

Asthma Is Associated with a Lower Risk of Sepsis and Sepsis-related Mortality

To the Editor:

The immunopathology of asthma is complex. Although classic type 2 helper T-cell (Th2) immune responses are one major mechanism underlying asthma, other contributing mechanisms include activation of IL-17-mediated neutrophilic inflammation and innate Toll-like receptor responses to pathogens. These pathways are important to normal host response to pathogens and may potentially benefit patients with asthma. Greater mast cell degranulation and release of mediators, such as tumor necrosis factor- α and IL-6, may benefit outcomes of infections through enhanced neutrophil influx and killing of bacteria (1). Parasitic worms, which drive Th2 polarization, enhance clearance of *Klebsiella* in a septic peritonitis murine model and improve survival (2). In humans, circulating Th2 levels are higher among survivors as compared with matched patients who died after *Staphylococcus aureus* infection in a case-control study (3). Non-Th2 pathways also likely benefit patients with asthma. Toll-like receptors are linked to asthma and are primary sensors of invading pathogens (4–6). Heightened innate responses would enable faster pathogen clearance. Cecal puncture-induced sepsis in mice deficient in IL-17 receptor leads to less neutrophil recruitment into the peritoneal cavity, greater spread of infection, greater inflammatory response, and increased mortality as compared with wild-type mice (7). We hypothesized that individuals with asthma, characterized by activation of proinflammatory pathways, have a lower incidence of sepsis and/or sepsis-related mortality.

We investigated this using the 2012 Healthcare Cost and Utilization Project–National Inpatient Sample (NIS), and validated results with additional data sources: 2007, 2008, and 2011 NIS and Cleveland Clinic Health System (CCHS) admissions between 2010 and 2014 for patients hospitalized with pneumonia, urinary tract infection (UTI), or skin and soft tissue infection (SSTI). The NIS is the largest all-payer inpatient database available in the United States and an important component of the Healthcare Cost and Utilization Project. In accordance with data use agreement, we analyzed a 20% weighted sample of U.S. hospital discharges, constituting more than 7 million discharges in each year. Deidentified data of patients hospitalized at the Cleveland Clinic from 2010 through 2014 were extracted using *eResearch* (Cleveland Clinic Enterprise Data Center, Cleveland, OH). The study was approved by the Cleveland Clinic Institution Review Board.

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The impact of asthma on rates of septicemia, sepsis, severe sepsis, and septic shock was determined among patients hospitalized for any of three common infections, that is, pneumonia, UTI, and SSTI. Adjusted effects in models account for patient's age, sex, race, median household income quartiles for ZIP code, hospital location, and the modified Elixhauser comorbidity index, which summarizes disease burden and predicts hospital mortality (8).

In 2008, the Centers for Disease Control and Prevention (CDC) recommended pneumococcal vaccination of patients with asthma and who are 65 years of age and younger, which could introduce endogeneity bias, that is, through change in clinical practice. Thus we analyzed data sets from before (2007), during (2008), and after (2011, 2012) the CDC recommendation.

The NIS contains up to 25 diagnoses recorded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD9_CM) and lists up to 29 comorbid conditions. The ICD9_CM codes were used to identify individuals hospitalized for pneumonia, UTI, and SSTI. Patients with a principal diagnosis of sepsis, severe sepsis, or septic shock, followed by secondary diagnoses of pneumonia, UTI, and SSTI were also included. This approach ensured inclusion of all patients with infections and sepsis, despite differing coding practices across the United States. Septicemia and asthma were also identified using ICD9_CM codes (Table 1). Data were excluded for those younger than 6 or older than 80 years, for patients with a history of current or past smoking, or when chronic lung disease other than asthma was present. Similar methods were applied in CCHS analyses.

To account for observed covariate differences between patients with and without asthma in each of our databases, we used inverse weighting on the propensity score. The propensity score for each patient is the predicted probability of asthma from a nonparsimonious logistic regression model using the covariates specified in Figure 1. After weighting, the resulting groups appear to have similar distributions of all covariates (Figure 1 for NIS 2012), and thus weighted groups can be compared more directly on the outcomes of interest. The resulting comparisons account for differences between groups on variables included in the propensity score, but not for any other potential differences. Similar propensity-weighting approaches were applied in the other databases. All statistical analyses were conducted with R, version 3.3.1 (R Project for Statistical Computing, Vienna, Austria).

