OPEN

Postoperative Adverse Outcomes in Patients With Asthma

A Nationwide Population-based Cohort Study

Chao-Shun Lin, MD, PhD, Chuen-Chau Chang, MD, PhD, Chun-Chieh Yeh, MD, PhD,
Chi-Li Chung, MD, Ta-Liang Chen, MD, PhD, and Chien-Chang Liao, PhD, MPH

Abstract: Outcome after surgery in patients with asthma remains unknown. The purpose of this study is to investigate postoperative major complications and mortality in surgical patients with asthma.

Using reimbursement claims from the Taiwan National Health Insurance Research Database, the authors identified 24,109 surgical patients with preoperative asthma and 24,109 nonasthma patients undergoing major surgeries using matching procedure with propensity score by sociodemographics, coexisting medical conditions, and surgical characteristics. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for 30-day postoperative complications and mortality associated with asthma were analyzed in the multivariate logistic regressions.

Asthma increased postoperative pneumonia (OR 1.48; 95% CI 1.34–1.64), septicemia (OR 1.11; 95% CI 1.02–1.21), and urinary tract infection (OR 1.17; 95% CI 1.09–1.26). Preoperative emergency care for asthma was significantly associated with postoperative 30-day in-hospital mortality, with an OR of 1.84 (95% CI 1.11–3.04). Preoperative emergency service, hospitalizations, admission to intensive care unit, and systemic use of corticosteroids for asthma were also associated with higher postoperative complication rates for asthmatic patients.

Postoperative complications and mortality were significantly increased in asthmatic patients. We suggest urgent efforts to revise protocols for asthma patients' perioperative care.

(*Medicine* 95(3):e2548)

Abbreviations: CI = confidence interval, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, OR = odds ratio.

INTRODUCTION

Asthma is a common clinical condition characterized by variable airway obstruction and hyper-responsiveness sustained by chronic inflammation.[1,2] It is a worldwide problem, with an estimated 300 million affected individuals, and it is believed to contribute to one of every 250 deaths.[3,4] The annual economic cost of asthma was $56 billion in the United States between 2002 and 2007.[5] Days lost from work have also been reported as a substantial economic and social consequence of asthma in the United States, the United Kingdom, and Asian regions.[6–8]

Patients with asthma are noted to face higher risk of pulmonary complications during the perioperative period and increased risks of various complications after surgeries.[9–11] Asthma increased risk of respiratory complications after adenotonsillectomy in children with obstructive breathing during sleep.[9] Although the incidence of perioperative bronchospasm and laryngospasm was low, complications increased in elderly patients and in those with active asthma.[10] These studies, however, were limited to asthma patients without adequate control, or focused on a single type of surgery or single outcome after surgery.[9–11]

The association between preoperative asthma and postoperative adverse events was not completely understood. We conducted this nationwide retrospective matched-cohort study using Taiwan's National Health Insurance Research Database to investigate comprehensive postoperative major complications and mortality for patients with asthma when receiving major surgeries. The impacts of various severity-related clinical characteristics of asthma on patients' postoperative adverse events were also evaluated.

METHODS

Data Sources

Retrospective data were collected from reimbursement claims of Taiwan's National Health Insurance Program, which was implemented in March 1995 and covers more than 99% of the 22.6 million Taiwan residents. The National Health Research Institutes of Taiwan established a National Health Insurance Research Database that records all beneficiaries' medical services, including inpatient and outpatient demographics, primary and secondary diagnoses, procedures, prescriptions and medical expenditures for public research interest.

The validity of this database has been favorably evaluated, and research articles based on it have been accepted in prominent scientific journals worldwide.[12–14]

Ethical Approval

Insurance reimbursement claims from the National Health Insurance Research Database are available for public access. To protect personal privacy, the electronic database with patient identifications was decoded and scrambled for further research access. Although informed consent was not required because of this privacy protection, this study was approved both by the Taiwan's National Health Research Institutes (NHIRD-103-121) and Taipei Medical University's Institutional Review Board (TMU-JIRB-201505055; TMU-JIRB-201404070).[12–14]

Study Population

We examined medical claims and identified 24,109 patients ≥20 years of age with preoperative asthma from 1,834,149 surgical patients who underwent major inpatient surgeries between 2008 and 2010 in Taiwan. These surgeries required general, epidural, or spinal anesthesia and hospitalization for more than 1 day. To identify patients with asthma more strictly and to avoid those with minor or borderline asthma, the current study required at least 2 visits for medical care with primary diagnosis of asthma from physicians specialized in pulmonary medicine within the 24-month preoperative period of index surgery. Using matching procedure by propensity score with age, sex, low income, types of surgery, risk of surgery, types of anesthesia, operation in teaching hospital, and coexisting medical conditions, we selected 24,109 surgical patients from surgical patient populations who were free from diagnosis of asthma, preoperatively.

