

# Burden of Chronic Oral Corticosteroid Use by Adults with Persistent Asthma



Robert S. Zeiger, MD, PhD<sup>a</sup>, Michael Schatz, MD, MS<sup>a</sup>, Qiaowu Li, MS<sup>a</sup>, Wansu Chen, MS, PhD<sup>a</sup>,

Deepak B. Khatry, MS, MA, PhD<sup>b</sup>, and Trung N. Tran, MD, PhD<sup>c</sup> *San Diego and Pasadena, Calif; and Gaithersburg, Md*

**What is already known about this topic?** Chronic oral corticosteroid (C-OCS) use in asthma is an indicator of disease severity, but factors associated with C-OCS use in adults with persistent asthma need to be identified.

**What does this article add to our knowledge?** Patients with asthma requiring C-OCS use have significant disease burden, comorbidities, and elevated blood eosinophil counts. Prior C-OCS use was the strongest independent predictor of future C-OCS use.

**How does this study impact current management guidelines?** Population care management programs need to identify C-OCS users to institute more intensive patient management and treatment.

**BACKGROUND:** Chronic oral corticosteroid (C-OCS) use in asthma is an indicator of disease severity, but its risk factors are largely unknown.

**OBJECTIVE:** To describe patient characteristics and disease burden associated with C-OCS use by adults with persistent asthma.

**METHODS:** We identified 9546 patients aged 18 to 64 years in a large managed care organization who met the Healthcare Effectiveness Data and Information Set 2-year criteria (2009–2010) for persistent asthma. A subgroup had blood eosinophil counts. We calculated cumulative OCS dispensed per patient in 2010 and examined the distribution of disease characteristics by

average daily amounts of OCS dispensed. C-OCS use was defined as 2.5 mg/d or more. Baseline factors (2010) associated with C-OCS use during follow-up (2011) were investigated by multivariable Poisson regression.

**RESULTS:** At baseline, 782 (8.2%) patients were C-OCS users. Compared with patients who received no or less than 2.5 mg/d OCS, C-OCS users were older and more often female and ethnic minorities; and had more comorbidities, asthma specialist care, greater step-care level, controllers, asthma exacerbations, and greater blood eosinophil counts (all  $P < .01$ ). Baseline factors significantly associated with C-OCS use in the follow-up year included (1) demographic characteristics: older age, females, blacks versus whites, and whites versus others/unknown ethnicities; (2) disease burden: more asthma emergency department or hospitalization visits, greater step-care level, excessive short-acting  $\beta_2$ -agonist dispensed, theophylline use, asthma specialist care, and nasal polyposis; (3) greater blood eosinophil counts; and (4) most strongly, C-OCS use.

**CONCLUSIONS:** C-OCS use was associated with more asthma burden, comorbidities, and greater blood eosinophil counts. Prior C-OCS use was the strongest predictor of future C-OCS use. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1050–60)

**Key words:** Administrative data; Corticosteroid; Comorbidities; Allergist; Asthma specialist; Asthma control; Blood eosinophil count; Chronic oral corticosteroid use; Controller medication; Exacerbations; Asthma guidelines; Managed care; Persistent asthma; Short-acting  $\beta_2$ -agonists

Refractory, uncontrolled asthma is estimated to account for less than 5% of all cases of asthma.<sup>1</sup> We have reported a prevalence of severe uncontrolled asthma of 2.4%, defined by 2 or more asthma exacerbations and high controller medication dispensing in a managed care organization.<sup>2</sup> Moreover, patients with severe asthma use more oral corticosteroid (OCS) for their asthma treatment.<sup>2,3</sup> However, patients with frequent or chronic oral corticosteroid (C-OCS) exposure may be refractory to

<sup>a</sup>Departments of Allergy and Research and Evaluation, Kaiser Permanente Southern California, San Diego and Pasadena, Calif

<sup>b</sup>Statistical Sciences, MedImmune LLC, Gaithersburg, Md

<sup>c</sup>Observational Research Center, AstraZeneca, Gaithersburg, Md

AstraZeneca (Gaithersburg, Md) funded a research grant to the Southern California Permanente Medical Group Research and Evaluation Department to perform the study. The sponsor participated in the study discussions and provided comments to the protocol, data analysis, and manuscript.

Conflicts of interest: R. S. Zeiger has received research support from AstraZeneca, Aerocrine, Genentech, MedImmune, and Merck; has received consultancy fees from AstraZeneca, Genentech, Novartis, Teva, GlaxoSmithKline, Theravance BioPharma, and DBV Technologies; and has received personal fees from the AllImmune data monitoring committee. M. Schatz has received research support from AstraZeneca/MedImmune, GlaxoSmithKline, and Merck; has received consultancy fees from GlaxoSmithKline, Amgen, and Boston Scientific; and receives royalties from UpToDate. Q. Li has received research support from AstraZeneca. D. B. Khatry is employed by MedImmune/AstraZeneca; has a patent with MedImmune (patent no. 8961965 granted to MedImmune on February 24, 2015); and has stock and stock options in AstraZeneca. T. N. Tran is employed by AstraZeneca. W. Chen declares no relevant conflicts of interest.

Received for publication November 15, 2016; revised December 13, 2016; accepted for publication December 28, 2016.

Available online February 10, 2017.

Corresponding author: Robert S. Zeiger, MD, PhD, Department of Allergy, Kaiser Permanente Medical Center, 7060 Clairemont Mesa Blvd, San Diego, CA 92111. E-mail: [robert.s.zeiger@kp.org](mailto:robert.s.zeiger@kp.org).

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2016.12.023>

*Abbreviations used*

C-OCS- Chronic oral corticosteroid

ED- Emergency department

GINA- Global Initiative for Asthma

HEDIS- Healthcare Effectiveness Data and Information Set

ICS- Inhaled corticosteroid

OCS- Oral corticosteroid

RR- Risk ratio

SABA- Short-acting  $\beta_2$ -agonist

standard asthma treatments or adhere poorly to present therapy regimens. Regardless of reason, patients requiring high OCS use may be at increased risks for severe exacerbations, as well as increased morbidity and mortality.<sup>3,4</sup> A longitudinal study of patients with asthma at least 12 years of age from a US Medicaid registry who received at least 5 mg of prednisone equivalent per day for 6 months reported a significant exposure-response relationship between C-OCS use and risk of future asthma exacerbations, OCS-associated adverse effects, and cost of care.<sup>4</sup> A confirmatory cross-sectional observational study in the United Kingdom noted that OCS-related adverse effects, including diabetes, osteoporosis, gastric ulcer disease, and cataracts, were more common in severe than in mild to moderate asthma.<sup>3</sup>

We and others have demonstrated that an elevated blood eosinophil count is an independent predictor of future exacerbations in adults<sup>5</sup> and children<sup>6</sup> with persistent asthma in a US managed care cohort and for adolescents and adults with asthma in a UK primary care cohort.<sup>7</sup> Although the eosinopenic effect of OCS is understood,<sup>8,9</sup> it is unknown whether lowering of eosinophil concentrations by chronic OCS use mitigates the relationship of eosinophil concentration as a predictor of asthma exacerbations.

Nevertheless, studies are few and findings are inconsistent for the risks associated with C-OCS use in asthma.<sup>4,10</sup> As such, it is important to determine for adults with persistent asthma the prevalence, patient characteristics, disease burden, comorbidities, and corticosteroid-related complications of C-OCS use, as well as the factors (including blood eosinophil count) that may be associated with future C-OCS use. We hypothesized that prior C-OCS exposure would be the predominant independent predictor of future chronic use for adults with persistent asthma.

## METHODS

### Study population and setting

The present study was a retrospective observational cohort study of adults with persistent asthma.<sup>5</sup> We used longitudinal, administrative pharmacy and health care utilization data captured from the Kaiser Permanente Southern California Research Data Warehouse to identify the study patients (Figure 1, A). The Kaiser Permanente Southern California Institutional Review Board approved the study with waiver of written consent.

We identified 9546 patients aged 18 to 64 years who met the Healthcare Effectiveness Data and Information Set (HEDIS) 2-year criteria (2009 and 2010) for persistent asthma and had continuous health plan enrollment and pharmacy benefit from 2009 to 2011 (no gap of >45 days within each calendar year). The HEDIS definition for persistent asthma required 1 of the following criteria to be met in both calendar years 2009 and 2010: an asthma hospitalization, an asthma emergency department (ED) visit, 4 or more

asthma outpatient visits and 2 or more asthma drugs dispensed, or 4 or more asthma drugs dispensed. Exclusions included encounter diagnoses of chronic obstructive pulmonary disease and other chronic conditions (see this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).<sup>5</sup>

### OCS use determination

OCS use was determined as average daily amount in baseline (2009) and future outcome (2010) years. The average daily amount of OCS dispensed (mg/d) was calculated as follows: The total milligrams of prednisone equivalent for each OCS dispensing were calculated by multiplying the number of pills by their strengths. The total cumulative milligrams of prednisone equivalent dispensed in a year (the sum of all OCS dispensed in a year) was then divided by 365 days to yield the average daily OCS use. Through a sensitivity analyses, we also studied OCS use by examining the number of courses of OCS, captured as the sum of the number of separate OCS dispensed prescriptions. There was no differentiation between OCS courses dispensed for long-term maintenance or for treatment of acute exacerbations.

### Definition of covariates

An asthma exacerbation was defined as either (1) an ED visit or hospitalization with a primary asthma diagnosis or secondary asthma diagnosis with a primary respiratory diagnosis based on *International Classification of Diseases, Ninth Revision* coding or (2) worsening asthma requiring systemic corticosteroids within 7 days before or after an outpatient visit using Kaiser Permanente Southern California extension codes indicating uncontrolled asthma (ie, acute exacerbation, status asthmaticus, acute asthma attack, not controlled asthma, or asthmatic bronchitis). A period of at least 8 days between episodes defined a new exacerbation.<sup>11</sup>

Socioeconomic information, including head of household education level and household income, was determined by geocoding address information to the census block level, and then linking the level to census-based block group-level. Determination of a patient's Global Initiative of Asthma (GINA) medication step-care level and dosage of inhaled corticosteroid (ICS) at baseline (2010) was based on a published algorithm and formula.<sup>12</sup> We determined the number and frequency of asthma controller medication and short-acting  $\beta_2$ -agonists (SABAs) using the number of individual canisters dispensed. Classification of ICS dosing into low, medium, and high dosages was based on National Asthma Education and Prevention Program guidelines. The Asthma Medication Ratio was defined as the number of dispensed asthma controller units (inhaled controller medication canisters or 30-day supplies of oral controller medications) divided by the total number of controller units and SABA canisters dispensed. The Asthma Medication Ratio is a validated administrative-data quality marker predictive of future asthma ED or hospital care.<sup>13</sup> An Asthma Medication Ratio of 0.5 or more is the minimum quality measure cutoff point set by HEDIS to define adequate controller medication dispensing.<sup>14</sup> Prescribing 9 or more units of controllers per year, equivalent to at least 75% adherence,<sup>15</sup> was used as a proxy for adherence to treatment.

Specific comorbidities were determined from *International Classification of Diseases, Ninth Revision* codes (see this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)) and overall comorbidities by Charlson comorbidity index.<sup>16</sup> Asthma-related comorbidities included gastroesophageal reflux disease, pneumonia, rhinitis, chronic sinusitis, acute upper respiratory tract infection, nasal polyps, eczema, and urticaria.<sup>17</sup> Potential OCS-related comorbidities

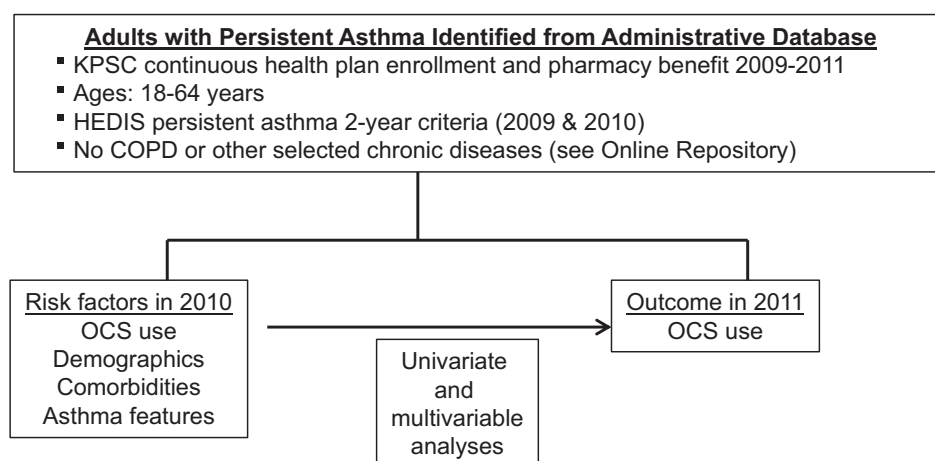
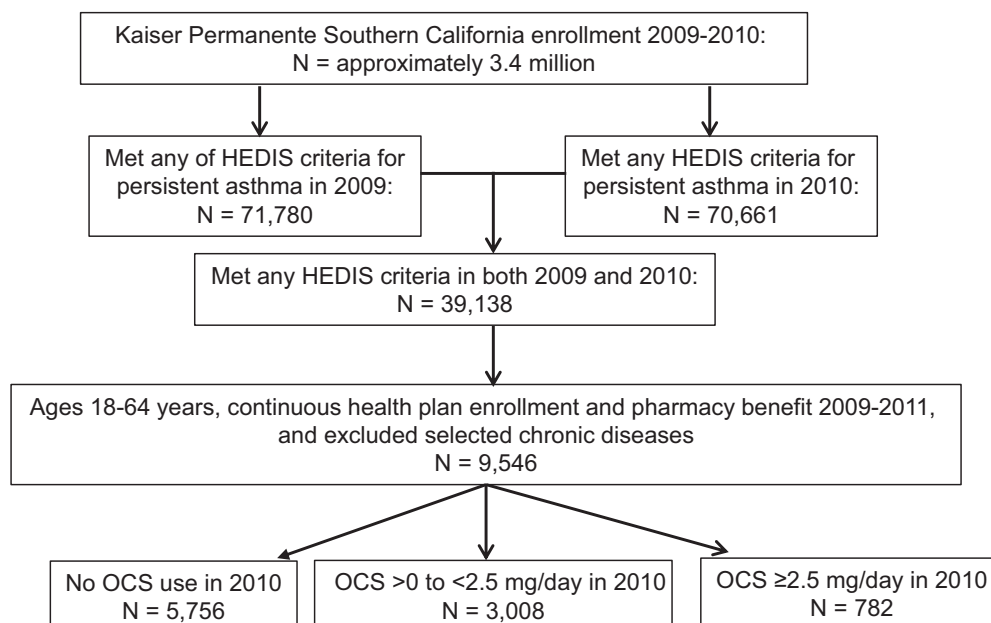
**A Chronic Oral Corticosteroid (OCS) Study Design****B Cohort Identification from Administrative Data**