In the NIS 2012 sample, which includes 20% of all U.S. hospital discharges, 23,386 patients with asthma (10%) and 203,603 patients without asthma (90%) were hospitalized across the United States with pneumonia, UTI, or SSTI (Table 1). Patients with asthma had decreased risk for hospital mortality (adjusted odds ratio [aOR], 0.41; 95% confidence interval [CI], 0.37–0.45), septicemia (aOR, 0.60; 95% CI, 0.58–0.61), sepsis (aOR, 0.59; 95% CI, 0.56–0.62), severe sepsis (aOR, 0.60; 95% CI, 0.58–0.63), and septic shock (aOR, 0.74; 95% CI, 0.71–0.78) across all infections. Risk reductions were also statistically significant within each specific type of infection. Asthma was associated with lower risk for intensive care unit admission (aOR, 0.80; 95% CI, 0.64–0.99) and sepsis-related organ failure such as acute kidney injury (aOR, 0.65; 95% CI, 0.63–0.68). Hospital length of stay was shorter for patients with asthma,

Table 1. Demographics and Clinical Outcome of Patients with Asthma Hospitalized for Pneumonia, Urinary Tract Infection, and Skin and Soft Tissue Infection

Demographics*	NIS 2012		NIS 2011		NIS 2008		NIS 2007		CCHS Data	
	Nonasthma (n = 203,603)	Asthma (n = 23,366)	Nonasthma (n = 228,095)	Asthma (n = 25,721)	Nonasthma (n = 224,725)	Asthma (n = 23,862)	Nonasthma (n = 207,969)	Asthma (n = 23,678)	Nonasthma (n = 11,705)	Asthma (n = 2,590)
Age, yr, mean (SD) [†]	55.54 (18.28)	49.82 (20.80)	55.67 (18.19)	50.68 (20.42)	55 (19)	50 (21)	54 (19)	50 (21)	42.13 (21.06)	33.16 (21.83)
Sex, female, n (%) [†]	110,815 (54.4)	16,011 (68.5)	124,370 (54.5)	17,788 (69.2)	121,101 (54)	16,218 (68)	108,440 (54)	15,514 (66)	6,130 (55.2)	1,507 (58.2)
Race, black, n (%) [†]	29,134 (14.3)	3,961 (16.9)	34,144 (15.0)	4,424 (17.2)	26,173 (12)	3,277 (14)	22,999 (11.4)	2,970 (13)	3,279 (29.5)	906 (35.0)
Outcomes*	NIS 2012		NIS 2011		NIS 2008		NIS 2007		CCHS Data	
	Unadjusted OR (95% CI)	Weighted aOR (95% CI)	Unadjusted OR (95% CI)	Weighted aOR (95% CI)	Unadjusted OR (95% CI)	Weighted aOR (95% CI)	Unadjusted OR (95% CI)	Weighted aOR (95% CI)	Unadjusted OR (95% CI)	Weighted aOR (95% CI)
Hospital mortality	0.44 (0.40 to 0.48)	0.41 (0.37 to 0.45)	0.46 (0.42 to 0.50)	0.43 (0.39 to 0.47)	0.32 (0.28 to 0.35)	0.31 (0.28 to 0.34)	0.41 (0.35 to 0.43)	0.35 (0.31 to 0.39)	0.65 (0.49 to 0.85)	0.89 (0.67 to 1.19)
Sepsis	0.60 (0.57 to 0.62)	0.59 (0.56 to 0.62)	0.57 (0.54 to 0.59)	0.55 (0.53 to 0.58)	0.38 (0.35 to 0.41)	0.37 (0.34 to 0.40)	0.44 (0.41 to 0.47)	0.41 (0.38 to 0.44)	0.40 (0.39 to 0.63)	0.66 (0.52 to 0.84)