Measures and Definitions

We identified income status by defining low-income patients as those qualifying for waived medical copayment, because this status is verified by the Taiwan Bureau of National Health Insurance. Also recorded were whether the surgery was performed in a teaching hospital and the types of surgery and anesthesia. We used the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) to define preoperative medical diseases and postoperative complications. Preoperative asthma (ICD-9-CM 493) was defined as the major exposure. Coexisting medical conditions were determined from medical claims for the 24-month preoperative period, including hypertension (ICD-9-CM 401–405), mental disorders (ICD-9-CM 290–319), diabetes (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272.0, 272.1, 272.2), congestive heart failure (ICD-9-CM 428), liver cirrhosis (ICD-9-CM 571.2 and 571.5), and renal dialysis (administration code D8, D9). Thirty-day in-hospital mortality after the index surgery and postoperative complications were considered as the study's outcomes. These complications included pneumonia (ICD-9-CM 480–486), septicemia (ICD-9-CM 038 and 998.5), and urinary tract infection (ICD-9-CM 599.0).

This study also considered patients receiving asthma-related systemic corticosteroids, such as methylprednisolone, prednisolone, dexamethasone or hydrocortisone orally or intravenously. We also identified patients receiving emergency care, hospitalization or intensive care unit (ICU) admissions for asthma within the 24 months, preoperatively.

Statistical Analysis

We used propensity score-matched pair method to analyze asthma patients and nonasthma controls. We developed a nonparsimonious multivariable logistic regression model to estimate a propensity score for preoperative asthma, irrespective of outcome. Clinical significance guided the initial choice of covariates in this model: age, sex, low income, hypertension, mental disorders, diabetes, hyperlipidemia, congestive heart failure, liver cirrhosis, renal dialysis, operation in teaching hospital, types of surgery, risk of surgery, and types of anesthesia. The χ^2 tests were used to measure covariate balance and a P-value <0.05 was suggested to represent meaningful covariate imbalance. We matched patients with asthma to nonasthma patients using a greedy-matching algorithm with a calliper width of 0.2 standard deviations of the log odds of the estimated propensity score. This method could remove 98% of the bias from measured covariates.[12,15]

Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for 30-day postoperative pneumonia, septicemia, urinary tract infection and mortality between patients with and without asthma were analyzed with multivariate logistic regression by controlling sex, age, types of surgery and anesthesia, risk of surgery, operation in teaching hospital and preoperative coexisting medical conditions. The adjusted ORs and 95% CIs of 30-day postoperative pneumonia, septicemia, urinary tract infection, and mortality associated with preoperative asthma-related emergency care, hospitalizations, ICU admissions and use of systemic corticosteroids were calculated in the multivariate logistic regressions. SAS version 9.1 (SAS Institute Inc, Cary, NC) statistical software was used for data analyses; 2-sided P value <0.05 indicated significant differences between groups.

RESULTS

After being matched by propensity score procedure, there were no significant differences between surgical patients with and without asthma relating to age, sex, low income, types of surgery, risk of surgery, types of anesthesia, operation in teaching hospital, hypertension, mental disorders, diabetes, hyperlipidemia, congestive heart failure, liver cirrhosis, and renal dialysis (Table 1).

