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References

[1] Ly NP, Ruiz-Pérez B, Onderdonk AB, et al. Mode of delivery and cord blood cytokines: a birth cohort study. *Clin Mol Allergy*. 2006;4:1.
[2] Soh SE, Lee SS, Hoon SW, et al. The methodology of the GUSTO cohort study: a novel approach in studying pediatric allergy. *Asia Pac Allergy*. 2012;2:144–148.
[3] Khoo J, Shek LP, Khor ES, Wang DY, Lee BW. Pattern of sensitization to common environmental allergens amongst atopic Singapore children in the first 3 years of life. *Asian Pac J Allergy Immunol*. 2001;19:225–229.
[4] Maitra A, Sherriff A, Strachan D, Henderson J. Mode of delivery is not associated with asthma or atopy in childhood. *Clin Exp Allergy*. 2004;34:1349–1355.
[5] Leung JY, Li AM, Leung GM, Schooling CM. Mode of delivery and childhood hospitalizations for asthma and other wheezing disorders. *Clin Exp Allergy*. 2015;45:1109–1117.
[6] Magnus MC, Håberg SE, Stigum H, et al. Delivery by cesarean section and early childhood respiratory symptoms and disorders: the Norwegian Mother and Child Cohort Study. *Am J Epidemiol*. 2011;174:1275–1285.
[7] Tollånes MC, Moster D, Daltveit AK, Irgens LM. Cesarean section and risk of severe childhood asthma: a population-based cohort study. *J Pediatr*. 2008;153:112–116.e1.
[8] Spahr JE, Krawiec ME. The early origins of asthma: nature, nurture, or parturition? *Ann Allergy Asthma Immunol*. 2005;94:211–212.
[9] Almqvist C, Cnattingius S, Lichtenstein P, Lundholm C. The impact of birth mode of delivery on childhood asthma and allergic diseases: a sibling study. *Clin Exp Allergy*. 2012;42:1369–1376.
[10] Sausenthaler S, Koletzko S, Schaaf B, et al. Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. *Am J Clin Nutr*. 2007;85:530–537.

Cost and health care utilization in patients with asthma and high oral corticosteroid use

For patients with asthma, oral corticosteroids (OCSs) have long been a component of disease management,[1] although known adverse events[2–5] have led to a greater reliance on inhaled corticosteroids.[6] OCSs also are a well-established treatment for patients with chronic obstructive pulmonary disease (COPD). Even with treatment, OCS-dependent patients have frequent, severe exacerbations and higher costs.[7,8] We compared the clinical and economic outcomes between high-OCS and low-OCS users to identify evidence of the risks and benefits of OCS treatment in patients with asthma and in the subgroup with concomitant COPD.

This retrospective cohort study used a Health Insurance Portability and Accountability Act-compliant database containing de-identified data from electronic medical records and administrative claims. The study was exempt from review by a human subjects protection committee.

We identified patients who had moderate to severe persistent asthma in 2013 based on definitions in the National Heart, Lung, and Blood Institute Expert Panel Report 3 (EPR-3) and determined their OCS use.[9] Using a validated method, we identified patients at least 18 years of age who received therapy steps 4 to 6.[10] High-OCS users were defined, based on prior research, as those with at least 1 OCS fill with at least 30 days of supply or at least 6 bursts of OCS.[5] Low-OCS users were those who had no OCS fills with at least 30 days of supply and no more than 1 burst of OCS. A subgroup of patients with asthma and COPD was defined by the presence of a claim for COPD (*International Classification of Diseases, Ninth Revision,* Clinical Modification codes 491.x, 496.x, 492.x).

The main outcomes of interest were overall and asthma-related health care use and costs. Additional variables included demographics, smoking and COPD status, use of asthma medications, and evidence of poor asthma control (asthma-related hospitalization or emergency department visit, ≥2 OCS bursts, or ≥6 short-acting β_2-agonist fills in 1 year).[9,10]

To compare outcomes between high- and low-OCS users, analysis of covariance and logistic regression were used for continuous and dichotomous variables, respectively. Adjustors were patient demographics and characteristics, such as age group, sex, race, region, usual physician specialty, Charlson comorbidity index, pneumonia or influenza hospitalization, and EPR-3 step therapy. Adjusted means and odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina). All tests were 2-sided with a significance level of .05.