**FIGURE 1.** Depiction of the study design, administrative logistics for patient identification, and number of patients identified with administrative databases. **A**, Summary of study design. **B**, Administrative algorithm for patient identification of adult persistent asthma cohort and distribution of OCS dispensing in 2010. *COPD*, Chronic obstructive pulmonary disorder; *KPSC*, Kaiser Permanente Southern California.

included adrenal corticosteroid poisoning, glaucoma, cataracts, osteoporosis, fractures, hypertension, infections, anxiety, depression, ulcer disease, and diabetes.<sup>18</sup>

Total peripheral blood eosinophil counts, determined in a subgroup of the cohort, were calculated from the last complete blood cell count with differential obtained in 2010.<sup>5</sup>

### Statistical analyses

Patients' demographic characteristics, comorbidities, asthma clinical characteristics, and blood eosinophil count in 2010 were compared between OCS strata by chi-square and Fisher exact tests

for categorical variables and by Wilcoxon rank sum test for continuous variables. Poisson regression models with a robust error variance were used to fit the data.<sup>12</sup> Quasi-likelihood via the independence model criterion was used to compare models in a stepwise approach. Adjusted risk ratios (RRs) and their 95% CIs for future C-OCS use were then calculated.<sup>19</sup> The covariates determined in 2010, which were considered in model selection, included age (continuous), sex, ethnicity, insurance type, geocoded income, geocoded education (less than high-school diploma vs high-school diploma or higher), enrollment duration (continuous), smoking status, obesity ( $\geq 30$  kg/m<sup>2</sup>), Charlson comorbidity index

**TABLE I.** Description of baseline demographic characteristics and asthma features by average cumulative daily OCS dosages in 2010 for adult patients with persistent asthma

| Baseline demographic characteristics and asthma burden           | Average cumulative daily OCS dosages in 2010<br>Data as N (%) or mean ± SD |                     |                   | P value* |
|------------------------------------------------------------------|----------------------------------------------------------------------------|---------------------|-------------------|----------|
|                                                                  | OCS                                                                        | OCS                 | Total (N = 9,546) |          |
|                                                                  | 0 or <2.5 mg/d (N = 8,764)                                                 | ≥2.5 mg/d (N = 782) |                   |          |
| Demographic characteristics                                      |                                                                            |                     |                   |          |
| Age (y)                                                          | 45.8 ± 12.8                                                                | 48.3 ± 11.3         | 46.0 ± 12.7       | <.001    |
| Sex: female                                                      | 5,357 (61.1)                                                               | 535 (68.4)          | 5,892 (61.7)      | <.001    |
| Ethnicity                                                        |                                                                            |                     |                   | <.001    |
| White                                                            | 4,049 (46.2)                                                               | 307 (39.3)          | 4,356 (45.6)      |          |
| Black                                                            | 1,194 (13.6)                                                               | 120 (15.3)          | 1,314 (13.8)      |          |
| Hispanic                                                         | 2,145 (24.5)                                                               | 244 (31.2)          | 2,389 (25.0)      |          |
| Asian/Pacific Islanders                                          | 679 (7.7)                                                                  | 73 (9.3)            | 752 (7.9)         |          |
| Others, unknown                                                  | 697 (8.0)                                                                  | 38 (4.9)            | 735 (7.7)         |          |
| Estimated household median income by geocoding (\$)              | 68,979 ± 28,943                                                            | 68,192 ± 30,078     | 68,915 ± 29,037   | .31      |
| Estimated family education level up to grade 12 by geocoding (%) | 22.4 ± 17.3                                                                | 23.9 ± 18.6         | 22.5 ± 17.4       | .07      |
| Duration of health plan enrollment (y)                           | 16.2 ± 10.3                                                                | 17.5 ± 10.7         | 16.3 ± 10.4       | <.001    |
| Insurance†                                                       |                                                                            |                     |                   |          |
| Commercial                                                       | 7,868 (89.8)                                                               | 704 (90.0)          | 8,572 (89.8)      | .83      |
| State programs                                                   | 370 (4.2)                                                                  | 35 (4.5)            | 405 (4.2)         | .74      |
| Medicare                                                         | 193 (2.2)                                                                  | 19 (2.4)            | 212 (2.2)         | .68      |
| Private pay                                                      | 496 (5.7)                                                                  | 41 (5.2)            | 537 (5.6)         | .63      |
| Smoking status                                                   |                                                                            |                     |                   | <.001    |
| Yes                                                              | 652 (7.4)                                                                  | 27 (3.5)            | 679 (7.1)         |          |
| Passive                                                          | 103 (1.2)                                                                  | 10 (1.3)            | 113 (1.2)         |          |
| Quit                                                             | 1,993 (22.7)                                                               | 200 (25.6)          | 2,193 (23.0)      |          |
| Never                                                            | 5,432 (62.0)                                                               | 531 (67.9)          | 5,963 (62.5)      |          |
| Missing                                                          | 584 (6.7)                                                                  | 14 (1.8)            | 598 (6.3)         |          |
| Asthma burden                                                    |                                                                            |                     |                   |          |
| Allergist visit                                                  | 1,422 (16.2)                                                               | 315 (40.3)          | 1,737 (18.2)      | <.001    |
| Pulmonologist visit                                              | 290 (3.3)                                                                  | 150 (19.2)          | 440 (4.6)         | <.001    |
| Any asthma specialist visit                                      | 1,654 (18.9)                                                               | 413 (52.8)          | 2,067 (21.7)      | <.001    |
| Global Initiative for Asthma step-care level                     |                                                                            |                     |                   | <.001    |
| 1                                                                | 943 (10.8)                                                                 | 39 (5.0)            | 982 (10.3)        |          |
| 2                                                                | 1,305 (14.9)                                                               | 64 (8.2)            | 1,369 (14.3)      |          |
| 3                                                                | 3,135 (35.8)                                                               | 200 (25.6)          | 3,335 (34.9)      |          |
| 4                                                                | 3,364 (38.4)                                                               | 422 (54.0)          | 3,786 (39.7)      |          |
| 5                                                                | 5 (0.1)                                                                    | 55 (7.0)            | 60 (0.6)          |          |
| Unclassified                                                     | 12 (0.1)                                                                   | 2 (0.3)             | 14 (0.1)          |          |
| ICS                                                              |                                                                            |                     |                   | <.001    |
| Low-dosage                                                       | 1,680 (19.2)                                                               | 103 (13.2)          | 1,783 (18.7)      |          |
| Medium-dosage                                                    | 4,449 (50.8)                                                               | 328 (41.9)          | 4,777 (50.0)      |          |
| High-dosage                                                      | 1,291 (14.7)                                                               | 294 (37.6)          | 1,585 (16.6)      |          |
| None                                                             | 1,344 (15.3)                                                               | 57 (7.3)            | 1,401 (14.7)      |          |
| ICS-long-acting β <sub>2</sub> -agonist                          |                                                                            |                     |                   | <.001    |
| Low-dosage                                                       | 644 (7.3)                                                                  | 48 (6.1)            | 692 (7.2)         |          |
| Medium-dosage                                                    | 1,999 (22.8)                                                               | 181 (23.1)          | 2,180 (22.8)      |          |
| High-dosage                                                      | 993 (11.3)                                                                 | 241 (30.8)          | 1,234 (12.9)      |          |
| None                                                             | 5,128 (58.5)                                                               | 312 (39.9)          | 5,440 (57.0)      |          |
| Leukotriene modifiers                                            | 1,491 (17.0)                                                               | 253 (32.4)          | 1,744 (18.3)      | <.001    |
| Theophylline                                                     | 170 (1.9)                                                                  | 21 (2.7)            | 191 (2.0)         | .15      |
| Omalizumab                                                       | 6 (0.1)                                                                    | 9 (1.2)             | 15 (0.2)          | <.001    |
| Controller equivalent canisters                                  | 7.2 ± 5.7                                                                  | 9.2 ± 6.7           | 7.4 ± 5.8         | <.001    |
| ≥9 equivalent canisters                                          | 3,180 (36.3)                                                               | 356 (45.5)          | 3,536 (37.0)      | <.001    |
| Asthma Medication Ratio, ≥0.5                                    | 5,372 (61.3)                                                               | 488 (62.4)          | 5,860 (61.4)      | .54      |

(continued)

TABLE I. (Continued)

| Baseline demographic characteristics and asthma burden | Average cumulative daily OCS dosages in 2010<br>Data as N (%) or mean $\pm$ SD |                                  |                   | P value* |
|--------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------|-------------------|----------|
|                                                        | OCS<br>0 or <2.5 mg/d (N = 8,764)                                              | OCS<br>$\geq 2.5$ mg/d (N = 782) | Total (N = 9,546) |          |
| $\geq 7$ short-acting $\beta_2$ -agonist canisters     | 2,740 (31.3)                                                                   | 322 (41.2)                       | 3,062 (32.1)      | <.001    |
| Asthma exacerbations                                   |                                                                                |                                  |                   |          |
| Rate                                                   | 0.3 $\pm$ 0.6                                                                  | 1.6 $\pm$ 1.7                    | 0.4 $\pm$ 0.8     | <.001    |
| $\geq 1$                                               | 1,916 (21.9)                                                                   | 512 (65.5)                       | 2,428 (25.4)      | <.001    |
| $\geq 2$                                               | 415 (4.7)                                                                      | 336 (43.0)                       | 751 (7.9)         | <.001    |
| $\geq 1$ ED visit                                      | 491 (5.6)                                                                      | 129 (16.5)                       | 620 (6.5)         | <.001    |
| $\geq 1$ Hospitalization                               | 69 (0.8)                                                                       | 57 (7.3)                         | 126 (1.3)         | <.001    |
| $\geq 1$ ED visit or hospitalization                   | 499 (5.7)                                                                      | 133 (17.0)                       | 632 (6.6)         | <.001    |
| OCS dosage (mg/d)                                      | 0.3 $\pm$ 0.6                                                                  | 5.3 $\pm$ 3.9                    | 0.7 $\pm$ 1.8     | <.001    |
| Eosinophil count determined                            | N = 2,076                                                                      | N = 316                          | N = 2,392         |          |
| cells/mm <sup>3</sup>                                  | 258 $\pm$ 256                                                                  | 299 $\pm$ 404                    | 263 $\pm$ 280     | .13      |
| $\geq 150$ cells/mm <sup>3</sup>                       | 1,317 (63.4)                                                                   | 178 (56.3)                       | 1,495 (62.5)      | .02      |
| $\geq 300$ cells/mm <sup>3</sup>                       | 611 (29.4)                                                                     | 108 (34.2)                       | 719 (30.1)        | .09      |
| $\geq 400$ cells/mm <sup>3</sup>                       | 365 (17.6)                                                                     | 72 (22.8)                        | 437 (18.3)        | .03      |

\*P values determined by chi-square test or Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

†Patients may have more than 1 insurance plan.

(continuous), comorbidities (gastroesophageal reflux, rhinitis, chronic sinusitis, acute respiratory infections, pneumonia, pharyngitis, nasal polyps, eczema, urticaria, and conjunctivitis), medication dispensings (leukotriene modifiers, theophylline, omalizumab, controller canisters, and  $\geq 7$  SABA canisters dispensed), GINA step-care level, history of asthma ED visit or hospitalization, and average cumulative OCS dosages (ie, low, medium, and high). We used separate models for the subgroup of patients who had blood eosinophil counts at cutoff points of 150 cells/mm<sup>3</sup>, 300 cells/mm<sup>3</sup>, and 400 cells/mm<sup>3</sup>, as reported previously.<sup>5</sup> All analyses were conducted using SAS (version 9.3 for Unix, SAS Institute, Cary, NC). Statistical significance was set at a P value of .05 (2-sided).

## RESULTS

### Study patients

The study cohort consisted of 9546 adults with persistent asthma (Figure 1, B). Patients were on average aged 46.0  $\pm$  12.7 years, with the majority being women (61.7%) and nonwhite (54.4%). Median household income was \$68,915  $\pm$  \$29,037, and mean duration of health plan membership was 16.3  $\pm$  10.4 years.

### Determination of C-OCS use

Of the study patients, 3790 of 9546 (39.7%) were dispensed OCS in 2010. Initially, average daily OCS use was classified by 5 strata: no OCS dispensed, more than 0 to less than 2.5 mg/d, 2.5 or more to less than 5 mg/d, 5 or more to less than 7.5 mg/d, and 7.5 mg/d or more, to determine trends in asthma disease characteristics and comorbidities by increments of daily OCS usage at baseline (see Table E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Grouping the study cohort by 2.5-mg/d increments of OCS dispensed in 2010 revealed significant demographic, comorbidity, and asthma burden differences between the 5 subgroups, with greater dosages associated with more comorbidities and asthma burden (Table E1).