Compared with surgical patients without asthma (Table 2), asthmatic patients had higher risks of postoperative pneumonia (OR = 1.48; 95% CI 1.34–1.64), septicemia (OR = 1.11; 95% CI 1.02–1.21), and urinary tract infection (OR = 1.17; 95% CI 1.09–1.26). Use of emergency medical services because of asthma within the 3 preoperative months was associated with higher rates for pneumonia (OR = 2.03; 95% CI 1.57–2.63), septicemia (OR = 1.44; 95% CI 1.13–1.85), and postoperative mortality (OR = 1.84; 95% CI 1.11–3.04). Increased risks of postoperative pneumonia (OR = 2.68; 95% CI 1.86–3.85) and urinary tract infection (OR = 1.75; 95% CI 1.27–2.41) were also noted in asthmatic patients who were hospitalized for asthma in the 3 months before the index surgery. The adjusted ORs for postoperative pneumonia, septicemia, and urinary tract infection associated with preoperative inpatient care ≥11 cumulative days for asthma in the 24 months before the surgery were 1.69 (95% CI 1.29–2.21), 1.69 (95% CI 1.35–2.12), and 1.71 (95% CI 1.39–2.11), respectively. Among patients with asthma, those with preoperative admission to ICU because of asthma had significantly higher risk of postoperative pneumonia (OR = 1.64; 95% CI 1.37–1.97), septicemia (OR = 1.75; 95% CI 1.50–2.05), urinary tract infection (OR = 1.85; 95% CI 1.60–2.15), and mortality (OR = 1.88; 95% CI 1.35–2.62).

Table 3 shows that the medication of systemic corticosteroids for surgical patients with primary diagnosis of asthma within 3 months preoperatively was an independent risk factor for

TABLE 1. Baseline Characteristics of Surgical Patients With Asthma and Controls[*]

	Controls (N = 24,109)		Asthma (N = 24,109)		*P* Value
Age, y	n	(%)	n	(%)	1.00
20−29	1560	(6.5)	1560	(6.5)	
30−39	2110	(8.8)	2110	(8.8)	
40−49	2691	(11.2)	2691	(11.2)	
50−59	4210	(17.5)	4210	(17.5)	
60−69	4722	(19.6)	4722	(19.6)	
≥70	8816	(36.6)	8816	(36.6)	
Sex					1.00
Female	13,433	(55.7)	13,433	(55.7)	
Male	10,676	(44.3)	10,676	(44.3)	
Low income	710	(2.9)	710	(2.9)	1.00
Coexisting medical conditions					
Hypertension	8088	(33.6)	8088	(33.6)	1.00
Mental disorders	5476	(22.7)	5476	(22.7)	1.00
Diabetes	3381	(14.0)	3381	(14.0)	1.00
Hyperlipidemia	1487	(6.2)	1487	(6.2)	1.00
Congestive heart failure	1102	(4.6)	1102	(4.6)	1.00
Liver cirrhosis	480	(2.0)	480	(2.0)	1.00
Renal dialysis	273	(1.1)	273	(1.1)	1.00
Operation in teaching hospital	22,113	(91.7)	22,113	(91.7)	1.00
Types of surgery					1.00
Skin	369	(1.5)	369	(1.5)	
Breast	352	(1.5)	352	(1.5)	
Musculoskeletal	6724	(27.9)	6724	(27.9)	
Respiratory	1850	(7.7)	1850	(7.7)	
Cardiovascular	980	(4.1)	980	(4.1)	
Digestive	5043	(20.9)	5043	(20.9)	
Kidney, ureter, bladder	1730	(7.2)	1730	(7.2)	
Delivery, CS, abortion	1078	(4.5)	1078	(4.5)	
Neurosurgery	2620	(10.9)	2620	(10.9)	
Eye	227	(0.9)	227	(0.9)	
Others	3136	(13.0)	3136	(13.0)	
Risk of surgery					1.00
Very low	1829	(7.6)	1829	(7.6)	
Low	6755	(28.0)	6755	(28.0)	
Moderate	6709	(27.8)	6709	(27.8)	
High	3775	(15.7)	3775	(15.7)	
Very high	5041	(20.9)	5041	(20.9)	
Types of anesthesia					1.00
General	16,621	(68.9)	16,621	(68.9)	
Epidural or spinal	7488	(31.1)	7488	(31.1)	

[*] Controls were matched by age, sex, low income, hypertension, mental disorders, diabetes, hyperlipidemia, congestive heart failure, liver cirrhosis, renal dialysis, operation in teaching hospital, types of surgery, risk of surgery, and types of anesthesia.

postoperative pneumonia (OR = 1.75; 95% CI 1.44–2.11), septicemia (OR = 1.53; 95% CI 1.29–1.82), urinary tract infection (OR = 1.39; 95% CI 1.18–1.63), and mortality (OR = 1.53; 95% CI 1.04–2.25). Asthmatic patients' emphysema (OR = 2.16; 95% CI 1.24–3.74), chronic bronchitis (OR = 1.84; 95% CI 1.58–2.14), and bronchiectasis (OR = 2.40; 95% CI 1.67–3.43) have impacts on postoperative pneumonia.