We identified 17,225 patients with moderate to severe persistent asthma. Of these, 3,117 were younger than 18 years; 8,852 did not receive EPR-3 therapy steps 4 to 6; 871 were not continuously enrolled for the 12-month study period; and 1,030 did not meet the definition of high- or low-OCS use. The primary study cohort included 3,355 patients of whom 30.8% (n = 1,035) had concomitant COPD.

Mean age was 58.8 years (SD 15.9), 66.6% were women, and 8.9% (n = 300) were current smokers and 29.2% (n = 979) were former smokers. There were 517 patients (15.4%) classified as high-OCS users. Patients with asthma alone had a mean age of 56.8 years among high-OCS users and a mean age of 54.6 years among low-OCS users. In patients with asthma and COPD, mean ages were 67.1 and 67.9 years, respectively. High-OCS users had more all-cause office visits than low-OCS users overall (22.4 vs 14.9; $P < .001$) and in the asthma-only and asthma plus COPD subgroups. High-OCS users also had more hospitalizations and emergency department visits compared with low-OCS users (with the same pattern in subgroups). Mean total annual health care costs were $63,939 in high-OCS users and $27,494 ($P < .001$) in low-OCS users. In patients with asthma alone, high-OCS users had a mean total annual health care cost of $40,933 compared with $19,365 for low-OCS users ($P < .001$). In patients with asthma and COPD, high-OCS users had a mean total annual health care cost of $80,580 compared with $50,752 ($P < .001$) for low-OCS users.

In adjusted analyses, of patients with asthma alone, high-OCS users had higher odds of hospitalization than low-OCS users (all-cause OR 1.81, 95% CI 1.25–2.62; asthma-related OR 4.95, 95% CI 1.98–12.40; Fig 1). They had an excess of $17,122 (SE $2,395; $P < .001$) in total annual health care costs compared with low-OCS users. High-OCS users also had an excess of 7.2 (SE 0.9; $P < .001$) annual office visits and 2.0 (SE 0.2; $P < .001$) annual asthma-related office visits. In patients with asthma and COPD, the OR for all-cause hospitalization in high- vs low-OCS users was 2.03 (95% CI 1.52–2.71) and the OR for

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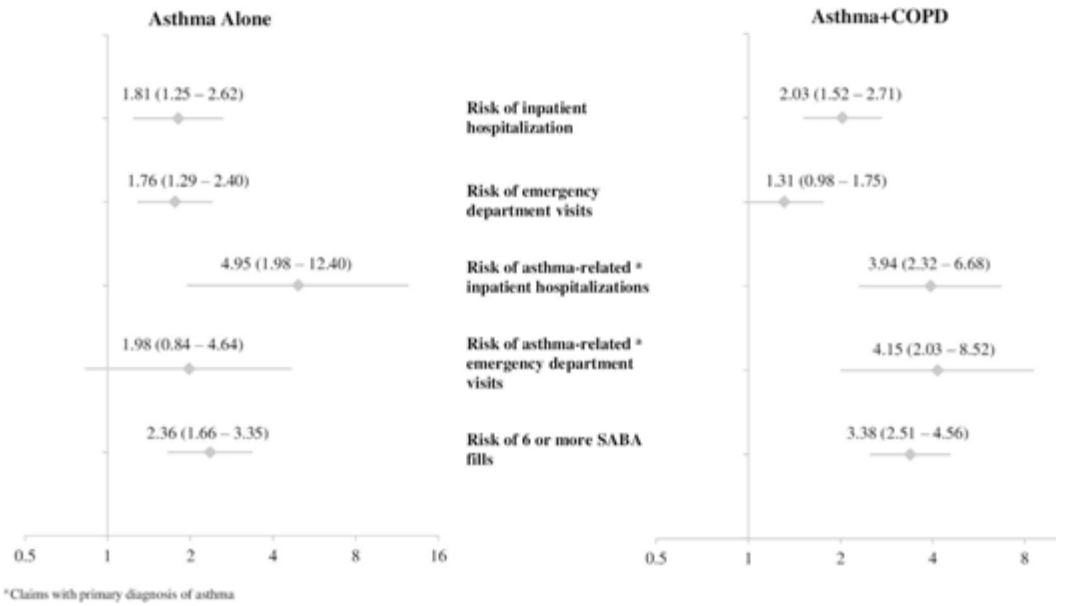