Severe sepsis	0.65 (0.62 to 0.68)	0.60 (0.58 to 0.62)	0.63 (0.60 to 0.66)	0.59 (0.56 to 0.62)	0.47 (0.44 to 0.50)	0.46 (0.43 to 0.49)	0.52 (0.49 to 0.56)	0.48 (0.45 to 0.52)	0.40 (0.23 to 0.65)	0.51 (0.30 to 0.85)
Septic shock	0.78 (0.74 to 0.81)	0.74 (0.71 to 0.78)	0.76 (0.72 to 0.80)	0.72 (0.68 to 0.76)	0.49 (0.47 to 0.52)	0.51 (0.48 to 0.53)	0.50 (0.47 to 0.53)	0.49 (0.46 to 0.52)	0.39 (0.22 to 0.62)	0.51 (0.31 to 0.87)
Septicemia	0.61 (0.59 to 0.63)	0.60 (0.58 to 0.61)	0.58 (0.56 to 0.59)	0.55 (0.54 to 0.57)	0.41 (0.40 to 0.43)	0.42 (0.40 to 0.43)	0.45 (0.43 to 0.47)	0.42 (0.40 to 0.44)	0.49 (0.39 to 0.59)	0.65 (0.53 to 0.81)
Outcomes*	NIS 2012		NIS 2011		NIS 2008		NIS 2007		CCHS Data	
	Unadjusted Mean Difference (95% CI)	Adjusted Mean Difference (95% CI)	Unadjusted Mean Difference (95% CI)	Adjusted Mean Difference (95% CI)	Unadjusted Mean Difference (95% CI)	Adjusted Mean Difference (95% CI)	Unadjusted Mean Difference (95% CI)	Adjusted Mean Difference (95% CI)	Unadjusted Mean Difference (95% CI)	Adjusted Mean Difference (95% CI)
Hospital LOS, d	−0.59 (−0.69 to 0.50)	−0.84 (−0.94 to −0.73)	−0.72 (−0.81 to −0.65)	−0.95 (−1.03 to −0.86)	−1.16 (−1.24 to −1.08)	−1.28 (−1.36 to −1.19)	−0.8 (−0.7 to 0.9)	−1 (−0.9 to −1.1)	−0.86 (−1.21 to −0.51)	−0.08 (−0.42 to 0.25)
Total cost, US\$	−1,693 (−2,005 to −1,381)	−2,680 (−2,994 to −2,327)	−1,508 (−1,603 to −1,164)	−2,117 (−2,351 to −1,882)	−2,967 (−3,159 to −2,776)	−3,406 (−3,610 to −3,202)	−1,892 (−2,080 to −1,704)	−2,639 (−2,845 to −2,434)		
ICU LOS, d									−0.45 (−0.62 to −0.28)	−0.22 (−0.37 to −0.06)
Outcomes*	NIS 2012: Pneumonia, Asthma (n = 12,373) vs. Nonasthma (n = 64,201)		NIS 2012: UTI, Asthma (n = 5,233) vs. Nonasthma (n = 76,121)		NIS 2012: SSTI, Asthma (n = 5,780) vs. Nonasthma (n = 63,281)					
	Unadjusted OR (95% CI)	Weighted aOR (95% CI)	Unadjusted OR (95% CI)	Weighted aOR (95% CI)	Unadjusted OR (95% CI)	Weighted aOR (95% CI)				
Hospital mortality	0.29 (0.25–0.32)	0.34 (0.30–0.38)	0.58 (0.48–0.70)	0.49 (0.40–0.59)	0.52 (0.37–0.72)	0.33 (0.24–0.47)				
Sepsis	0.35 (0.32–0.39)	0.39 (0.35–0.42)	1.04 (0.97–1.11)	1.07 (1.01–1.15)	0.89 (0.81–0.97)	0.80 (0.73–0.88)				
Severe sepsis	0.45 (0.42–0.48)	0.50 (0.46–0.53)	0.91 (0.84–0.98)	0.82 (0.76–0.88)	0.83 (0.73–0.94)	0.60 (0.53–0.69)				
Septic shock	0.59 (0.59–0.63)	0.64 (0.60–0.68)	0.81 (0.73–0.89)	0.71 (0.64–0.78)	0.74 (0.62–0.88)	0.51 (0.42–0.60)				
Septicemia	0.44 (0.42–0.46)	0.48 (0.46–0.51)	0.95 (0.90–1.00)	0.92 (0.86–0.97)	0.84 (0.78–0.90)	0.68 (0.63–0.73)				

