22 **100** Olmsted County, MN between 1998 and 2007 and 259 birthday-, gender-, and residency-
23
24 **101** matched controls.
25

26
27 **102 Primary and secondary outcome measures:** Only community-acquired *E. coli* BSI cases as the
28
29 **103** primary outcome was included. Asthma status as an exposure was ascertained by predetermined
30
31 **104** criteria. An adjusted odds ratio (OR) and 95% confidence interval (CI) for the association
32
33 **105** between asthma and risk of community-acquired *E. coli* BSI was calculated using conditional
34
35 **106** logistic regression.
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39 **107 Results:** Of 259 eligible cases, 179 (69 %) were female and mean age was 61±22 years. Thirty-
40
41 **108** seven of 259 cases (14%) and 16 of 259 controls (6%) had a prior history of asthma (adjusted
42
43 **109** OR: 2.74; 95% CI: 1.11-6.76; p=0.029). The population attributable risk of asthma for
44
45 **110** community-acquired *E. coli* BSI was 9%. Although not statistically significant, there was a
46
47 **111** borderline association between having a history of food allergy and increased risk of community-
48
49 **112** acquired *E. coli* BSI (6% vs 2%; adjusted OR: 3.51; 95% CI: 0.94-13.11, p=0.062).
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53 **113 Conclusions:** Based on the findings of the current population-based, case-control investigation, a
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55 **114** history of asthma may be associated with risk of community-acquired *E. coli* BSI. The impact of
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115 asthma on risk of microbial infections may go beyond airways.

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117 **Abstract Word Count:** 246

118 INTRODUCTION

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

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

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

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3 137 factors,[⁽²⁰⁾] suggesting that unrecognized risk factors exist that are associated with the
4
5 138 development of community-acquired *E. coli* BSI.
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8 139 Investigating the relationship between asthma and non-airway-related serious bacterial
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10 140 infections will advance our understanding on the extent to which asthma impacts susceptibility to
11
12 141 microbial infections and whether asthma could be an unrecognized risk factor for non-airway-
13
14 142 related bacterial infections.
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17 143 We hypothesize that individuals with asthma have an increased risk of community-
18
19 144 acquired *E. coli* BSI, as compared to those without asthma. To test this hypothesis, we conducted
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21 145 a population-based retrospective case-control study.
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164 **METHODS**

165 The study was approved by the Institutional Review Boards of both Mayo Clinic and

166 Olmsted Medical Center. This study was designed as a population-based case-control study.

167 **Study population and setting**

168 Olmsted County, Minnesota is an excellent setting to conduct a population-based
169 epidemiologic study such as this because medical care is virtually self-contained within the
170 community (nearly all Olmsted County residents receive medical cares from two medical centers
171 in the community). The population characteristics of Olmsted County residents are similar to
172 those of non-Hispanic white.(21) If one grants the authorization for using medical record for
173 research (almost 95% of Olmsted County residents), each patient is assigned a unique identifier
174 under the auspices of the Rochester Epidemiology Project (REP).(22) Using REP resources, we
175 previously demonstrated that incidence rates of asthma for this community are similar to other
176 communities. The annual incidence rate of asthma in Rochester was 238 cases per 100,000
177 persons, which is comparable to those in other communities such as Tecumseh, Michigan
178 (250/100,000).(23)

179 **Study subjects: Case ascertainment**

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

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3 183 previously.(19) Briefly, using the microbiology databases at Mayo Clinic Rochester and Olmsted
4
5 184 Medical Center, all eligible children and adults with monomicrobial *E. coli* BSI (n=274) among
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8 185 Olmsted County residents from January 1, 1998 to December 31, 2007 (i.e., a population-based
9
10 186 all incident cases of *E. coli* BSI) were identified based on the criteria suggested by Freidman et
11
12 187 al.(24) As *E. coli* BSI is required for inpatient parental treatment, community-acquired *E. coli*
13
14 188 BSI was defined by isolation of *E. coli* from blood cultures at the time of hospital admission or
15
16 189 within 48 hours after hospital admission for patients who did not fit criteria for health care–
17
18 190 associated infection according to the Freidman’s criteria.(24) Medical records of all subjects
19
20 191 were reviewed by investigators of the previous study (MNA) to confirm the diagnosis of
21
22 192 community-acquired *E. coli* BSI, assess clinical features, and determine the eligibility. Only
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24 193 community-acquired *E. coli* BSI was included because nosocomial and health care-associated *E.*
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26 194 *coli* BSI are unsuitable to address the aim of the present study (clinically, they are a high-risk
27
28 195 population for *E. coli* BSI and not representative of the study population). The index date of BSI
29
30 196 was defined as the date when blood cultures that eventually grew *E. coli* were obtained.
31
32 197 Exclusion criteria for cases (and controls) included: 1) polymicrobial BSI caused by more than
33
34 198 one microorganism, 2) blood cultures acquired at autopsy, 3) nosocomial and health care-
35
36 199 associated *E. coli* BSI, 4) non-Olmsted County residency at the time of index date of BSI, 5) no
37
38 200 research authorization for using medical record for research, and 6) health conditions making
39
40 201 ascertainment of asthma difficult listed in Table 1.