From the distribution of asthma characteristics and comorbidities by the 5-strata classification of daily OCS dosages at baseline, a dosage of 2.5 mg/d or more was selected as the

clinically relevant cutoff for C-OCS, consistent with previous studies of corticosteroid-related adverse effects with an average use of at least 2.5 mg/d.<sup>20-22</sup>

For sensitivity analyses, the number of courses was stratified initially into 4 levels: none, 1 to 3 courses, 4 or 5 courses, and 6 or more courses (see Table E2 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Increasing courses of OCS, like observed for increasing OCS dosages (Table E1), were associated with increasing comorbidities, asthma burden, and blood eosinophil characteristics (Table E2). C-OCS use was defined as 4 or more courses per year on the basis of the clinical relevance of this cutoff (Table E2) and the small number of patients in the 5 or more category.

### Characteristics, comorbidities, and asthma burden associated with C-OCS

Of the study cohort, 782 (8.2%) were defined as C-OCS with at least 2.5 mg/d OCS dispensed in 2010. Compared with patients with nonchronic OCS, patients with C-OCS were more likely to have been older, female, of nonwhite ethnicity, have had a greater duration of health plan membership, and have been less likely to be smokers (all  $P < .01$ ) (Table I). Those with C-OCS were also more likely to have had asthma specialist care, greater GINA step-care level, more use of asthma controller medication (ICS, ICS/long-acting  $\beta_2$ -agonist; combination, theophylline, and omalizumab), more excessive SABA use, and more asthma exacerbations, including ED visits and hospitalizations (all  $P < .01$ ) (Table I). In the subgroup of 2392 patients (25.1% of the cohort) with blood eosinophil determination, greater daily OCS use was associated with greater eosinophil count (at  $\geq 400$  cells/mm<sup>3</sup> cutoff point) ( $P = .03$ ) (Table I).

Compared with nonchronic OCS users, those who were C-OCS users at baseline were more likely to have had asthma-related comorbidities, including gastroesophageal reflux, pneumonia, rhinitis, nasal polyps, and eczema, as well as more corticosteroid-related complications, including adrenal corticosteroid poisoning,

**TABLE II.** Asthma and OCS-related comorbidities by average cumulative daily OCS dosages in 2010 for adult patients with persistent asthma

| Comorbidities                            | Average cumulative daily OCS dosages in 2010 |                                  |                   | P value* |
|------------------------------------------|----------------------------------------------|----------------------------------|-------------------|----------|
|                                          | Data as N (%) or mean $\pm$ SD               |                                  |                   |          |
|                                          | OCS<br>0 or <2.5 mg/d (N = 8,764)            | OCS<br>$\geq 2.5$ mg/d (N = 782) | Total (N = 9,546) |          |
| Asthma-related comorbidities             |                                              |                                  |                   |          |
| Charlson comorbidity index               | 1.0 $\pm$ 0.8                                | 1.3 $\pm$ 0.7                    | 1.1 $\pm$ 0.8     | <.001    |
| Body mass index (kg/m <sup>2</sup> )     | 31.2 $\pm$ 7.7                               | 32.5 $\pm$ 8.1                   | 31.3 $\pm$ 7.7    | <.001    |
| Obesity $\geq 30$ kg/m <sup>2</sup>      | 4,198 (47.9)                                 | 443 (56.6)                       | 4,641 (48.6)      | <.001    |
| Missing                                  | 213 (2.4)                                    | 4 (0.5)                          | 217 (2.3)         |          |
| Gastroesophageal reflux disease          | 1,215 (13.9)                                 | 231 (29.5)                       | 1,446 (15.1)      | <.001    |
| Pneumonia                                | 235 (2.7)                                    | 74 (9.5)                         | 309 (3.2)         | <.001    |
| Rhinitis                                 | 2,492 (28.4)                                 | 394 (50.4)                       | 2,886 (30.2)      | <.001    |
| Chronic sinusitis                        | 1,135 (13.0)                                 | 241 (30.8)                       | 1,376 (14.4)      | <.001    |
| Acute upper respiratory tract infections | 1,150 (13.1)                                 | 194 (24.8)                       | 1,344 (14.1)      | <.001    |
| Nasal polyps                             | 107 (1.2)                                    | 54 (6.9)                         | 161 (1.7)         | <.001    |
| Eczema                                   | 159 (1.8)                                    | 30 (3.8)                         | 189 (2.0)         | <.001    |
| Urticaria                                | 165 (1.9)                                    | 19 (2.4)                         | 184 (1.9)         | .29      |
| Corticosteroid-related comorbidities     |                                              |                                  |                   |          |
| Poisoning by adrenal corticosteroids     | 11 (0.1)                                     | 12 (1.5)                         | 23 (0.2)          | <.001    |
| Cataracts                                | 363 (4.1)                                    | 45 (5.8)                         | 408 (4.3)         | .03      |
| Glaucoma                                 | 181 (2.1)                                    | 22 (2.8)                         | 203 (2.1)         | .16      |
| Osteoporosis                             | 259 (3.0)                                    | 39 (5.0)                         | 298 (3.1)         | .002     |
| Fractures                                | 419 (4.8)                                    | 59 (7.5)                         | 478 (5.0)         | <.001    |
| Hypertension                             | 2,566 (29.3)                                 | 298 (38.1)                       | 2,864 (30.0)      | <.001    |
| Infections                               | 1,451 (16.6)                                 | 192 (24.6)                       | 1,643 (17.2)      | <.001    |
| Anxiety                                  | 928 (10.6)                                   | 127 (16.2)                       | 1,055 (11.1)      | <.001    |
| Depression                               | 1,082 (12.3)                                 | 102 (13.0)                       | 1,184 (12.4)      | .57      |
| Diabetes                                 | 957 (10.9)                                   | 94 (12.0)                        | 1,051 (11.0)      | .35      |
| Ulcer disease                            | 19 (0.2)                                     | 6 (0.8)                          | 25 (0.3)          | .004     |

\*P values determined by chi-square test or Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

cataracts, osteoporosis, fractures, hypertension, infections, anxiety, and ulcer disease (all  $P < .05$ ) (Table II).

With 4 or more OCS courses per year as an indicator for C-OCS use, 429 (4.5%) of the cohort had 4 or more OCS courses in 2010 (see Table E3 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Of those 429 patients with 4 or more courses of OCS, 377 (87.9%) also had an average cumulative dosage of 2.5 mg/d OCS or more in 2010. Compared with 0 to 3 courses of OCS in 2010, patients with C-OCS defined as 4 or more courses in 2010 had more asthma comorbidities, greater blood eosinophil counts, and asthma burden (Table E3), like that observed for patients with C-OCS defined as 2.5 mg/d or more in 2010.

### Relationship of baseline characteristics to future C-OCS use

**Univariate analyses.** The following characteristics in 2010 were associated with future C-OCS use in 2011: (1) demographic characteristics (increasing age, female sex, nonwhite ethnicity, and less current smoking), (2) comorbidities (Charlson comorbidity index, obesity, gastroesophageal reflux disease, rhinitis, chronic sinusitis, and nasal polyp disease); and (3) asthma burden (asthma specialist care,  $\geq 7$  dispensed SABA canisters, asthma controller use, greater GINA step-care level, asthma exacerbations including ED visits and hospitalizations, and prior OCS use) (all  $P < .001$ ;

Table III). For the subset of the study cohort who had blood eosinophils evaluated, greater blood eosinophil counts (at  $\geq 300$  cells/mm<sup>3</sup> and  $\geq 400$  cells/mm<sup>3</sup> cutoff points) were associated with C-OCS ( $P < .001$ ) (Table III). The sensitivity analyses using 4 or more courses of OCS in 2011 indicated similar findings (see Table E4 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

**Multivariable analyses.** Prior C-OCS use ( $\geq 2.5$  mg/d) was a strong risk factor for future C-OCS use compared with no prior OCS use (RR, 13.69; 95% CI, 11.03-16.99) and with prior OCS use of more than 0 to less than 2.5 mg/d (RR, 4.56; 95% CI, 3.89-5.35) (Figure 2). Other baseline variables associated with increased risk of future C-OCS use were increasing age (RR, 1.01; 95% CI, 1.00-1.02), nasal polyp disease (RR, 1.58; 95% CI, 1.24-2.03), 7 or more SABA canisters dispensed (RR, 1.28; 95% CI, 1.12-1.47), theophylline use (RR, 1.44; 95% CI, 1.09-1.91), GINA step-care level 4 or 5 versus 1 or 2 (RR, 1.29; 95% CI, 1.06-1.57), and asthma specialist care (RR, 1.27; 95% CI, 1.09-1.47) (Figure 2). Those patients with private insurance (vs those without) and those with other or unknown ethnicity (vs white) had a lesser risk of future C-OCS (RR, 0.71; 95% CI, 0.53-0.96 and RR, 0.58; 95% CI, 0.38-0.88, respectively) (Figure 2).

From sensitivity analyses with C-OCS outcome defined as 4 or more OCS courses in 2011, 4 or more OCS courses versus

**TABLE III.** Unadjusted analysis of association of baseline variables in 2010 and average cumulative daily OCS dosages in 2011 for adults with persistent asthma (N = 9,546)

| Baseline variables                                 | Average cumulative daily OCS dosages in 2011<br>Data as N (%) or mean $\pm$ SD |                                  | P value* |
|----------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------|----------|
|                                                    | OCS<br>0 or <2.5 mg/d (N = 8,838)                                              | OCS<br>$\geq 2.5$ mg/d (N = 708) |          |
| Age (y)                                            | 45.8 $\pm$ 12.8                                                                | 48.3 $\pm$ 11.5                  | <.001    |
| Sex: female                                        | 5,397 (61.1)                                                                   | 495 (69.9)                       | <.001    |
| Ethnicity                                          |                                                                                |                                  | <.001    |
| White                                              | 4,056 (45.9)                                                                   | 300 (42.4)                       |          |
| Black                                              | 1,189 (13.5)                                                                   | 125 (17.7)                       |          |
| Hispanic                                           | 2,196 (24.8)                                                                   | 193 (27.3)                       |          |
| Asian/Pacific Islanders                            | 685 (7.8)                                                                      | 67 (9.5)                         |          |
| Others/unknown                                     | 712 (8.1)                                                                      | 23 (3.2)                         |          |
| Education: geocoded up to grade 12 (%)             | 22.4 $\pm$ 17.4                                                                | 23.3 $\pm$ 17.7                  | .12      |
| Enrollment duration (y)                            | 16.2 $\pm$ 10.4                                                                | 17.7 $\pm$ 10.6                  | <.001    |
| Private insurance                                  | 510 (5.8)                                                                      | 27 (3.8)                         | .03      |
| Current smoking                                    | 655 (7.4)                                                                      | 24 (3.4)                         | <.001    |
| Missing                                            | 580 (6.6)                                                                      | 18 (2.5)                         |          |
| Charlson comorbidity index                         | 1.0 $\pm$ 0.8                                                                  | 1.2 $\pm$ 0.8                    | <.001    |
| Obesity, $\geq 30$ kg/m <sup>2</sup>               | 4,262 (48.2)                                                                   | 379 (53.5)                       | .002     |
| Missing                                            | 211 (2.4)                                                                      | 6 (0.8)                          |          |
| Gastroesophageal reflux disease                    | 1,276 (14.4)                                                                   | 170 (24.0)                       | <.001    |
| Rhinitis                                           | 2,556 (28.9)                                                                   | 330 (46.6)                       | <.001    |
| Chronic sinusitis                                  | 1,187 (13.4)                                                                   | 189 (26.7)                       | <.001    |
| Nasal polyp disease                                | 115 (1.3)                                                                      | 46 (6.5)                         | <.001    |
| Eczema                                             | 165 (1.9)                                                                      | 24 (3.4)                         | .005     |
| Asthma specialist visit                            | 1,755 (19.9)                                                                   | 312 (44.1)                       | <.001    |
| $\geq 7$ short-acting $\beta_2$ -agonist canisters | 2,777 (31.4)                                                                   | 285 (40.3)                       | <.001    |
| Leukotriene modifiers                              | 1,536 (17.4)                                                                   | 208 (29.4)                       | <.001    |
| Theophylline                                       | 164 (1.9)                                                                      | 27 (3.8)                         | <.001    |
| Omalizumab                                         | 10 (0.1)                                                                       | 5 (0.7)                          | .004     |
| Global Initiative for Asthma step-care level       |                                                                                |                                  | <.001    |
| 1 or 2                                             | 2,246 (25.4)                                                                   | 105 (14.8)                       |          |
| 3                                                  | 3,140 (35.5)                                                                   | 195 (27.5)                       |          |
| 4 or 5                                             | 3,440 (38.9)                                                                   | 406 (57.3)                       |          |
| Unclassified                                       | 12 (0.1)                                                                       | 2 (0.3)                          |          |
| Asthma Medication Ratio, $\geq 0.5$                | 5,405 (61.2)                                                                   | 455 (64.3)                       | .10      |
| Asthma exacerbations                               |                                                                                |                                  |          |
| $\geq 1$                                           | 2,083 (23.6)                                                                   | 345 (48.7)                       | <.001    |
| $\geq 2$                                           | 561 (6.3)                                                                      | 190 (26.8)                       | <.001    |
| $\geq 1$ ED visit or hospitalization               | 527 (6.0)                                                                      | 105 (14.8)                       | <.001    |
| OCS dispensed, average cumulative dosage           |                                                                                |                                  | <.001    |
| None                                               | 5,625 (63.6)                                                                   | 131 (18.5)                       |          |
| >0-<2.5 mg/d                                       | 2,770 (31.3)                                                                   | 238 (33.6)                       |          |
| $\geq 2.5$ mg/d                                    | 443 (5.0)                                                                      | 339 (47.9)                       |          |
| OCS dispensed, courses                             |                                                                                |                                  | <.001    |
| None                                               | 5,625 (63.6)                                                                   | 131 (18.5)                       |          |
| 1-3                                                | 2,995 (33.9)                                                                   | 366 (51.7)                       |          |
| $\geq 4$                                           | 218 (2.5)                                                                      | 211 (29.8)                       |          |
| Eosinophil count (cells/mm <sup>3</sup> )          | N = 2,153                                                                      | N = 239                          |          |
| cells/mm <sup>3</sup>                              | 252 $\pm$ 257                                                                  | 362 $\pm$ 426                    | .02      |
| $\geq 150$ cells/mm <sup>3</sup>                   | 1,336 (62.1)                                                                   | 159 (66.5)                       | .18      |
| $\geq 300$ cells/mm <sup>3</sup>                   | 623 (28.9)                                                                     | 96 (40.2)                        | <.001    |
| $\geq 400$ cells/mm <sup>3</sup>                   | 368 (17.1)                                                                     | 69 (28.9)                        | <.001    |