Definition of abbreviations: aOR = adjusted odds ratio; CCHS = Cleveland Clinic Health System; CI = confidence interval; ICU = intensive care unit; LOS = length of stay; NIS = National Inpatient Sample; OR = odds ratio; SSTI = skin and soft tissue infection; UTI = urinary tract infection.

Asthma is identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD9, CM) code 493.xx; pneumonia by ICD9, CM codes 480.x, 481, 482.xx, 483.x, 484.x, 486, 487.0, 488.01, 488.11, and 488.81; urinary tract infection by ICD9, CM code 490.xx; skin and soft tissue infection by ICD9, CM codes 528.3, 681.x, and 686.x; sepsis by ICD9, CM code 995.91; severe sepsis by ICD9, CM code 995.92; and septic shock by ICD9, CM code 785.52. Mean difference compares the mean value for patients with asthma minus the mean value for patients without asthma.

*Patients hospitalized across the United States and at the Cleveland Clinic Health System with any of the three common infections (i.e., pneumonia, urinary tract infection, or skin and soft tissue infection). Analyses adjusted with the use of inverse probability weighting.

†Clinical outcome results, stratified by type of infection, of patients with asthma compared with patients without asthma hospitalized for pneumonia, urinary tract infection, and skin and soft tissue infection. Analyses adjusted with the use of inverse probability weighting.

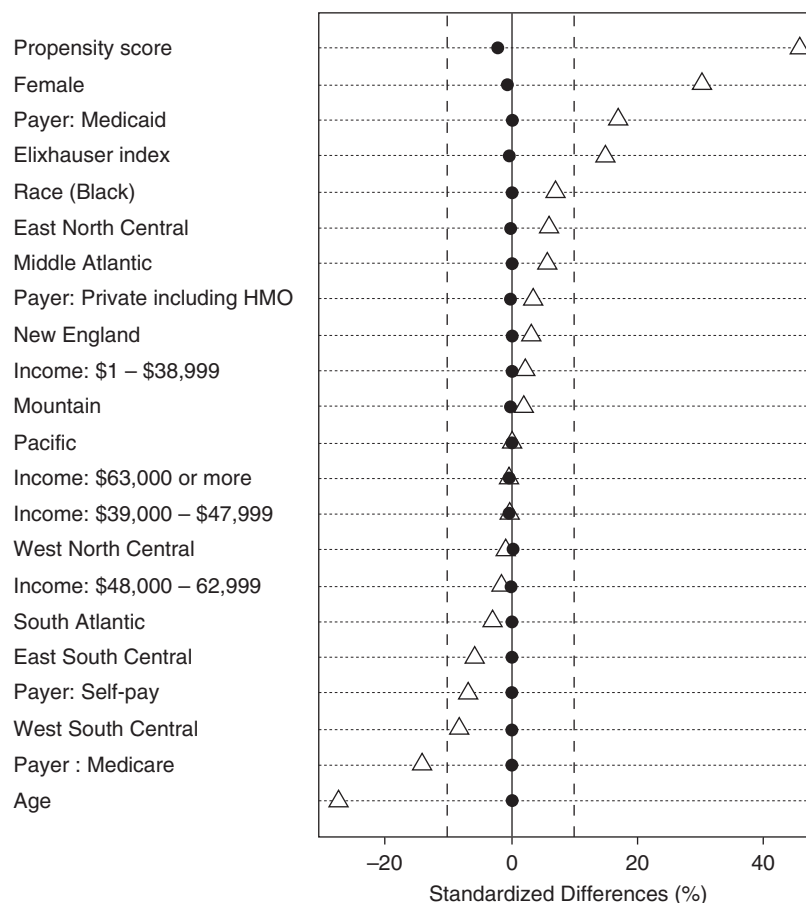


Figure 1. Standardized mean differences before and after inverse probability of treatment weighting for the 2012 National Inpatient Sample. Covariates included in the propensity score are age, sex, race (two categories), payer (four categories), hospital location (nine geographic regions), Elixhauser comorbidity index, and neighborhood median household income (four categories). The *open triangles* show the standardized mean differences for each covariate comparing patients with and without asthma before weighting, and the *solid circles* show the differences after weighting. After weighting, the differences between groups on these covariates are much better balanced. HMO = health maintenance organization.

which yielded lower in-hospital costs for patients with asthma with infections (Table 1). Similar risk reduction was seen in patients with other atopic conditions such as allergic rhinitis (data not shown).

Analyses of other NIS years and CCHS data sets confirmed that asthma is associated with lower risk for sepsis, severe sepsis, septic shock, and mortality (Table 1). The lower risk of mortality, septicemia, severe sepsis, and septic shock was consistently observed within each stratified infection type (i.e., pneumonia, UTI, and SSTI). However, risk of sepsis was lower in patients admitted with pneumonia and SSTI but not UTI. This may be related to different types of organisms, typically involved in each infection, influencing the response (Table 1). Patients with asthma had a lower average cost for infection-related hospitalizations, consistent with observed lower rates of sepsis and its complications, including length of stay (Table 1).

Five large data sets show a protective association for asthma against sepsis. This challenges findings in prior case-control studies, which suggested asthma was associated with higher risk for invasive pneumococcal and nonrespiratory infections (9, 10). Compared with previous studies, we excluded patients with a remote or current smoking history to minimize bias

of smoke-related airway disease. Unfortunately, the cross-sectional administrative nature of our data limited evaluation of asthma severity and specific infectious organisms.