DISCUSSION

This is the first nationwide population-based cohort study using propensity score-matched procedure and multivariate adjustment to evaluate postoperative major adverse outcomes in surgical patients with various clinical scenarios of asthma. Our findings showed patients with asthma had higher risks of

postoperative pneumonia, septicemia, and urinary tract infection when compared with nonasthmatic patients. Among surgical patients with asthma, preoperative emergency visits, hospitalizations, or ICU stay because of asthma significantly increased postoperative adverse events. Preoperative use of systemic corticosteroids was also identified as an independent risk factor for postoperative complications and mortality.

Cardiovascular diseases, mental disorders, diabetes, and hyperlipidemia were identified as common coexisting medical conditions for patients with asthma and contributed to increased health care use, poor quality of life, and inadequate control for asthma.[16–19] These comorbidities may change the asthma phenotype and act as confounding factors in assessment of asthma control and outcomes.[17] Coexisting medical conditions,

TABLE 2. Risk of Complications Associated With Asthma in the Multiple Logistic Regression Models

Preoperative characteristics within 24 months	n	Mortality		Pneumonia		Septicemia		UTI	
		OR	(95% CI)*	OR	(95% CI)*	OR	(95% CI)*	OR	(95% CI)*
People without asthma	24,109	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Asthmatic patients	24,109	1.09	(0.88–1.35)	1.48	(1.34–1.64)	1.11	(1.02–1.21)	1.17	(1.09–1.26)
Preoperative emergency care for asthma	4461	1.48	(1.09–2.01)	1.72	(1.48–2.00)	1.36	(1.19–1.56)	1.37	(1.21–1.54)
Within recent 12 months	2493	1.48	(1.02–2.15)	1.76	(1.46–2.11)	1.26	(1.06–1.49)	1.26	(1.07–1.47)
Within recent 6 months	1426	1.51	(0.95–2.39)	1.83	(1.47–2.29)	1.31	(1.07–1.62)	1.22	(1.00–1.49)
Within recent 3 months	844	1.84	(1.11–3.04)	2.03	(1.57–2.63)	1.44	(1.13–1.85)	1.05	(0.80–1.36)
Preoperative inpatient care for asthma	2330	1.29	(0.84–1.97)	1.46	(1.19–1.79)	1.65	(1.41–1.94)	1.54	(1.33–1.78)
Within recent 12 months	1302	1.52	(0.91–2.54)	1.58	(1.23–2.04)	1.63	(1.32–2.00)	1.49	(1.23–1.81)
Within recent 6 months	734	1.63	(0.87–3.05)	1.78	(1.30–2.43)	1.28	(0.96–1.71)	1.42	(1.11–1.83)
Within recent 3 months	378	1.81	(0.83–3.96)	2.68	(1.86–3.85)	1.43	(0.97–2.09)	1.75	(1.27–2.41)
Cumulative length of stay for asthma treatment									
1–5 days	922	0.85	(0.37–1.94)	1.44	(1.04–2.01)	1.53	(1.18–1.99)	1.31	(1.03–1.68)
6–10 days	754	1.50	(0.75–2.97)	1.24	(0.86–1.80)	1.55	(1.18–2.04)	1.41	(1.10–1.81)
≥11 days	979	1.63	(0.96–2.77)	1.69	(1.29–2.21)	1.69	(1.35–2.12)	1.71	(1.39–2.11)
Preoperative ICU stay for asthma treatment	1883	1.88	(1.35–2.62)	1.64	(1.37–1.97)	1.75	(1.50–2.05)	1.85	(1.60–2.15)

CI = confidence interval, ICU = intensive care unit, OR = odds ratio, UTI = urinary tract infection.
* Adjusted for age, sex, low income, hypertension, mental disorders, diabetes, hyperlipidemia, congestive heart failure, liver cirrhosis, renal dialysis, operation in teaching hospital, types of surgery, risk of surgery, and types of anesthesia.

including diabetes, schizophrenia and liver cirrhosis, have been associated with postoperative adverse outcomes.[12–14] To reduce confounding bias, these potential confounding factors were properly adjusted under matching procedure with propensity score and multivariate regression models in this study.