\*P values determined by chi-square test or Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

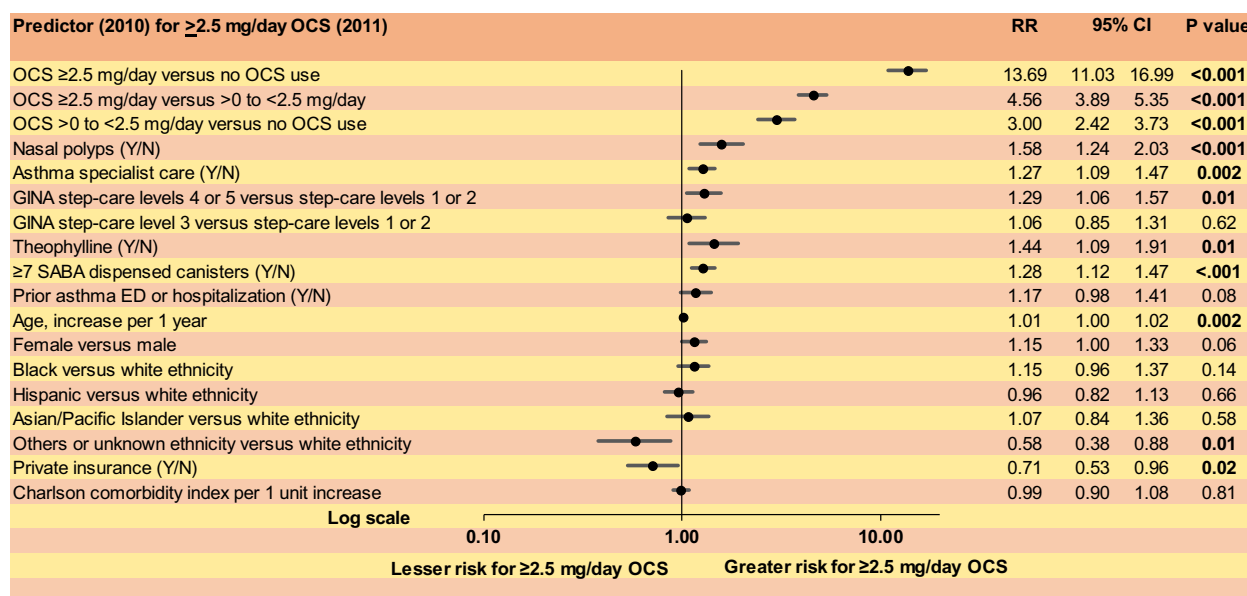


**FIGURE 2.** Adjusted RR (95% CI) for C-OCS use, defined as 2.5 mg/d in 2011, for each covariate (predictor) determined in 2010 in the regression model in 9546 adult patients with persistent asthma. Poisson regression models with robust error variance were used to estimate the adjusted RR and their 95% CIs. N, No; Y, yes.

both no OCS use and versus 0 to 3 courses at baseline (2010) was a strong risk factor for future C-OCS use in 2011 (RR, 23.05; 95% CI, 16.69-31.83 and RR, 5.15; 95% CI, 4.18-6.36, respectively) (Figure 3). Other baseline characteristics statistically significant in the multivariable model included increasing age, black versus white ethnicity, chronic sinusitis, asthma specialist care, and 7 or more SABA canisters dispensed (Figure 3).

**Blood eosinophils.** In multivariable analyses of the subgroup with baseline blood eosinophil counts, greater blood eosinophil counts in 2010 ( $\geq 150$  cells/mm<sup>3</sup>,  $\geq 300$  cells/mm<sup>3</sup>, and  $\geq 400$  cells/mm<sup>3</sup>) were all associated with increased risk for future C-OCS use, defined as 2.5 mg/d or more (all  $P < .01$ ; Figure 4). Prior C-OCS use, increasing age, white versus other/unknown ethnicities, theophylline use, and asthma ED visit or hospitalization in the previous year were associated with an increased risk for future C-OCS use (see Figure E1 for eosinophil cutoff point of 400 cells/mm<sup>3</sup>). The same covariates were found significant for the 150 cells/mm<sup>3</sup> or more and 300 cells/mm<sup>3</sup> or more cutoffs (data not shown).

Similar to the above findings, sensitivity analyses for 4 or more courses per year for C-OCS determination indicated that blood eosinophil cutoff points at 300 cells/mm<sup>3</sup> or more and 400 cells/mm<sup>3</sup> or more were associated with future C-OCS ( $P < .05$ ; Figure 4). Only previous frequent OCS courses and elevated eosinophil counts of 300 cells/mm<sup>3</sup> or more and 400 cells/mm<sup>3</sup> or more were associated with future C-OCS use, defined as 4 or more OCS courses per year (see Figure E2 for the 400 cells/mm<sup>3</sup> cutoff point and data not shown for 300 cells/mm<sup>3</sup>).

## DISCUSSION

Chronic OCS use at baseline, either defined as 2.5 mg/d or more (Figure 2) or as 4 or more OCS courses per year (Figure 3), was a strong independent risk factor for future C-OCS use in a managed care setting, with controlling for potential confounders.

After receiving greater dosages or more courses of OCS, patients were more likely to have continued to receive them in the future. In addition, associations between C-OCS use and nasal polyp disease, chronic sinusitis, excessive SABA use, and GINA step-care level 4 or 5 remained statistically significant in the final model.<sup>2,5</sup>

We found that increasing dosages (Table E1), increasing courses (Table E2), and C-OCS use (Table I) were associated with greater degrees of asthma burden and corticosteroid-related comorbidities.<sup>3,4</sup> Specifically, patients with persistent asthma with an average daily OCS use of at least 2.5 mg/d during a year or at least 4 OCS courses per year exhibited greater prevalences of several corticosteroid-related comorbidities, including cataracts, fractures, hypertension, infections, ulcer disease, and anxiety (see Tables II and E3). Our findings are consistent with a recent large commercial claims database study that reported a dose-response relationship between long-term systemic corticosteroid use and related complications in patients with severe asthma compared with patients without OCS use.<sup>23</sup> The absolute frequency of the corticosteroid-related comorbidities we found may be different than those observed in other studies,<sup>3,4,23</sup> because of the exclusion of many diseases in establishing the cohort of adults with persistent asthma in the present study and selection of a lesser C-OCS cutoff point. Nonetheless, the more frequent occurrence of corticosteroid-related comorbidities with both increasing amounts of OCS dispensed and number of OCS courses we observed attest to the importance of these associations. Moreover, these findings highlight the need and opportunity of health plans and providers to identify proactively C-OCS users for whom more intensive asthma and comorbidity management could be implemented to reduce C-OCS use.

Similar to previous studies that also revealed the relationships between elevated blood eosinophil counts at baseline and increased risk of future exacerbations for adolescents and adults with persistent asthma,<sup>5,7</sup> we found a relationship between

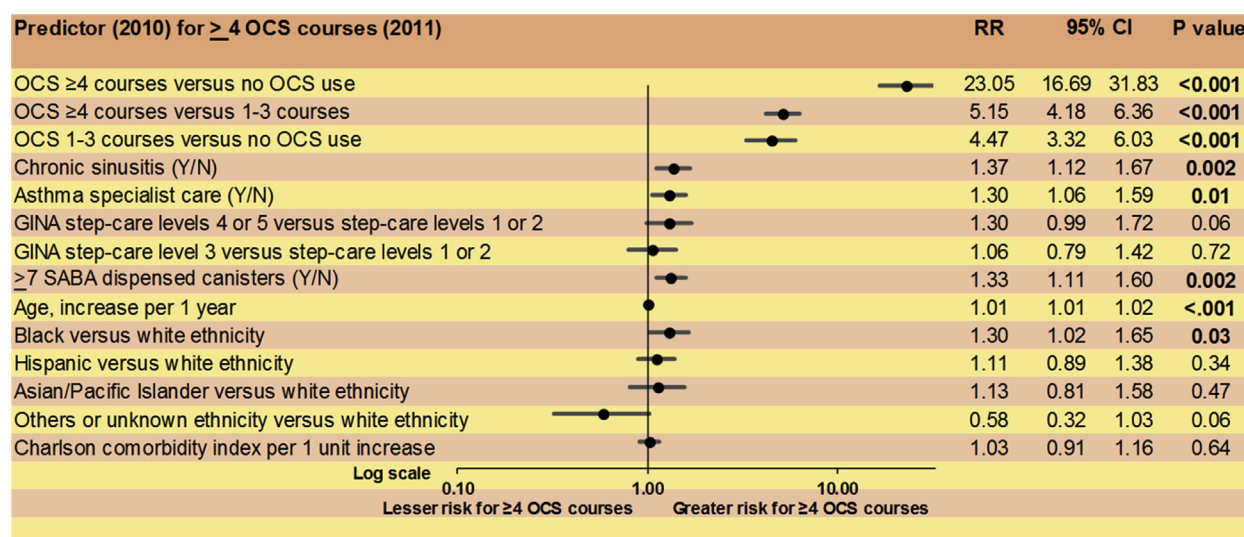


**FIGURE 3.** Sensitivity analysis for OCS use stratified as 4 or more OCS courses or 1 to 3 OCS courses in 2011. Adjusted RRs (95% CI) for each covariate (predictor) determined in 2010 in the regression model in 9546 adult patients with persistent asthma. Poisson regression models with robust error variance was used to estimate the adjusted RRs and their 95% CIs. *N*, No; *Y*, yes.

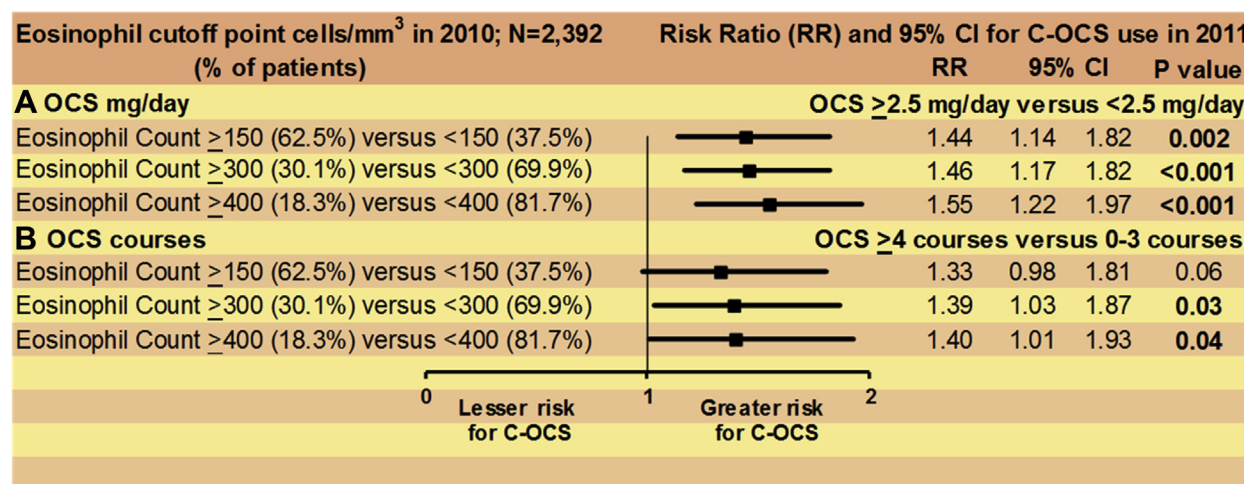


**FIGURE 4.** Adjusted RR (95% CI) of various eosinophil cutoffs in 2010 on C-OCS as 2.5 mg/d or more (A) or 4 or more courses (B) in 2011 in subgroup (N = 2392) with a blood eosinophil count in 2010. Poisson regression models with robust error variance were used to estimate the adjusted RR and their 95% CIs. Candidate variables include age (continuous), female versus male, ethnicity (black, Asian Hispanic, and others/unknown separately vs white), private pay insurance (Y/N), Charlson comorbidity index, nasal polyp (Y/N), asthma specialist care (Y/N), 7 or more SABA canisters (Y/N), theophylline (Y/N), GINA step-care levels 4 or 5 (high) and 3 (moderate) separately versus 1 or 2 (low), OCS use in mg/d or courses, blood eosinophil cutoff point, and 1 or more asthma ED visit or hospitalization in 2010. Eosinophil count of 400 or more is used for model selection, then selected variables were used for eosinophil cutoffs for 150 cells/mm<sup>3</sup> and 300 cells/mm<sup>3</sup> models. *N*, No; *Y*, yes.

elevated baseline blood eosinophil counts and increased risk of future C-OCS use, albeit at even lower eosinophil counts. Although most future OCS use may have been for the treatment of asthma exacerbations, this finding helps confirm the role of elevated blood eosinophils in determining overall asthma severity.