Observational studies are subject to bias. At times, endogeneity bias can persist even with rigorous statistical adjustments. The results in this study, adjusted to sex, age, income, race, and comorbidities, across 4 different years are consistent across 5 independent large data sets that include a total of 99,257 patients with asthma among nearly 1 million hospitalized individuals. Differences in sample size, exclusion criteria, and methodology may underlie the differences in our results as compared with previously published reports (9, 10). Future work on types of immune responses that benefit asthma may suggest approaches to avoid sepsis-related outcomes in people without asthma. ■

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Hyoid Arch Displacement with Hypoglossal Nerve Stimulation

To the Editor:

A new treatment for obstructive sleep apnea (OSA) is unilateral hypoglossal nerve stimulation, an approach shown to decrease the severity and symptoms of OSA in selected patients (1, 2). Drug-induced sedation endoscopy suggests that upper airway stimulation

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(UAS) therapy enlarges the oropharyngeal (retroglossal area) and velopharyngeal (retropalate) airway channels, the former through forward movement of the tongue and the latter presumed to be by a linkage through tissues moved by UAS (3). Physiological studies in anesthetized dogs indicate such a linkage exists in that pulling the hyoid bone and its attachments forward opens not only the oropharynx but also the velopharynx (4). This hyoid arch (i.e., the bones, muscles, and ligaments) forms the anterior pharyngeal wall, and is known for its actions in speech and swallowing. A forward movement of the hyoid arch also occurs with glossopharyngeal breathing. This is a useful method for independent breathing in ventilator-dependent patients with post-polio myelitis syndrome, whereby air is first gulped into the oropharynx through the nose and then pushed into lungs (5, 6). The hypothesis here was that UAS would displace the hyoid arch forward, increasing upper airway volume through an action similar to the inspiratory mechanics in this phenomenon.

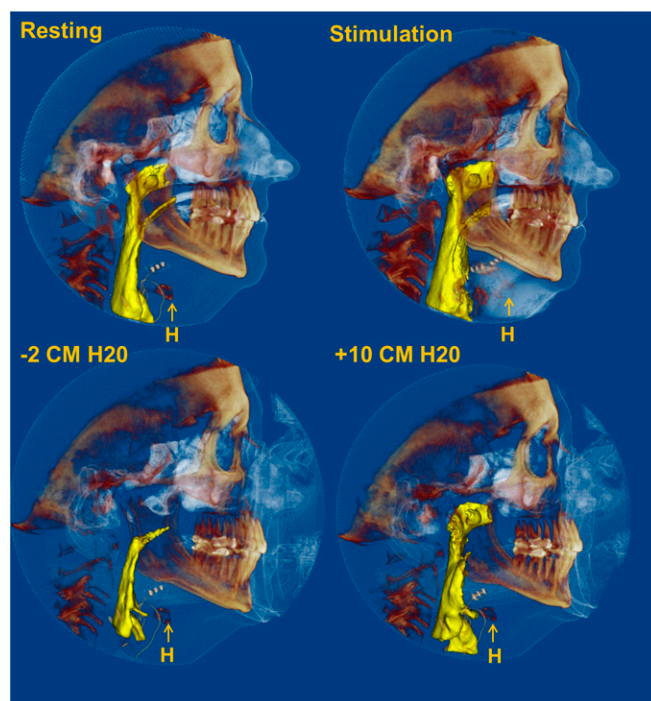


Figure 1. Three-dimensional rendering images of the upper airway with cone beam computed tomography for one patient. The segmented airway is colored yellow. The arrow labeled with an H points to the hyoid bone. The stimulation cuff electrode (on the right hypoglossal nerve) is represented by the three linear, yellow dots above the hyoid. *Top left:* Resting breathing. Sagittal view during a cycle of resting breathing showing an upper airway volume (yellow area) of 29.5 cm³. *Top right:* Stimulation. Sagittal view during stimulation of the hypoglossal nerve with an increase in upper airway volume (43.7 cm³, +48%) from baseline. The hyoid bone (H) and the submental soft tissue (haziness resulting from movement artifact) move anteriorly during stimulation and produce an outward bulge in submental contour. *Bottom left:* Application of negative pressure (–2 cm H₂O) by facemask, shown as a shadow on the face. Sagittal view during application of –2 cm H₂O with a decrease in upper airway volume (20.9 cm³, –29%). The velopharynx is completely closed, explaining the lack of yellow in that region. The position of the hyoid and the cuff electrode are unchanged. *Bottom right:* Application of positive pressure (+10 cm H₂O) by facemask. Sagittal view during application of +10 cm H₂O with an increase in airway volume (37.8 cm³, +28%). The position of the hyoid and the cuff electrode are unchanged.

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