202 **Selection of control subjects**

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

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3 206 Medical Center and who met the matching criteria was generated and randomly selected from the
4
5 207 REP database for the present study. The matching criteria included: 1) gender, 2) birth date
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8 208 (within six months for those <18 years of age and within one year for those > 18 years of age), 3)
9
10 209 the same clinic registration year as matched case (within one year), and 4) closest clinic visit to
11
12 210 index date of matched case within one year. The index date for control subjects was defined as
13
14 211 the closest (within one year) clinic visit date to index date of BSI for their corresponding
15
16 212 matched case. Based on the number of cases and controls enrolled in this present study (259
17
18 213 pair), assuming 8% of asthma prevalence among controls, this present study had 80% power to
19
20 214 detect an effect size of 2.27 of odds ratio (16.5% of asthma in cases). This effect size was
21
22 215 smaller than the reported effect sizes for the association between asthma and risk of microbial
23
24 216 infection (OR: 2.4-6.7) suggesting adequate statistical power to address the study aim.(6, 10)

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29 217 **Exposure ascertainment (asthma status)**

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31 218 For determining asthma status of all cases and controls, we conducted comprehensive
32
33 219 medical record reviews to apply predetermined criteria for asthma as performed in our previous
34
35 220 work.(5, 6) The criteria are delineated in Table 1. These criteria have been extensively used in
36
37 221 research for asthma epidemiology and were found to have high reliability.(25-30) We included
38
39 222 both definite and probable asthma according to the criteria prior to the index date of BSI cases
40
41 223 because most probable asthmatics become definite over time.(6, 31) The incidence dates (the
42
43 224 first date when one met the criteria for asthma) for all asthmatic patients were determined; thus,
44
45 225 we were able to discern the temporal relationship between asthma status (exposure) and *E coli*
46
47 226 BSI (outcome). The risk of *E. coli* BSI was assessed in relation to the current asthma status(32):
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49 227 remission (no asthma symptoms, no asthma-related visits, or no asthma medications for at least
50
51 228 three years prior to index date); active or current asthma (presence of clinical symptoms, asthma-
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229 related visits, or asthma medications within one year prior to index date); and inactive (not
230 current) asthma (presence of asthma symptoms, asthma-related visits, or asthma medications
231 within 1-3 years prior to index date).

232 **Other variables**

233 Pertinent covariates and confounders were collected from medical records:
234 sociodemographic variables (age, gender, ethnicity, and educational status), asthma medications
235 including inhaled and systemic corticosteroids, family history of asthma, atopic status based on
236 sensitization against aeroallergens and food allergens, smoking status (either active or passive
237 exposure to tobacco smoke), vaccination status, and co-morbid conditions at the time of index
238 date as listed in Table 2. The period of data collection was from October 1, 2011 to May 30,
239 2012.

240 **Statistical analysis**

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

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256 RESULTS**257 Study subjects**

258 Of the 274 patients who were identified in the original study, 259 were eligible for the present
259 study. Fifteen patients were excluded; five for consistent FEV1 < 50%, two for restrictive lung
260 disease, two for significant kyphoscoliosis, two for bronchiectasis, one for cystic fibrosis, one for
261 pulmonary fibrosis, and two due to non-Olmsted County residency. Of the eligible 259 cases,
262 179 (69%) were female, 249 (96%) were 18 years of age or older (age mean±standard deviation,
263 61±22 years), and 222 (86%) were Caucasian. The characteristics of the cases and their matched
264 controls, and the individual associations with community-acquired *E. coli* BSI, are summarized
265 in Table 2. There were only 10 asthmatics on moderate- or high-dose inhaled corticosteroid (ICS)
266 and two asthmatics on systemic corticosteroid at the time of the index date. Comparing subjects
267 with asthma versus those without, there was no significant difference in the proportions, who had
268 received influenza vaccine (40% vs. 40%, p=0.99) or PPV23 (49% vs. 44%, p=0.49) within one
269 year prior to index date.