Population care management represents an important process to improve asthma care and reduce asthma burden. The present study supports the addition of C-OCS use to the risk factors used to identify high-risk patients with asthma.<sup>24,25</sup> Computerized

programs for real-time identification of C-OCS use need development in medical organizations and practices with access to electronic pharmacy or medical data, as noted previously, for excessive SABA use or asthma exacerbations.<sup>26</sup> Other risk factors already identified epidemiologically and simply captured from administrative health care databases include minority ethnicity, obesity, smoking, previous asthma disease burden (exacerbations, ED visits and hospitalization, SABA overuse, high GINA step care), and inadequate adherence.<sup>27-29</sup>

Limitations of the study include its retrospective, observational design. The lack of spirometry data, conducted only for a minority of the present cohort, limits the specificity of the asthma diagnosis. However, identification of the cohort using the 2-year HEDIS criteria for persistent asthma based on asthma diagnosis by *International Classification of Diseases, Ninth Revision* coding, coding of asthma ED visits and hospitalization, and dispensed asthma medications is an accepted administrative definition of persistent asthma.<sup>30</sup> Although we included all available covariates, some relevant variables for adjustment were not available in the administrative data we used. As is also common to all administrative data studies, dependability of diagnostic coding rests on the consistency and accuracy of coding by providers or coders. Our managed care organization has ongoing educational programs to enhance optimal coding by provider and trained coders. For the present study, it was important to relate cumulative amounts or courses of OCS dispensed to the overall burden of C-OCS, acknowledging that although the OCS was dispensed for patients with persistent asthma, not all OCS dispensed was specifically for asthma. The study cannot be generalized to all adults with persistent asthma, because its design excluded many chronic diseases and conditions that patients with asthma also experience, especially autoimmune diseases, immune deficiency, transplantations, immunosuppressive treatments, cancer, HIV, drug addiction, and major psychiatric disorders. Moreover, the study was conducted in a managed care organization that has many proactive asthma population management programs to reduce asthma burden,<sup>25,31-34</sup> which may have impacted the actual prevalence of C-OCS use in the present study. In addition, the C-OCS use in our study may be different from C-OCS use for patients with persistent asthma in non-managed care settings.

In summary, using comprehensive health care and pharmacy databases, we demonstrated that about 8% of adults with persistent asthma were C-OCS users, defined as an average OCS dispensing of at least 2.5 mg/d. C-OCS users experienced more asthma disease burden and corticosteroid-related comorbidities, and had greater blood eosinophil counts. Moreover, C-OCS use was the major independent predictor of future C-OCS use. These findings strongly support real-time identification of C-OCS users, which should prompt physicians to implement more aggressive asthma management to reduce C-OCS use.

We thank Joanna S. Zeiger, MS, PhD, for assistance in creating the forest plots.

## REFERENCES

1. Proceedings of the ATS Workshop on Refractory Asthma: current understanding, recommendations, and unanswered questions. *Am J Respir Crit Care Med* 2000;162:2341-51.
2. Zeiger RS, Schatz M, Dalal AA, Qian L, Chen W, Ngor EW, et al. Utilization and costs of severe uncontrolled asthma in a managed-care setting. *J Allergy Clin Immunol Pract* 2015;4:120-9.
3. Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax* 2016;71:339-46.
4. Lefebvre P, Duh MS, Lefeuvre MH, Gozalo L, Desai U, Robitaille MN, et al. Acute and chronic systemic corticosteroid-related complications in patients with severe asthma. *J Allergy Clin Immunol* 2015;136:1488-95.
5. Zeiger RS, Schatz M, Li Q, Chen W, Gossage D, Khatry D, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. *J Allergy Clin Immunol Pract* 2014;2:741-50.
6. Zeiger RS, Schatz M, Li Q, Chen W, Khatry DB, Gossage D, et al. The association of blood eosinophil counts to future asthma exacerbations in children with persistent asthma. *J Allergy Clin Immunol Pract* 2015;3:283-7.
7. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015;3:849-58.
8. Kellegren J, Janus O. The eosinopenic response to cortisone and ACTH in normal subjects. *BMJ* 1951;2:1183-7.
9. Fleishaker DL, Mukherjee A, Whaley FS, Daniel S, Zeiger BG. Safety and pharmacodynamic dose response of short-term prednisone in healthy adult subjects: a dose ranging, randomized, placebo-controlled, crossover study. *BMC Musculoskelet Disord* 2016;17:293.
10. Sarnes E, Crofford L, Watson M, Dennis G, Kan H, Bass D. Incidence and US costs of corticosteroid-associated adverse events: a systematic literature review. *Clin Ther* 2011;33:1413-32.
11. Zeiger RS, Schatz M, Zhang F, Crawford WW, Kaplan MS, Roth RM, et al. Elevated exhaled nitric oxide is a clinical indicator of future uncontrolled asthma in asthmatic patients on inhaled corticosteroids. *J Allergy Clin Immunol* 2011;128:412-4.
12. Zeiger RS, Schatz M, Li Q, Zhang F, Purdum AS, Chen W. Step-up care improves impairment in uncontrolled asthma: an administrative data study. *Am J Manag Care* 2010;16:897-906.
13. Schatz M, Zeiger RS, Vollmer WM, Mosen D, Mendoza G, Apter AJ, et al. The controller-to-total asthma medication ratio is associated with patient-centered as well as utilization outcomes. *Chest* 2006;130:43-50.
14. National Committee of Quality Assurance. HEDIS quality measurements. Available from: <http://www.ncqa.org/HEDISQualityMeasurement.aspx>. 2015. Accessed April 19, 2015.
15. US Department of Health and Human Services - Agency for Healthcare Research and Quality. National Quality Measures Clearinghouse. <http://www.qualitymeasures.ahrq.gov/content.aspx?id=47173&search=Anti-Asthmatic+Agents>. 2014. Accessed April 19, 2015.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
17. Lee HY, Ye YM, Kim SH, Ban GY, Kim JH, et al. Identification of phenotypic clusters of nonsteroidal anti-inflammatory drugs exacerbated respiratory disease. *Allergy* 2017;72:616-26.
18. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol* 2013;9:30.
19. Pan W. Akaike's information criterion in generalized estimating equations. *Biometrics* 2001;57:120-5.
20. van Staa TP, Leufkens HG, Abenham L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000;15:993-1000.
21. van Staa TP. The pathogenesis, epidemiology and management of glucocorticoid-induced osteoporosis. *Calcif Tissue Int* 2006;79:129-37.
22. Civitelli R, Zimbaras K. Epidemiology of glucocorticoid-induced osteoporosis. *J Endocrinol Invest* 2008;31:2-6.
23. Dalal AA, Duh MS, Gozalo L, Robitaille MN, Albers F, Yancey S, et al. Dose-response relationship between long-term systemic corticosteroid use and related complications in patients with severe asthma. *J Manag Care Spec Pharm* 2016;22:833-47.
24. Schatz M, Stempel D. Asthma quality-of-care measures using administrative data: relationships to subsequent exacerbations in multiple databases. *Ann Allergy Asthma Immunol* 2008;101:235-9.
25. Schatz M, Zeiger RS. Improving asthma outcomes in large populations. *J Allergy Clin Immunol* 2011;128:273-7.
26. Zeiger RS, Schatz M, Li Q, Solari PG, Zazzali JL, Chen W. Real-time asthma outreach reduces excessive short-acting beta2-agonist use: a randomized study. *J Allergy Clin Immunol Pract* 2014;2:445-56. e1-5.
27. Schatz M. Predictors of asthma control: what can we modify? *Curr Opin Allergy Clin Immunol* 2012;12:263-8.
28. Schatz M, Zeiger RS, Zhang F, Chen W, Yang SJ, Carmargo CA. Overweight/obesity and risk of seasonal asthma exacerbations. *J Allergy Clin Immunol Pract* 2013;1:618-22.
29. Tsai CL, Delclos GL, Huang JS, Hanania NA, Camargo CA Jr. Age-related differences in asthma outcomes in the United States, 1988-2006. *Ann Allergy Asthma Immunol* 2013;110:240-6. e1.
30. Mosen DM, Macy E, Schatz M, Mendoza G, Stibolt TB, McGaw J, et al. How well do the HEDIS asthma inclusion criteria identify persistent asthma? *Am J Manag Care* 2005;11:650-4.

31. Schatz M, Zeiger RS, Mosen D, Apter AJ, Vollmer WM, Stibolt TB, et al. Improved asthma outcomes from allergy specialist care: a population-based cross-sectional analysis. *J Allergy Clin Immunol* 2005;116:1307-13.
32. Schatz M, Cook EF, Nakahiro R, Petitti D. Inhaled corticosteroids and allergy specialty care reduce emergency hospital use for asthma. *J Allergy Clin Immunol* 2003;111:503-8.
33. Zeiger RS, Heller S, Mellon MH, Wald J, Falkoff R, Schatz M. Facilitated referral to asthma specialist reduces relapses in asthma emergency room visits. *J Allergy Clin Immunol* 1991;87:1160-8.
34. Vollmer WM, Feldstein A, Smith DH, Dubanoski JP, Waterbury A, Schneider JL, et al. Use of health information technology to improve medication adherence. *Am J Manag Care* 2011;17:SP79-87.

## METHODS

Exclusions: encounter diagnoses of chronic obstructive lung disease, emphysema, cystic fibrosis, chronic bronchitis, bronchiectasis, Churg Strauss, Wegener's, sarcoidosis, pulmonary hypertension, cerebral palsy, transplantation of major organs (2004-2010), other clinically relevant non-asthma pulmonary disorders such as autoimmunity, immune deficiency, immunosuppression treatments (procedural codes), cancer, HIV, drug addiction and major psychiatric disorder (2009-2010).

The following *International Classification of Diseases, Ninth Revision* codes were used to identify specific conditions/diseases.

Gastroesophageal reflux disease: 530.81  
Pneumonia: 480.x thru 483.x, 485.x, 486.x  
Rhinitis: 472.0, 477.x  
Chronic sinusitis: 473.x  
Acute upper respiratory tract infections: 465.x  
Nasal polyps: 471.x

Atopic dermatitis: 691.8

Urticaria: 708.x

Poisoning by adrenal corticosteroids: 962.0, E932.0

Cataracts: 366.xx, 998.82, V45.61

Glaucoma: 354.22, 365.xx, 377.14,

Osteoporosis: 733.00, 733.01, 733.02, 733.09, 733.90

Fractures: 733.10, 733.10 thru 733.98, 800.xx thru 829.xx, E887

Hypertension: 401.0x, 401.1x, 401.9x, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404x, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99

Infections: 001-139

Anxiety: 293.89, 300.00, 300.01, 300.02, 300.22, 300.23, 300.3x, 308.3x, 309.81

Depression: 296.2x, 293.3x, 300.4x, 311.x

Diabetes: 250.x, 357.2x, 362.0x, 366.41, 648.0x

Ulcer disease: 531.x, 533.x, 532.9x

**TABLE E1.** Description of baseline demographic characteristics, comorbidities, and asthma features by average cumulative daily OCS dosages in 2010 for adults with persistent asthma