Figure 1. Adjusted odds ratios for high vs low usage of oral corticosteroids. For each listed outcome, diamonds indicate the point estimate for the adjusted odds ratio of that event occurring in high vs low users of oral corticosteroids. Horizontal lines represent the 95% confidence interval of the given odds ratio. SABA, short-acting β_2-agonist.

asthma-related hospitalization was 3.94 (95% CI 2.32–6.68). High-OCS users had an excess of $23,180 (SE $5,422; $P < .001$) in total annual health care costs compared with low-OCS users. They also had an excess of 3.9 (SE 0.9; $P < .001$) annual office visits and 0.8 (SE 0.2; $P < .001$) annual asthma-related office visits.

Oral corticosteroids are associated with significant adverse effects.[2–6] Efforts to decrease OCS use have focused on alternative therapies such as inhaled corticosteroids. Despite the availability of these treatments, our study demonstrates that patients heavily treated with steroids, whether the use is long term (OCS fills ≥30 days in a year) or sporadic (≥6 bursts in a year), have more than double the odds of all-cause hospitalizations and 4 times the odds of asthma-related hospitalizations compared with their low-OCS using counterparts, even after adjusting for multiple patient- and disease-related factors. Results were consistent whether examining patients with asthma alone or those with asthma and COPD. Costs also were dramatically higher in high-OCS users than in low-OCS users—nearly double in patients with asthma alone and more than 40% higher in patients with asthma and COPD.

Limitations include the lack of a direct measurement of disease severity, possible miscoding of asthma and COPD, and missing data. Not all differences between groups could be adjusted for in models. High-OCS users are likely to have worse underlying disease. They also might be insensitive to steroids or nonadherent to other therapy. Thus, our findings do not necessarily suggest that the use of OCSs increases cost or usage. Rather, in patients with asthma with and without COPD, high-OCS exposure could be a marker for disease severity and lack of control with a resultant increase in resource use and costs. Care for these patients by clinicians with significant expertise could decrease usage.

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References

[1] Chu EK, Drazen JM. Asthma: one hundred years of treatment and onward. *Am J Respir Crit Care Med*. 2005;171:1202–1208.
[2] Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M. Glucocorticoid-induced osteoporosis: a systematic review and cost-utility analysis. *Health Technol Assess*. 2007;11. iii–iv, ix–xi, 1–231.
[3] Van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HGM. Public health impact of adverse bone effects of oral corticosteroids. *Br J Clin Pharmacol*. 2002;51:601–607.
[4] Ruiz-Arruza I, Ugarte A, Cabezas-Rodriguez I, Medina J-A, Moran M-A, Ruiz-Irastorza G. Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. *Rheumatology*. 2014;53:1470–1476.
[5] Zazzali JL, Broder MS, Omachi TA, Chang E, Sun GH, Raimundo K. Risk of corticosteroid-related adverse events in asthma patients with high oral corticosteroid use. *Allergy Asthma Proc*. 2015;36:268–274.
[6] Brown HM, Storey G, George WH. Beclomethasone dipropionate: a new steroid aerosol for the treatment of allergic asthma. *Br Med J*. 1972;1:585–590.
[7] Prazma CM, Wenzel S, Barnes N, Douglass JA, Hartley BF, Ortega H. Characterisation of an OCS-dependent severe asthma population treated with mepolizumab. *Thorax*. 2014;69:1141–1142.
[8] O'Neill S, Sweeney J, Patterson CC, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. *Thorax*. 2015;70:376–378.
[9] National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* 2007. Bethesda, MD: National Heart, Lung, and Blood Institute, http://www.ncbi.nlm.nih.gov/books/NBK7232/.
[10] Broder MS, Chang EY, Kamath T, Sapra S. Poor disease control among insured users of high-dose combination therapy for asthma. *Allergy Asthma Proc*. 2010;31:60–67.