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

271 Thirty-seven of 259 (14%) cases had a history of asthma prior to the index date of community-
272 acquired *E. coli* BSI, compared with 16 of 259 (6%) controls (unadjusted OR: 2.75; 95% CI:
273 1.42-5.32; p=0.003). Of the 37 case subjects with asthma, 33 (89%) had definite asthma and 4
274 (11%) had probable asthma. Of the 16 controls with asthma, 12 (75%) had definite asthma and 4

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3 275 (25%) had probable asthma. Among all 53 asthmatics, 18 were on ICS therapy at the index date
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6 276 (8 on low-dose ICS and 10 on moderate to high-dose ICS therapy). The effect of asthma on risk
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8 277 of community-acquired *E. coli* BSI, independent of other risk factors, is summarized in Table 3.
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10 278 Subjects with a history of asthma by predetermined criteria for asthma in Table 1 had a nearly 3-
11
12 279 fold higher risk of developing community-acquired *E. coli* BSI compared to those without
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14 280 asthma, controlling for all potential confounding factors (adjusted OR: 2.74; 95% CI: 1.11-6.76;
15
16 281 $p=0.029$). The PAR% of asthma by predetermined criteria for asthma in Table 1 for the risk of *E.*
17
18 282 *coli* BSI was 9%. The p -values for testing a significant interaction between asthma and
19
20 283 categorized age were as follows: $p=0.285$ for age cutoff of 65 years (i.e., ≥ 65 vs. <65 years),
21
22 284 $p=0.958$ for age cutoff of 40 years (i.e., ≥ 40 vs. <40 years), and $p=0.417$ for age cutoffs of 40
23
24 285 years and 65 years (i.e., <40 , 40-65, vs. >65 years). As a result, we have no evidence of a
25
26 286 differential asthma effect across age strata. Additional characteristics of asthma were also
27
28 287 evaluated for an association with risk of community-acquired *E. coli* BSI (see Table 4). Adjusted
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30 288 for other factors, active asthma was associated with increased risk of *E. coli* BSI but for
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32 289 asthmatics on ICS therapy compared to non-asthmatics, but the overall 3-level effect was not
33
34 290 statistically significant ($p=0.079$).

291 **Other variables and *E. coli* BSI**

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

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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

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3 321 unlikely and also there was no significant difference in symptom duration from BSI-related
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5 322 symptom to index date between asthma and non-asthma in cases (4.7 ± 5.5 vs 5.2 ± 5.5 days,
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8 323 $p=0.61$). Since detection of asthma depends on follow-up duration from registration to index
9
10 324 date of community-acquired *E. coli* BSI, we designed our study to ensure that duration was
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12 325 similar between cases and controls. Asthma prevalence in controls in our study was 6%, which is
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14 326 similar to that in adults (7%) in the United States (5.5% for males and 9.7% for females).(36)
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16 327 Also, the prevalence of other common chronic condition such as coronary heart disease in our
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18 328 study (15%) was similar to the national average (7.1% for adults aged 45-64 years and 19.8% for
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20 329 adults aged ≥ 65 years) suggesting that our control group may reasonably represent a general
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22 330 population of adults in the United States.(3) There were no significant differences in influenza
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24 331 and PPV23 vaccination rates between cases and controls, which may imply similar access to
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26 332 health care services. Also, food allergy approached to statistical significant association with risk
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28 333 of *E coli* BSI but other atopic conditions were not. This is probably due to greater
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30 334 misclassification bias of ascertainment of allergic rhinitis and atopic dermatitis by ICD-9 code
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32 335 compared to asthma status and food allergy by predetermined criteria in our study. Taken
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34 336 together, our study results suggest that asthma status is independently associated with risk of
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36 337 community-acquired *E. coli* BSI.