| Baseline variables                                               | Average cumulative daily OCS dosages in 2010<br>Data as N (%) or mean $\pm$ SD |                                    |                                         |                                         |                                     |                      |
|------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------|-----------------------------------------|-----------------------------------------|-------------------------------------|----------------------|
|                                                                  | No OCS<br>(N = 5,756)                                                          | OCS<br>>0-<2.5 mg/d<br>(N = 3,008) | OCS<br>$\geq 2.5$ -<5 mg/d<br>(N = 516) | OCS<br>$\geq 5$ -<7.5 mg/d<br>(N = 144) | OCS<br>$\geq 7.5$ mg/d<br>(N = 122) | Total<br>(N = 9,546) |
|                                                                  |                                                                                |                                    |                                         |                                         |                                     |                      |
| Demographic characteristics                                      |                                                                                |                                    |                                         |                                         |                                     |                      |
| Age (y)                                                          | 45.8 $\pm$ 12.8                                                                | 45.9 $\pm$ 12.7                    | 47.9 $\pm$ 11.2                         | 48.3 $\pm$ 11.2                         | 50.1 $\pm$ 11.4                     | 46.0 $\pm$ 12.7      |
| Sex: female                                                      | 3,319 (57.7)                                                                   | 2,038 (67.8)                       | 355 (68.8)                              | 107 (74.3)                              | 73 (59.8)                           | 5,892 (61.7)         |
| Ethnicity                                                        |                                                                                |                                    |                                         |                                         |                                     |                      |
| White                                                            | 2,794 (48.5)                                                                   | 1,255 (41.7)                       | 199 (38.6)                              | 60 (41.7)                               | 48 (39.3)                           | 4,356 (45.6)         |
| Black                                                            | 718 (12.5)                                                                     | 476 (15.8)                         | 68 (13.2)                               | 23 (16.0)                               | 29 (23.8)                           | 1,314 (13.8)         |
| Hispanic                                                         | 1,278 (22.2)                                                                   | 867 (28.8)                         | 171 (33.1)                              | 43 (29.9)                               | 30 (24.6)                           | 2,389 (25)           |
| Asian/Pacific Islanders                                          | 436 (7.6)                                                                      | 243 (8.1)                          | 49 (9.5)                                | 12 (8.3)                                | 12 (9.8)                            | 752 (7.9)            |
| Unknown                                                          | 530 (9.2)                                                                      | 167 (5.6)                          | 29 (5.6)                                | 6 (4.2)                                 | 3 (2.5)                             | 735 (7.7)            |
| Estimated household median income by geocoding (\$)              | 69,791 $\pm$ 28,703                                                            | 67,426 $\pm$ 29,339                | 68,100 $\pm$ 31,246                     | 70,393 $\pm$ 27,000                     | 65,985 $\pm$ 28,493                 | 68,915 $\pm$ 29,037  |
| Estimated family education level up to grade 12 by geocoding (%) | 21.5 $\pm$ 16.8                                                                | 24.1 $\pm$ 18.1                    | 24.1 $\pm$ 18.9                         | 22.5 $\pm$ 17.4                         | 24.7 $\pm$ 18.9                     | 22.5 $\pm$ 17.4      |
| Duration of health plan enrollment (y)                           | 16.3 $\pm$ 10.4                                                                | 16.1 $\pm$ 10.2                    | 16.9 $\pm$ 10.4                         | 18.2 $\pm$ 11.4                         | 19.2 $\pm$ 10.8                     | 16.3 $\pm$ 10.4      |
| Insurance*                                                       |                                                                                |                                    |                                         |                                         |                                     |                      |
| Commercial                                                       | 5,160 (89.6)                                                                   | 2,708 (90)                         | 467 (90.5)                              | 131 (91.0)                              | 106 (86.9)                          | 8,572 (89.8)         |
| State programs                                                   | 226 (3.9)                                                                      | 144 (4.8)                          | 18 (3.5)                                | 8 (5.6)                                 | 9 (7.4)                             | 405 (4.2)            |
| Medicare                                                         | 136 (2.4)                                                                      | 57 (1.9)                           | 8 (1.6)                                 | 4 (2.8)                                 | 7 (5.7)                             | 212 (2.2)            |
| Private pay                                                      | 352 (6.1)                                                                      | 144 (4.8)                          | 29 (5.6)                                | 5 (3.5)                                 | 7 (5.7)                             | 537 (5.6)            |
| Smoking status                                                   |                                                                                |                                    |                                         |                                         |                                     |                      |
| Yes                                                              | 455 (7.9)                                                                      | 197 (6.5)                          | 17 (3.3)                                | 2 (1.4)                                 | 8 (6.6)                             | 679 (7.1)            |
| Passive                                                          | 66 (1.1)                                                                       | 37 (1.2)                           | 8 (1.6)                                 | 2 (1.4)                                 | 0 (0)                               | 113 (1.2)            |
| Quit                                                             | 1,278 (22.2)                                                                   | 715 (23.8)                         | 140 (27.1)                              | 25 (17.4)                               | 35 (28.7)                           | 2,193 (23.0)         |
| Never                                                            | 3,458 (60.1)                                                                   | 1,974 (65.6)                       | 344 (66.7)                              | 110 (76.4)                              | 77 (63.1)                           | 5,963 (62.5)         |
| Missing                                                          | 499 (8.7)                                                                      | 85 (2.8)                           | 7 (1.4)                                 | 5 (3.5)                                 | 2 (1.6)                             | 499 (8.7)            |
| Asthma burden                                                    |                                                                                |                                    |                                         |                                         |                                     |                      |
| Allergist visit                                                  | 694 (12.1)                                                                     | 728 (24.2)                         | 207 (40.1)                              | 62 (43.1)                               | 46 (37.7)                           | 1,737 (18.2)         |
| Pulmonologist visit                                              | 139 (2.4)                                                                      | 151 (5.0)                          | 79 (15.3)                               | 37 (25.7)                               | 34 (27.9)                           | 440 (4.6)            |
| Any asthma specialist visit                                      | 815 (14.2)                                                                     | 839 (27.9)                         | 261 (50.6)                              | 84 (58.3)                               | 68 (55.7)                           | 2,067 (21.7)         |
| GINA step-care level                                             |                                                                                |                                    |                                         |                                         |                                     |                      |
| 1                                                                | 716 (12.4)                                                                     | 227 (7.5)                          | 21 (4.1)                                | 6 (4.2)                                 | 12 (9.8)                            | 982 (10.3)           |
| 2                                                                | 950 (16.5)                                                                     | 355 (11.8)                         | 43 (8.3)                                | 13 (9)                                  | 8 (6.6)                             | 1,369 (14.3)         |
| 3                                                                | 2,057 (35.7)                                                                   | 1,078 (35.8)                       | 152 (29.5)                              | 23 (16)                                 | 25 (20.5)                           | 3,335 (34.9)         |
| 4                                                                | 2,020 (35.1)                                                                   | 1,344 (44.7)                       | 296 (57.4)                              | 96 (66.7)                               | 30 (24.6)                           | 3,786 (39.7)         |
| 5                                                                | 3 (0.1)                                                                        | 2 (0.1)                            | 4 (0.8)                                 | 5 (3.5)                                 | 46 (37.7)                           | 60 (0.6)             |
| Unclassified                                                     | 10 (0.2)                                                                       | 2 (0.1)                            | 0 (0)                                   | 1 (0.7)                                 | 1 (0.8)                             | 14 (0.1)             |
| Any ICS                                                          |                                                                                |                                    |                                         |                                         |                                     |                      |
| Low-dosage                                                       | 1,147 (19.9)                                                                   | 533 (17.7)                         | 73 (14.1)                               | 17 (11.8)                               | 13 (10.7)                           | 1,783 (18.7)         |
| Medium-dosage                                                    | 2,861 (49.7)                                                                   | 1,588 (52.8)                       | 229 (44.4)                              | 55 (38.2)                               | 44 (36.1)                           | 4,777 (50.0)         |
| High-dosage                                                      | 703 (12.2)                                                                     | 588 (19.5)                         | 183 (35.5)                              | 62 (43.1)                               | 49 (40.2)                           | 1,585 (16.6)         |
| None                                                             | 1,045 (18.2)                                                                   | 299 (9.9)                          | 31 (6.0)                                | 10 (6.9)                                | 16 (13.1)                           | 1,401 (14.7)         |
| ICS-long-acting $\beta_2$ -agonist                               |                                                                                |                                    |                                         |                                         |                                     |                      |
| Low-dosage                                                       | 442 (7.7)                                                                      | 202 (6.7)                          | 35 (6.8)                                | 7 (4.9)                                 | 6 (4.9)                             | 692 (7.2)            |
| Medium-dosage                                                    | 1,288 (22.4)                                                                   | 711 (23.6)                         | 115 (22.3)                              | 38 (26.4)                               | 28 (23.0)                           | 2,180 (22.8)         |
| High-dosage                                                      | 516 (9.0)                                                                      | 477 (15.9)                         | 145 (28.1)                              | 56 (38.9)                               | 40 (32.8)                           | 1,234 (12.9)         |
| None                                                             | 3,510 (61.0)                                                                   | 1,618 (53.8)                       | 221 (42.8)                              | 43 (29.9)                               | 48 (39.3)                           | 5,440 (57.0)         |
| Leukotriene modifiers                                            | 915 (15.9)                                                                     | 576 (19.1)                         | 156 (30.2)                              | 49 (34.0)                               | 48 (39.3)                           | 1,744 (18.3)         |
| Theophylline                                                     | 117 (2.0)                                                                      | 53 (1.8)                           | 6 (1.2)                                 | 5 (3.5)                                 | 10 (8.2)                            | 191 (2.0)            |

(continued)

TABLE E1. (Continued)

| Baseline variables                                 | Average cumulative daily OCS dosages in 2010<br>Data as N (%) or mean $\pm$ SD |                                    |                                         |                                         |                                     |                      |
|----------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------|-----------------------------------------|-----------------------------------------|-------------------------------------|----------------------|
|                                                    | No OCS<br>(N = 5,756)                                                          | OCS<br>>0-<2.5 mg/d<br>(N = 3,008) | OCS<br>$\geq 2.5$ -<5 mg/d<br>(N = 516) | OCS<br>$\geq 5$ -<7.5 mg/d<br>(N = 144) | OCS<br>$\geq 7.5$ mg/d<br>(N = 122) | Total<br>(N = 9,546) |
| Omalizumab                                         | 4 (0.1)                                                                        | 2 (0.1)                            | 2 (0.4)                                 | 4 (2.8)                                 | 3 (2.5)                             | 15 (0.2)             |
| Controller equivalent canisters                    | 7.1 $\pm$ 5.6                                                                  | 7.4 $\pm$ 5.9                      | 9.0 $\pm$ 6.6                           | 9.3 $\pm$ 6.5                           | 10.2 $\pm$ 7.4                      | 7.4 $\pm$ 5.8        |
| $\geq 9$ controller equivalent canisters           | 2,104 (36.6)                                                                   | 1,076 (35.8)                       | 224 (43.4)                              | 67 (46.5)                               | 65 (53.3)                           | 3,536 (37.0)         |
| Asthma Medication Ratio, $\geq 0.5$                | 3,524 (61.2)                                                                   | 1,848 (61.4)                       | 331 (64.1)                              | 93 (64.6)                               | 64 (52.5)                           | 5,860 (61.4)         |
| $\geq 7$ short-acting $\beta_2$ -agonist canisters | 1,783 (31)                                                                     | 957 (31.8)                         | 185 (35.9)                              | 65 (45.1)                               | 72 (59.0)                           | 3,062 (32.1)         |
| OCS courses                                        |                                                                                |                                    |                                         |                                         |                                     |                      |
| None                                               | 5756 (100)                                                                     | 0                                  | 0                                       | 0                                       | 0                                   | 5,756 (60.3)         |
| 1-3                                                | 0                                                                              | 2,956 (88.0)                       | 329 (9.8)                               | 48 (1.4)                                | 28 (0.8)                            | 3,361 (35.2)         |
| $\geq 4$                                           | 0                                                                              | 52 (12.1)                          | 187 (43.6)                              | 96 (23.4)                               | 94 (21.9)                           | 429 (4.5)            |
| Asthma exacerbations                               |                                                                                |                                    |                                         |                                         |                                     |                      |
| Rate                                               | 0.0 $\pm$ 0.2                                                                  | 0.8 $\pm$ 0.8                      | 1.5 $\pm$ 1.4                           | 1.8 $\pm$ 2.1                           | 1.6 $\pm$ 2.0                       | 0.4 $\pm$ 0.8        |
| $\geq 1$                                           | 109 (1.9)                                                                      | 1,807 (60.1)                       | 358 (69.4)                              | 85 (59.0)                               | 69 (56.6)                           | 2,428 (25.4)         |
| $\geq 2$                                           | 8 (0.1)                                                                        | 407 (13.5)                         | 226 (43.8)                              | 61 (42.4)                               | 49 (40.2)                           | 751 (7.9)            |
| $\geq 1$ ED visit                                  | 108 (1.9)                                                                      | 383 (12.7)                         | 71 (13.8)                               | 30 (20.8)                               | 28 (23.0)                           | 620 (6.5)            |
| $\geq 1$ hospitalization                           | 9 (0.2)                                                                        | 60 (2.0)                           | 28 (5.4)                                | 15 (10.4)                               | 14 (11.5)                           | 126 (1.3)            |
| $\geq 1$ ED visit or hospitalization               | 109 (1.9)                                                                      | 390 (13.0)                         | 73 (14.1)                               | 30 (20.8)                               | 30 (24.6)                           | 632 (6.6)            |
| OCS dosage (mg/d)                                  | 0 $\pm$ 0                                                                      | 1.0 $\pm$ 0.6                      | 3.4 $\pm$ 0.7                           | 6.0 $\pm$ 0.7                           | 12.4 $\pm$ 5.4                      | 0.7 $\pm$ 1.8        |
| Eosinophil count determined                        | N = 1,218                                                                      | N = 858                            | N = 194                                 | N = 60                                  | N = 62                              | N = 2,392            |
| cells/mm <sup>3</sup>                              | 250.8 $\pm$ 241.8                                                              | 268.3 $\pm$ 273.8                  | 270.4 $\pm$ 345.5                       | 374.4 $\pm$ 549.9                       | 314.3 $\pm$ 407.4                   | 263.4 $\pm$ 280.0    |
| $\geq 150$ cells/mm <sup>3</sup>                   | 786 (64.5)                                                                     | 531 (61.9)                         | 105 (54.1)                              | 37 (61.7)                               | 36 (58.1)                           | 1,495 (62.5)         |
| $\geq 300$ cells/mm <sup>3</sup>                   | 349 (28.7)                                                                     | 262 (30.5)                         | 65 (33.5)                               | 22 (36.7)                               | 21 (33.9)                           | 719 (30.1)           |
| $\geq 400$ cells/mm <sup>3</sup>                   | 195 (16.0)                                                                     | 170 (19.8)                         | 41 (21.1)                               | 14 (23.3)                               | 17 (27.4)                           | 437 (18.3)           |
| Asthma-related comorbidities                       |                                                                                |                                    |                                         |                                         |                                     |                      |
| Charlson comorbidity index                         | 1.0 $\pm$ 0.8                                                                  | 1.2 $\pm$ 0.7                      | 1.2 $\pm$ 0.7                           | 1.3 $\pm$ 0.8                           | 1.3 $\pm$ 0.9                       | 1.1 $\pm$ 0.8        |
| Body mass index (kg/m <sup>2</sup> )               | 30.7 $\pm$ 7.5                                                                 | 31.9 $\pm$ 8.0                     | 32.3 $\pm$ 7.7                          | 33.2 $\pm$ 9.5                          | 32.5 $\pm$ 8.2                      | 31.3 $\pm$ 7.7       |
| Obesity, $\geq 30$ kg/m <sup>2</sup>               | 2,606 (45.3)                                                                   | 1,592 (52.9)                       | 290 (56.2)                              | 86 (59.7)                               | 67 (54.9)                           | 4,641 (48.6)         |
| Missing                                            | 188 (3.3)                                                                      | 25 (0.8)                           | 1 (0.2)                                 | 2 (1.4)                                 | 1 (0.8)                             | 217 (2.3)            |
| Gastroesophageal reflux disease                    | 680 (11.8)                                                                     | 535 (17.8)                         | 149 (28.9)                              | 43 (29.9)                               | 39 (32.0)                           | 1,446 (15.1)         |
| Pneumonia                                          | 71 (1.2)                                                                       | 164 (5.5)                          | 51 (9.9)                                | 11 (7.6)                                | 12 (9.8)                            | 309 (3.2)            |
| Any rhinitis                                       | 1,297 (22.5)                                                                   | 1,195 (39.7)                       | 255 (49.4)                              | 78 (54.2)                               | 61 (50.0)                           | 2,886 (30.2)         |
| Chronic sinusitis                                  | 510 (8.9)                                                                      | 625 (20.8)                         | 156 (30.2)                              | 42 (29.2)                               | 43 (35.2)                           | 1,376 (14.4)         |
| Acute upper respiratory tract infection            | 514 (8.9)                                                                      | 636 (21.1)                         | 140 (27.1)                              | 26 (18.1)                               | 28 (23.0)                           | 1,344 (14.1)         |
| Nasal polyps                                       | 36 (0.6)                                                                       | 71 (2.4)                           | 30 (5.8)                                | 15 (10.4)                               | 9 (7.4)                             | 161 (1.7)            |
| Eczema                                             | 95 (1.7)                                                                       | 64 (2.1)                           | 19 (3.7)                                | 6 (4.2)                                 | 5 (4.1)                             | 189 (2.0)            |
| Urticaria                                          | 54 (0.9)                                                                       | 111 (3.7)                          | 13 (2.5)                                | 4 (2.8)                                 | 2 (1.6)                             | 184 (1.9)            |
| Corticosteroid-related comorbidities               |                                                                                |                                    |                                         |                                         |                                     |                      |
| Adrenal corticosteroid poisoning                   | 3 (0.1%)                                                                       | 8 (0.3)                            | 5 (1.0)                                 | 4 (2.8)                                 | 3 (2.5)                             | 23 (0.2)             |
| Cataracts                                          | 212 (3.7)                                                                      | 151 (5.0)                          | 21 (4.1)                                | 9 (6.3)                                 | 15 (12.3)                           | 408 (4.3)            |
| Glaucoma                                           | 118 (2.1)                                                                      | 63 (2.1)                           | 13 (2.5)                                | 4 (2.8)                                 | 5 (4.1)                             | 203 (2.1)            |
| Osteoporosis                                       | 164 (2.8)                                                                      | 95 (3.2)                           | 24 (4.7)                                | 7 (4.9)                                 | 8 (6.6)                             | 298 (3.1)            |
| Fractures                                          | 254 (4.4)                                                                      | 165 (5.5)                          | 37 (7.2)                                | 9 (6.3)                                 | 13 (10.7)                           | 478 (5.0)            |
| Hypertension                                       | 1,588 (27.6)                                                                   | 978 (32.5)                         | 194 (37.6)                              | 51 (35.4)                               | 53 (43.4)                           | 2,864 (30.0)         |
| Infections                                         | 823 (14.3)                                                                     | 628 (20.9)                         | 125 (24.2)                              | 31 (21.5)                               | 36 (29.5)                           | 1,643 (17.2)         |
| Anxiety                                            | 539 (9.4)                                                                      | 389 (12.9)                         | 91 (17.6)                               | 20 (13.9)                               | 16 (13.1)                           | 1,055 (11.1)         |
| Depression                                         | 639 (11.1)                                                                     | 443 (14.7)                         | 67 (13.0)                               | 18 (12.5)                               | 17 (13.9)                           | 1,184 (12.4)         |
| Ulcer disease                                      | 8 (0.1)                                                                        | 11 (0.4)                           | 5 (1.0)                                 | 1 (0.7)                                 | 0 (0)                               | 25 (0.3)             |
| Diabetes                                           | 624 (10.8)                                                                     | 333 (11.1)                         | 61 (11.8)                               | 16 (11.1)                               | 17 (13.9)                           | 1,051 (11.0)         |