Hospitalization for asthma and use of systemic corticosteroids during the preceding 6 months might increase risk of future hospital admissions for asthma.[20] This study showed history of asthma exacerbation in the prior 12 months is one of the strongest predictors of future exacerbations.[21] We also found that the history of asthma-specific emergency visits, hospitalizations, ICU stay, and use of systemic corticosteroids were independent contributing factors for postoperative major adverse outcomes in asthmatic patients. Surgical patients with emergency care for asthma in the preoperative 3 months had nearly doubled risk of postoperative mortality compared with controls. Patients who were hospitalized for asthma in the 3 months preceding surgery had almost 3 times the risk of developing postoperative pneumonia compared with controls. Cumulative asthma-specific hospital stay and ICU admissions because of asthma in the prior 24 months were significantly associated with increased risk of postoperative complications and mortality.

TABLE 3. Association between Preoperative Systemic Steroid Use and Postoperative Adverse Events in Patients With Asthma

Use of Steroid for Asthma Treatment*	n	Mortality		Pneumonia		Septicemia		UTI	
		OR	(95% CI)†	OR	(95% CI)†	OR	(95% CI)†	OR	(95% CI)†
People without asthma	24,109	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)	1.00	(Reference)
Asthma without corticosteroid use	14,393	0.84	(0.63–1.12)	1.40	(1.24–1.59)	0.91	(0.82–1.01)	1.02	(0.93–1.12)
Asthma with corticosteroid use	9716	1.32	(1.04–1.69)	1.56	(1.39–1.76)	1.35	(1.22–1.49)	1.36	(1.24–1.48)
Recent 12-month use	5378	1.31	(0.98–1.75)	1.70	(1.48–1.95)	1.42	(1.26–1.60)	1.37	(1.23–1.53)
Recent 6-month use	3171	1.40	(1.00–1.96)	1.69	(1.43–1.98)	1.53	(1.33–1.76)	1.34	(1.17–1.53)
Recent 3-month use	1926	1.53	(1.04–2.25)	1.75	(1.44–2.11)	1.53	(1.29–1.82)	1.39	(1.18–1.63)
Asthma without emphysema	20,660	1.02	(0.81–1.29)	1.58	(1.41–1.76)	1.04	(0.95–1.14)	1.17	(1.08–1.27)
Asthma with emphysema	164	1.60	(0.49–5.22)	2.16	(1.24–3.74)	1.75	(1.04–2.94)	1.45	(0.85–2.45)
Asthma without chronic bronchitis	16,598	1.03	(0.80–1.33)	1.48	(1.31–1.67)	0.98	(0.89–1.09)	1.10	(1.01–1.20)
Asthma with chronic bronchitis	4226	1.03	(0.73–1.45)	1.84	(1.58–2.14)	1.24	(1.08–1.42)	1.38	(1.22–1.56)
Asthma without bronchiectasis	20,328	1.03	(0.82–1.29)	1.56	(1.39–1.75)	1.04	(0.95–1.14)	1.16	(1.07–1.26)
Asthma with bronchiectasis	496	1.16	(0.47–2.88)	2.40	(1.67–3.43)	1.39	(0.98–1.97)	1.44	(1.06–1.94)

CI = confidence interval, OR = odds ratio, UTI = urinary tract infection.
* Asthma-related corticosteroids included methylprednisolone, prednisolone, dexamethasone, and hydrocortisone.
† Adjusted for age, sex, low income, hypertension, mental disorders, diabetes, hyperlipidemia, congestive heart failure, liver cirrhosis, renal dialysis, operation in teaching hospital, types of surgery, risk of surgery, and types of anesthesia.

Use of systemic corticosteroids is highly associated with the potential infectious complications because these inhibit the immune system and reduce inflammatory response, which may predispose patients to infection.[22] A retrospective cohort study reported that asthmatic patients treated preoperatively with systemic corticosteroids received surgical procedures with a relatively low incidence of complications, including postoperative bronchospasm and wound infection.[23] Another investigation showed corticosteroid-dependent asthmatic patients can tolerate surgical procedures well without serious pulmonary or wound complications.[24] These studies, however, are limited by small sample sizes and are prone to referral bias, or lack the power to identify independent predictors of morbidity and mortality in surgical patients with asthma. Our study showed that use of systemic corticosteroids within 3 months before surgery significantly increased postoperative morbidity and mortality in asthmatic patients. The use of systemic corticosteroids implied that patients might have been treated with steroids because of active asthma, exacerbation of chronic asthma, or in a state of possible immune-suppression, all of which might contribute to increased postoperative morbidity and mortality. As history of asthma exacerbation can be easily and reliably obtained in preoperative evaluation, this should be routinely checked during preoperative assessment of surgical risks for asthmatic patients, especially their use of systemic corticosteroids, emergency visits, hospitalization, or ICU admission for asthma.[25]