338 There are only a few previous studies, which assessed the incidence of *E. coli* BSI and
339 risk factors associated with its development, including asthma. One study showed a higher risk
340 of community-acquired *E. coli* BSI in asthmatics compared to non-asthmatics among those over
341 65 years of age (5.5% vs. 1%).(37) However, another study showed reduced risk of *E. coli* BSI
342 in asthmatics (rate ratio: 0.3; 95% CI: 0.2-0.4) compared to that in total regional population.(38)
343 These studies have significant limitations including no *a priori* hypothesis testing on the

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3 344 relationship between asthma and risk of community-acquired *E. coli* BSI, utilization of
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5 345 administrative data from health care organizations or case reports, ascertainment of *E. coli* BSI
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8 346 cases and asthma based on ICD-9 code, inclusion of only elderly patients aged over 65 years,(37)
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10 347 and no concurrent control group.(38) Thus, our study is the first population-based case-control
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12 348 study that demonstrated a relationship between asthma and risk of community-acquired *E. coli*
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14 349 BSI. Several studies showed increased risks of microbial infections in asthmatics[(5-7, 10, 11)
15
16 350 but these studies only addressed the relationship between asthma and airway infections.
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20 351 The mechanisms underlying the apparent association between asthma and risk of
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22 352 community-acquired *E. coli* BSI are unknown. Whether previously reported impaired innate
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24 353 immune factors that may predispose to infections due to viruses(13, 39, 40) and other bacteria
25
26 354 are operative in community-acquired *E. coli* BSI is undefined. Recently, Habibzay et al reported
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28 355 impaired innate immunity against pneumococci through impaired TLR-receptor signal
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30 356 transduction by house dust mite allergic sensitization resulting in reduced neutrophil recruitment
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32 357 and increased risk of pneumococcal infection in the airways.(11) It is worth investigating
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34 358 whether allergic sensitization can induce similar impairment of innate immunity through TLR-4
35
36 359 for gram-negative bacteria in genitourinary or gastrointestinal tracts in asthmatics. Also, an
37
38 360 adaptive immune response to gram-negative bacteria might be altered in asthmatics,(41) which
39
40 361 may affect susceptibility to gram-negative bacterial infection. For example, Koch et al reported
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42 362 impaired Type 1 helper T cell (Th1) response (interleukin-12-induced interferon- γ release from T
43
44 363 lymphocytes) to endotoxin from *Salmonella enteritidis* in asthmatics.(42) Further studies are
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46 364 needed to address our study findings.
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53 365 The main strengths of our study are a population-based study design and include the
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55 366 epidemiologic merits of self-contained health care environment with comprehensive medical
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3 367 record system for research. We identified population-based all incident community-acquired *E.*
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5 368 *coli* BSI cases based on the Freidman criteria. We ascertained asthma status by applying
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7
8 369 predetermined criteria independent of a physician diagnosis of asthma or ICD-9 code. Also, our
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10 370 study has inherent limitations as a retrospective study. We could not obtain detail information on
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12 371 certain variables such as atopic sensitization data or smoking history (e.g., duration or the
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14 372 number of cigarettes a day) but we assumed this data to be missing at random (i.e., it is subject to
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16 373 non-differential misclassification bias for comparison groups of interest). Although our criteria
17
18 374 for asthma was based on medical record review, given the absence of gold standard for asthma,
19
20 375 the retrospective investigation for feasibility (due to infrequent *E coli* BSI), and the extensive use
21
22 376 of the criteria in previous asthma research, we believe the criteria is unlikely to result in a
23
24 377 significant bias affecting interpretation of the results. Our study finding that asthma prevalence
25
26 378 among controls was similar to that at the national level should mitigate this concern. Our study
27
28 379 subjects were predominantly white which might limit generalizability of our results to other
29
30 380 ethnic groups. Our study subjects were relatively an older population affected by many
31
32 381 comorbid conditions, which might confound the study results. Therefore, we adjusted the
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34 382 association between asthma and risk of *E coli* BSI for each comorbid condition individually in
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36 383 our multivariate model. Since the prevalence of comorbid conditions is related to age, we
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38 384 examined the effect of the interaction between age and asthma. We found that the main results
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40 385 on the association between asthma and risk of *E coli* BSI did not appear to be significantly
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42 386 affected by various cutoffs of age suggesting the results did not differ by age group (younger vs.
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44 387 older group).

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388 In conclusion, asthmatics might be at an increased risk of non-respiratory tract bacterial
389 infections, including community-acquired *E. coli* BSI. The mechanisms responsible for this
390 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 FEV₁ or FVC less than 70% predicted and another with at least 20% improvement to an FEV₁ of higher 70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV₁
 - 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 alpha₁-antitrypsin
 - Cystic fibrosis
 - Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis
- FVC forced vital capacity; FEV₁, forced expiratory volume in 1 sec.

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- Pulmonary function tests that showed FEV₁ to be consistently below 50% predicted or diminished diffusion capacity

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

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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	

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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

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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
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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
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	(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.