\*Patients may have more than 1 insurance plan.

**TABLE E2.** Comparison of baseline demographic characteristics, comorbidities, and asthma features by OCS courses in 2010 for adult patients with persistent asthma

| Baseline variables                                         | OCS courses dispensed in 2010<br>Data as N (%) or mean ± SD |                                   |                                 |                                | Total<br>(N = 9,546) |
|------------------------------------------------------------|-------------------------------------------------------------|-----------------------------------|---------------------------------|--------------------------------|----------------------|
|                                                            | No OCS use<br>(N = 5,756)                                   | OCS<br>1-3 courses<br>(N = 3,361) | OCS<br>4-5 courses<br>(N = 293) | OCS<br>≥6 courses<br>(N = 136) |                      |
| Demographic characteristics                                |                                                             |                                   |                                 |                                |                      |
| Age (y)                                                    | 45.8 ± 12.8                                                 | 46.1 ± 12.6                       | 47.9 ± 11.5                     | 49.0 ± 10.6                    | 46.0 ± 12.7          |
| Sex: female                                                | 3,319 (57.7)                                                | 2,274 (67.7)                      | 204 (69.6)                      | 95 (69.9)                      | 5,892 (61.7)         |
| Ethnicity                                                  |                                                             |                                   |                                 |                                |                      |
| White                                                      | 2,794 (48.5)                                                | 1,401 (41.7)                      | 111 (37.9)                      | 50 (36.8)                      | 4,356 (45.6)         |
| Black                                                      | 718 (12.5)                                                  | 517 (15.4)                        | 48 (16.4)                       | 31 (22.8)                      | 1,314 (13.8)         |
| Hispanic                                                   | 1,278 (22.2)                                                | 977 (29.1)                        | 97 (33.1)                       | 37 (27.2)                      | 2,389 (25)           |
| Asian/Pacific Islanders                                    | 436 (7.6)                                                   | 276 (8.2)                         | 29 (9.9)                        | 11 (8.1)                       | 752 (7.9)            |
| Others/unknown                                             | 530 (9.2)                                                   | 190 (5.7)                         | 8 (2.7)                         | 7 (5.1)                        | 735 (7.7)            |
| Estimated household median income by geocoding (\$)        | 69,791 ± 28,703                                             | 67,763 ± 29,090                   | 66,312 ± 34,654                 | 65,906 ± 27,252                | 68,915 ± 29,037      |
| Estimated family education up to grade 12 by geocoding (%) | 21.5 ± 16.8                                                 | 23.9 ± 18.1                       | 27.0 ± 19.6                     | 23.0 ± 17.7                    | 22.5 ± 17.4          |
| Duration of health plan enrollment (y)                     | 16.3 ± 10.4                                                 | 16.3 ± 10.3                       | 15.9 ± 10.0                     | 18.8 ± 11.8                    | 16.3 ± 10.4          |
| Insurance*                                                 |                                                             |                                   |                                 |                                |                      |
| Commercial                                                 | 5,160 (89.6)                                                | 3,033 (90.2)                      | 262 (89.4)                      | 117 (86.0)                     | 8,572 (89.8)         |
| State programs                                             | 226 (3.9)                                                   | 150 (4.5)                         | 18 (6.1)                        | 11 (8.1)                       | 405 (4.2)            |
| Medicare                                                   | 136 (2.4)                                                   | 63 (1.9)                          | 9 (3.1)                         | 4 (2.9)                        | 212 (2.2)            |
| Private pay                                                | 352 (6.1)                                                   | 164 (4.9)                         | 14 (4.8)                        | 7 (5.1)                        | 537 (5.6)            |
| Smoking status                                             |                                                             |                                   |                                 |                                |                      |
| Yes                                                        | 455 (7.9)                                                   | 202 (6.0)                         | 13 (4.4)                        | 9 (6.6)                        | 679 (7.1)            |
| Passive                                                    | 66 (1.1)                                                    | 42 (1.2)                          | 4 (1.4)                         | 1 (0.7)                        | 113 (1.2)            |
| Quit                                                       | 1,278 (22.2)                                                | 800 (23.8)                        | 85 (29.0)                       | 30 (22.1)                      | 2,193 (23.0)         |
| Never                                                      | 3,458 (60.1)                                                | 2,221 (66.1)                      | 189 (64.5)                      | 95 (69.9)                      | 5,963 (62.5)         |
| Missing                                                    | 499 (8.7)                                                   | 96 (2.9)                          | 2 (0.7)                         | 1 (0.7)                        | 598 (6.3)            |
| Asthma burden                                              |                                                             |                                   |                                 |                                |                      |
| Allergist visit                                            | 694 (12.1)                                                  | 861 (25.6)                        | 122 (41.6)                      | 60 (44.1)                      | 1,737 (18.2)         |
| Pulmonologist visit                                        | 139 (2.4)                                                   | 205 (6.1)                         | 57 (19.5)                       | 39 (28.7)                      | 440 (4.6)            |
| Any asthma specialist visit                                | 815 (14.2)                                                  | 1,012 (30.1)                      | 159 (54.3)                      | 81 (59.6)                      | 2,067 (21.7)         |
| Global Initiative for Asthma step-care level               |                                                             |                                   |                                 |                                |                      |
| 1                                                          | 716 (12.4)                                                  | 244 (7.3)                         | 19 (6.5)                        | 3 (2.2)                        | 982 (10.3)           |
| 2                                                          | 950 (16.5)                                                  | 388 (11.5)                        | 25 (8.5)                        | 6 (4.4)                        | 1,369 (14.3)         |
| 3                                                          | 2,057 (35.7)                                                | 1,181 (35.1)                      | 69 (23.5)                       | 28 (20.6)                      | 3,335 (34.9)         |
| 4                                                          | 2,020 (35.1)                                                | 1,534 (45.6)                      | 166 (56.7)                      | 66 (48.5)                      | 3,786 (39.7)         |
| 5                                                          | 3 (0.1)                                                     | 11 (0.3)                          | 13 (4.4)                        | 33 (24.3)                      | 60 (0.6)             |
| Unclassified                                               | 10 (0.2)                                                    | 3 (0.1)                           | 1 (0.3)                         | 0 (0)                          | 14 (0.1)             |
| ICSs                                                       |                                                             |                                   |                                 |                                |                      |
| Low-dosage                                                 | 1,147 (19.9)                                                | 583 (17.3)                        | 37 (12.6)                       | 16 (11.8)                      | 1,783 (18.7)         |
| Medium-dosage                                              | 2,861 (49.7)                                                | 1,734 (51.6)                      | 127 (43.3)                      | 55 (40.4)                      | 4,777 (50)           |
| High-dosage                                                | 703 (12.2)                                                  | 715 (21.3)                        | 106 (36.2)                      | 61 (44.9)                      | 1,585 (16.6)         |
| None                                                       | 1,045 (18.2)                                                | 329 (9.8)                         | 23 (7.8)                        | 4 (2.9)                        | 1,401 (14.7)         |
| ICS-long-acting β <sub>2</sub> -agonist                    |                                                             |                                   |                                 |                                |                      |
| Low-dosage                                                 | 442 (7.7)                                                   | 231 (6.9)                         | 12 (4.1)                        | 7 (5.1)                        | 692 (7.2)            |
| Medium-dosage                                              | 1,288 (22.4)                                                | 788 (23.4)                        | 70 (23.9)                       | 34 (25.0)                      | 2,180 (22.8)         |
| High-dosage                                                | 516 (9.0)                                                   | 574 (17.1)                        | 88 (30.0)                       | 56 (41.2)                      | 1,234 (12.9)         |
| None                                                       | 3,510 (61.0)                                                | 1,768 (52.6)                      | 123 (42.0)                      | 39 (28.7)                      | 5,440 (57.0)         |
| Leukotriene modifiers                                      |                                                             |                                   |                                 |                                |                      |
| Theophylline                                               | 915 (15.9)                                                  | 672 (20.0)                        | 93 (31.7)                       | 64 (47.1)                      | 1,744 (18.3)         |
| Theophylline                                               | 117 (2.0)                                                   | 61 (1.8)                          | 9 (3.1)                         | 4 (2.9)                        | 191 (2.0)            |
| Omalizumab                                                 | 4 (0.1)                                                     | 4 (0.1)                           | 4 (1.4)                         | 3 (2.2)                        | 15 (0.2)             |

(continued)