Although the reason asthmatic patients had more postoperative adverse events than the general population is still unclear, several explanations can be considered. First, patients with asthma have increased risks of airway-related infections.[26–28] Impaired innate and adaptive immune functions among asthmatic patients have been suggested as potential underlying mechanisms.[29,30] Second, psychologic stress has been suspected as an asthma trigger in recent decades.[31,32] Rather than directly causing the asthma symptoms, stress modulates the immune system and increases the magnitude of airway inflammatory response to allergens and irritants.[33] Third, a number of perioperative medications, including anesthetics, can induce allergic reactions through histamine release. Neuromuscular blocking drugs are the most common medications to cause allergic reactions in the operating theatre, and some, such as mivacurium and atracurium, have histamine-releasing effects.[34] Intraoperative IgE-mediated anaphylaxis can be triggered by rocuronium, succinylcholine, and vecuronium.[35] There is a concern that nonsynthetic opioids such as morphine can induce bronchospasm through histamine release; however, few subject data support this.[36] In addition, bronchospasm can be provoked by cold inspired gases, tracheal intubation, tracheal extubation, and airway suctioning. Increased airway tone because of vagal stimulation can be caused by endoscopy or peritoneal or visceral stretching during surgery.[37] Finally, asthmatic patients were more likely to have psychiatric illness, which is a contributing factor for postoperative adverse events.[13,38]

This study has some limitations. First, Taiwan's National Health Insurance Research Database lacks data on asthmatic patients' current symptoms and lung function, as well as laboratory data that would facilitate analysis of the association between severity of asthma and postoperative adverse outcomes. Second, detailed information on sociodemographics, dietary habits, and lifestyle factors was not available in the insurance claims data for this study to validate the association of these factors with postoperative adverse outcomes. Third, although the surgical patients without asthma were those who had no medical visits for asthma within 24 months before the index surgery, some mild or borderline asthma may have existed in this group such that the influence of asthma on postoperative outcomes may be underestimated. Finally, although we used matching procedure and multivariate adjustment to control several confounders, residual confounding is possible.

In conclusion, we showed that asthma significantly increased postoperative pneumonia, sepsis, urinary tract infection and subsequent mortality, particularly for asthmatic patients with preoperative asthma-related emergency care, hospitalizations, ICU admissions, and use of systemic corticosteroids. These risk factors need to be routinely considered during preoperative assessment of surgical patients with asthma to provide better perioperative care for this population.

REFERENCES

1. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med.* 2006;355:2226–2235.

2. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma: summary Report 2007. *J Allergy Clin Immunol.* 2007;120:S94–S138.

3. Fanta CH. Asthma. *N Engl J Med.* 2009;360:1002–1014.

4. Masoli M, Fabian D, Holt S, et al. Global initiative for asthma program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy.* 2004;59:469–478.

5. Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002–2007. *J Allergy Clin Immunol.* 2011;127:145–152.

6. Lai CK, De Guia TS, Kim YY, et al. Asthma control in the asia-pacific region: the asthma insights and reality in asia-pacific study. *J Allergy Clin Immunol.* 2003;111:263–268.

7. Birnbaum HG, Berger WE, Greenberg PE, et al. Direct and indirect costs of asthma to an employer. *J Allergy Clin Immunol.* 2002;109:264–270.

8. Bahadori K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med.* 2009;19:9–24.

9. Kalra M, Buncher R, Amin RS. Asthma as a risk factor for respiratory complications after adenotonsillectomy in children with obstructive breathing during sleep. *Ann Allergy Asthma Immunol.* 2005;94:549–552.

10. Warner DO, Warner MA, Barnes RD, et al. Perioperative respiratory complications in patients with asthma. *Anesthesiology.* 1996;85:460–467.

11. Su FW, Beckman DB, Yarnold PA, et al. Low incidence of complications in asthmatic patients treated with preoperative corticosteroids. *Allergy Asthma Proc.* 2004;25:327–333.

12. Yeh CC, Liao CC, Chang YC, et al. Adverse outcomes after noncardiac surgery in patients with diabetes: a nationwide population-based retrospective cohort study. *Diabetes Care.* 2013;36:3216–3221.

13. Liao CC, Shen WW, Chang CC, et al. Surgical adverse outcomes in patients with schizophrenia: a population-based study. *Ann Surg.* 2013;257:433–438.

14. Lin CS, Lin SY, Chang CC, et al. Postoperative adverse outcomes after non-hepatic surgery in patients with liver cirrhosis. *Br J Surg.* 2013;100:1784–1790.

15. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *Am Stat.* 1985;39:33–38.

16. Cazzola M, Calzetta L, Bettoncelli G, et al. Asthma and comorbid medical illness. *Eur Respir J*. 2011;38:42–49.

17. Boulet LP. Influence of comorbid conditions on asthma. *Eur Respir J*. 2009;33:897–906.

18. Kuehn BM. Asthma linked to psychiatric disorders. *J Am Med Assoc*. 2008;299:158–160.

19. Gershon AS, Wang C, Guan J, et al. Burden of comorbidity in individuals with asthma. *Thorax*. 2010;65:612–618.

20. Lieu TA, Quesenberry CP, Sorel ME, et al. Computer-based models to identify high-risk children with asthma. *Am J Respir Crit Care Med*. 1998;157:1173–1180.

21. Bloomberg GR, Trinkaus KM, Fisher EB Jr et al. Hospital readmissions for childhood asthma: a 10-year metropolitan study. *Am J Respir Crit Care Med*. 2003;167:1068–1076.

22. Aberra FN, Lewis JD, Hass D, et al. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. *Gastroenterology*. 2003;125:320–327.

23. Kabalin CS, Yarnold PR, Grammer LC. Low complication rate of corticosteroid-treated asthmatics undergoing surgical procedures. *Arch Intern Med*. 1995;155:1379–1384.

24. Oh SH, Patterson R. Surgery in corticosteroid-dependent asthmatics. *J Allergy Clin Immunol*. 1974;53:345–351.

25. Fuhlbrigge A, Peden D, Apter AJ, et al. Asthma outcomes: exacerbations. *J Allergy Clin Immunol*. 2012;129:S34–S48.

26. Juhn YJ, Kita H, Yawn BP, et al. Increased risk of serious pneumococcal disease in patients with asthma. *J Allergy Clin Immunol*. 2008;122:719–723.

27. Klemets P, Lyytikäinen O, Ruutu P, et al. Risk of invasive pneumococcal infections among working age adults with asthma. *Thorax*. 2010;65:698–702.

28. Talbot TR, Hartert TV, Mitchel E, et al. Asthma as a risk factor for invasive pneumococcal disease. *N Engl J Med*. 2005;352:2082–2090.

29. Contoli M, Message SD, Laza-Stanca V, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med*. 2006;12:1023–1026.

30. Wark PA, Johnston SL, Bucchieri F, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med*. 2005;201:937–947.

31. Busse WW, Kiecolt-Glaser JK, Coe C, et al. NHLBI Workshop summary. Stress and asthma. *Am J Respir Crit Care Med*. 1995;151:249–252.

32. Wright RJ, Rodriguez M, Cohen S. Review of psychosocial stress and asthma: an integrated biopsychosocial approach. *Thorax*. 1998;53:1066–1074.

33. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. *Brain Behav Immun*. 2007;21:993–999.

34. Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth Analg*. 2003;97:1381–1395.

35. Sadleir PH, Clarke RC, Bunning DL, et al. Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011. *Br J Anaesth*. 2013;110:981–987.

36. Rosow CE, Moss J, Philbin DM, et al. Histamine release during morphine and fentanyl anesthesia. *Anesthesiology*. 1982;56:93–96.

37. Woods BD, Sladen RN. Perioperative considerations for the patient with asthma and bronchospasm. *Br J Anaesth*. 2009;103:i57–i65.

38. Miles JF, Garden GM, Tunnicliffe WS, et al. Psychological morbidity and coping skills in patients with brittle and non-brittle asthma: a case-control study. *Clin Exp Allergy*. 1997;27:1151–1159.