TABLE E2. (Continued)

| Baseline variables                                 | OCS courses dispensed in 2010<br>Data as N (%) or mean $\pm$ SD |                                   |                                 |                                      |                      |
|----------------------------------------------------|-----------------------------------------------------------------|-----------------------------------|---------------------------------|--------------------------------------|----------------------|
|                                                    | No OCS use<br>(N = 5,756)                                       | OCS<br>1-3 courses<br>(N = 3,361) | OCS<br>4-5 courses<br>(N = 293) | OCS<br>$\geq 6$ courses<br>(N = 136) | Total<br>(N = 9,546) |
| Controller equivalent canisters                    | 7.1 $\pm$ 5.6                                                   | 7.6 $\pm$ 6.0                     | 8.4 $\pm$ 6.3                   | 11.1 $\pm$ 7.1                       | 7.4 $\pm$ 5.8        |
| $\geq 9$ controller equivalent canisters           | 2,104 (36.6)                                                    | 1,239 (36.9)                      | 113 (38.6)                      | 80 (58.8)                            | 3,536 (37.0)         |
| Asthma Medication Ratio, $\geq 0.5$                | 3,524 (61.2)                                                    | 2,081 (61.9)                      | 175 (59.7)                      | 80 (58.8)                            | 5,860 (61.4)         |
| $\geq 7$ short-acting $\beta_2$ -agonist canisters | 1,783 (31.0)                                                    | 1,082 (32.2)                      | 123 (42.0)                      | 74 (54.4)                            | 3,062 (32.1)         |
| Asthma exacerbations                               |                                                                 |                                   |                                 |                                      |                      |
| Rate                                               | 0.0 $\pm$ 0.2                                                   | 0.8 $\pm$ 0.8                     | 1.8 $\pm$ 1.5                   | 3.1 $\pm$ 2.4                        | 0.4 $\pm$ 0.8        |
| $\geq 1$                                           | 109 (1.9)                                                       | 1,991 (59.2)                      | 218 (74.4)                      | 110 (80.9)                           | 2,428 (25.4)         |
| $\geq 2$                                           | 8 (0.1)                                                         | 479 (14.3)                        | 171 (58.4)                      | 93 (68.4)                            | 751 (7.9)            |
| $\geq 1$ asthma ED visit                           | 108 (1.9)                                                       | 409 (12.2)                        | 63 (21.5)                       | 40 (29.4)                            | 620 (6.5)            |
| $\geq 1$ asthma hospitalization                    | 9 (0.2)                                                         | 71 (2.1)                          | 25 (8.5)                        | 21 (15.4)                            | 126 (1.3)            |
| $\geq 1$ asthma ED or hospitalization              | 109 (1.9)                                                       | 418 (12.4)                        | 64 (21.8)                       | 41 (30.1)                            | 632 (6.6)            |
| OCS dosage (mg/d)                                  | 0.0 $\pm$ 0.0                                                   | 1.3 $\pm$ 1.6                     | 4.6 $\pm$ 3.1                   | 8.7 $\pm$ 5.2                        | 0.7 $\pm$ 1.8        |
| Eosinophil count determined                        | N = 1218                                                        | N = 976                           | N = 125                         | N = 73                               | N = 2,392            |
| cells/mm <sup>3</sup>                              | 251 $\pm$ 242                                                   | 268 $\pm$ 286                     | 289 $\pm$ 316                   | 368 $\pm$ 568                        | 263 $\pm$ 280        |
| $\geq 150$ cells/mm <sup>3</sup>                   | 786 (64.5)                                                      | 597 (61.2)                        | 69 (55.2)                       | 43 (58.9)                            | 1,495 (62.5)         |
| $\geq 300$ cells/mm <sup>3</sup>                   | 349 (28.7)                                                      | 296 (30.3)                        | 48 (38.4)                       | 26 (35.6)                            | 719 (30.1)           |
| $\geq 400$ cells/mm <sup>3</sup>                   | 195 (16.0)                                                      | 189 (19.4)                        | 30 (24.0)                       | 23 (31.5)                            | 437 (18.3)           |
| Asthma-related comorbidities                       |                                                                 |                                   |                                 |                                      |                      |
| Charlson comorbidity index                         | 1.0 $\pm$ 0.8                                                   | 1.2 $\pm$ 0.7                     | 1.3 $\pm$ 0.7                   | 1.3 $\pm$ 0.7                        | 1.1 $\pm$ 0.8        |
| Body mass index (kg/m <sup>2</sup> )               | 30.7 $\pm$ 7.5                                                  | 32.0 $\pm$ 7.9                    | 32.2 $\pm$ 7.7                  | 33.2 $\pm$ 10.0                      | 31.3 $\pm$ 7.7       |
| Obesity $\geq 30$ kg/m <sup>2</sup>                | 2,606 (45.3)                                                    | 1,793 (53.3)                      | 165 (56.3)                      | 77 (56.6)                            | 4,641 (48.6)         |
| Missing                                            | 188 (3.3)                                                       | 28 (0.8)                          | 0 (0)                           | 1 (0.7)                              | 217 (2.3)            |
| Gastroesophageal reflux disease                    | 680 (11.8)                                                      | 627 (18.7)                        | 96 (32.8)                       | 43 (31.6)                            | 1,446 (15.1)         |
| Pneumonia                                          | 71 (1.2)                                                        | 195 (5.8)                         | 26 (8.9)                        | 17 (12.5)                            | 309 (3.2)            |
| Any rhinitis                                       | 1,297 (22.5)                                                    | 1,342 (39.9)                      | 169 (57.7)                      | 78 (57.4)                            | 2,886 (30.2)         |
| Chronic sinusitis                                  | 510 (8.9)                                                       | 715 (21.3)                        | 101 (34.5)                      | 50 (36.8)                            | 1,376 (14.4)         |
| Acute upper respiratory tract infection            | 514 (8.9)                                                       | 704 (20.9)                        | 82 (28.0)                       | 44 (32.4)                            | 1,344 (14.1)         |
| Nasal polyps                                       | 36 (0.6)                                                        | 85 (2.5)                          | 25 (8.5)                        | 15 (11.0)                            | 161 (1.7)            |
| Eczema                                             | 95 (1.7)                                                        | 70 (2.1)                          | 17 (5.8)                        | 7 (5.1)                              | 189 (2.0)            |
| Urticaria                                          | 54 (0.9)                                                        | 114 (3.4)                         | 14 (4.8)                        | 2 (1.5)                              | 184 (1.9)            |
| Corticosteroid-related comorbidities               |                                                                 |                                   |                                 |                                      |                      |
| Adrenal corticosteroid poisoning                   | 3 (0.1)                                                         | 15 (0.4)                          | 1 (0.3)                         | 4 (2.9)                              | 23 (0.2)             |
| Cataracts                                          | 212 (3.7)                                                       | 164 (4.9)                         | 16 (5.5)                        | 16 (11.8)                            | 408 (4.3)            |
| Glaucoma                                           | 118 (2.1)                                                       | 74 (2.2)                          | 11 (3.8)                        | 0 (0)                                | 203 (2.1)            |
| Osteoporosis                                       | 164 (2.8)                                                       | 111 (3.3)                         | 15 (5.1)                        | 8 (5.9)                              | 298 (3.1)            |
| Fractures                                          | 254 (4.4)                                                       | 192 (5.7)                         | 20 (6.8)                        | 12 (8.8)                             | 478 (5.0)            |
| Hypertension                                       | 1,588 (27.6)                                                    | 1,117 (33.2)                      | 99 (33.8)                       | 60 (44.1)                            | 2,864 (30.0)         |
| Infections                                         | 823 (14.3)                                                      | 703 (20.9)                        | 73 (24.9)                       | 44 (32.4)                            | 1,643 (17.2)         |
| Anxiety                                            | 539 (9.4)                                                       | 456 (13.6)                        | 41 (14.0)                       | 19 (14.0)                            | 1,055 (11.1)         |
| Depression                                         | 639 (11.1)                                                      | 491 (14.6)                        | 36 (12.3)                       | 18 (13.2)                            | 1,184 (12.4)         |
| Ulcer disease                                      | 8 (0.1)                                                         | 13 (0.4)                          | 2 (0.7)                         | 2 (1.5)                              | 25 (0.3)             |
| Diabetes                                           | 624 (10.8)                                                      | 375 (11.2)                        | 33 (11.3)                       | 19 (14.0)                            | 1,051 (11.0)         |

\*Patients may have more than 1 insurance plan.

**TABLE E3.** Description of baseline demographic characteristics, comorbidities, and asthma features by number of OCS courses in 2010 for adult patients with persistent asthma

| Baseline variables                                               | Number of OCS courses dispensed in 2010<br>Data as N (%) or mean ± SD |                                |                      | P value* |
|------------------------------------------------------------------|-----------------------------------------------------------------------|--------------------------------|----------------------|----------|
|                                                                  | OCS<br>0-3 courses<br>(N = 9,117)                                     | OCS<br>≥4 courses<br>(N = 429) | Total<br>(N = 9,546) |          |
| Demographic characteristics                                      |                                                                       |                                |                      |          |
| Age (y)                                                          | 45.9 ± 12.7                                                           | 48.3 ± 11.2                    | 46.0 ± 12.7          | <.001    |
| Sex: female                                                      | 5,593 (61.3)                                                          | 299 (69.7)                     | 5,892 (61.7)         | <.001    |
| Ethnicity                                                        |                                                                       |                                |                      | <.001    |
| White                                                            | 4,195 (46.0)                                                          | 161 (37.5)                     | 4,356 (45.6)         |          |
| Black                                                            | 1,235 (13.5)                                                          | 79 (18.4)                      | 1,314 (13.8)         |          |
| Hispanic                                                         | 2,555 (24.7)                                                          | 134 (31.2)                     | 2,389 (25.0)         |          |
| Asian/Pacific Islanders                                          | 712 (7.8)                                                             | 40 (9.3)                       | 752 (7.9)            |          |
| Others or unknown                                                | 720 (7.9)                                                             | 15 (3.5)                       | 735 (7.7)            |          |
| Estimated household median income by geocoding (\$)              | 69,043 ± 28,861                                                       | 66,183 ± 32,459                | 68,915 ± 29,037      | .007     |
| Estimated family education level up to grade 12 by geocoding (%) | 22.4 ± 17.3                                                           | 25.7 ± 19.1                    | 22.5 ± 17.4          | <.001    |
| Duration of health plan enrollment (y)                           | 16.3 ± 10.4                                                           | 16.8 ± 10.7                    | 16.3 ± 10.4          | .35      |
| Insurance†                                                       |                                                                       |                                |                      |          |
| Commercial                                                       | 8,193 (89.9)                                                          | 379 (88.3)                     | 8,572 (89.8)         | .31      |
| State programs                                                   | 376 (4.1)                                                             | 29 (6.8)                       | 405 (4.2)            | .008     |
| Medicare                                                         | 199 (2.2)                                                             | 13 (3.0)                       | 212 (2.2)            | .24      |
| Private pay                                                      | 516 (5.7)                                                             | 21 (4.9)                       | 537 (5.6)            | .50      |
| Smoking status                                                   |                                                                       |                                |                      | <.001    |
| Yes                                                              | 657 (7.2)                                                             | 22 (5.1)                       | 679 (7.1)            |          |
| Passive                                                          | 108 (1.2)                                                             | 5 (1.2)                        | 113 (1.2)            |          |
| Quit                                                             | 2,078 (22.8)                                                          | 115 (26.8)                     | 2,193 (23.0)         |          |
| Never                                                            | 5,679 (62.3)                                                          | 284 (66.2)                     | 5,963 (62.5)         |          |
| Missing                                                          | 595 (6.5)                                                             | 3 (0.7)                        | 598 (6.3)            |          |
| Asthma burden                                                    |                                                                       |                                |                      |          |
| Allergist visit                                                  | 1,555 (17.1)                                                          | 182 (42.4)                     | 1,737 (18.2)         | <.001    |
| Pulmonologist visit                                              | 344 (3.8)                                                             | 96 (22.4)                      | 440 (4.6)            | <.001    |
| Any asthma specialist visit                                      | 1,827 (20.0)                                                          | 240 (55.9)                     | 2,067 (21.7)         | <.001    |
| Global Initiative for Asthma step-care level                     |                                                                       |                                |                      | <.001    |
| 1                                                                | 960 (10.5)                                                            | 22 (5.1)                       | 982 (10.3)           |          |
| 2                                                                | 1,338 (14.7)                                                          | 31 (7.2)                       | 1,369 (14.3)         |          |
| 3                                                                | 3,238 (35.5)                                                          | 97 (22.6)                      | 3,335 (34.9)         |          |
| 4                                                                | 3,554 (39.0)                                                          | 232 (54.1)                     | 3,786 (39.7)         |          |
| 5                                                                | 14 (0.2)                                                              | 46 (10.7)                      | 60 (0.6)             |          |
| Unclassified                                                     | 13 (0.1)                                                              | 1 (0.2)                        | 14 (0.1)             |          |
| Any ICS                                                          |                                                                       |                                |                      | <.001    |
| Low-dosage                                                       | 1,730 (19.0)                                                          | 53 (12.4)                      | 1,783 (18.7)         |          |
| Medium-dosage                                                    | 4,595 (50.4)                                                          | 182 (42.4)                     | 4,777 (50.0)         |          |
| High-dosage                                                      | 1,418 (15.6)                                                          | 167 (38.9)                     | 1,585 (16.6)         |          |
| None                                                             | 1,374 (15.1)                                                          | 27 (6.3)                       | 1,401 (14.7)         |          |
| Any ICS-long-acting β <sub>2</sub> -agonist                      |                                                                       |                                |                      | <.001    |
| Low-dosage                                                       | 673 (7.4)                                                             | 19 (4.4)                       | 692 (7.2)            |          |
| Medium-dosage                                                    | 2,076 (22.8)                                                          | 104 (24.2)                     | 2,180 (22.8)         |          |
| High-dosage                                                      | 1,090 (12.0)                                                          | 144 (33.6)                     | 1,234 (12.9)         |          |
| None                                                             | 5,278 (57.9)                                                          | 162 (37.8)                     | 5,440 (57.0)         |          |
| Leukotriene modifiers                                            | 1,587 (17.4)                                                          | 157 (36.6)                     | 1,744 (18.3)         | <.001    |
| Theophylline                                                     | 178 (2.0)                                                             | 13 (3.0)                       | 191 (2.0)            | .12      |
| Omalizumab                                                       | 8 (0.1)                                                               | 7 (1.6)                        | 15 (0.2)             | <.001    |
| Controller equivalent canisters                                  | 7.3 ± 5.8                                                             | 9.2 ± 6.7                      | 7.4 ± 5.8            | <.001    |
| ≥9 equivalent canisters                                          | 3,343 (36.7)                                                          | 193 (45.0)                     | 3,536 (37.0)         | <.001    |
| Asthma Medication Ratio, ≥0.5                                    | 5,605 (61.5)                                                          | 255 (59.4)                     | 5,860 (61.4)         | .40      |

(continued)

TABLE E3. (Continued)

| Baseline variables                                 | Number of OCS courses dispensed in 2010<br>Data as N (%) or mean $\pm$ SD |                                      |                      | P value* |
|----------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------|----------------------|----------|
|                                                    | OCS<br>0-3 courses<br>(N = 9,117)                                         | OCS<br>$\geq 4$ courses<br>(N = 429) | Total<br>(N = 9,546) |          |
| $\geq 7$ short-acting $\beta_2$ -agonist canisters | 2,865 (31.4)                                                              | 197 (45.9)                           | 3,062 (32.1)         | <.001    |
| Asthma exacerbations, mean $\pm$ SD                | 0.3 $\pm$ 0.6                                                             | 2.2 $\pm$ 1.9                        | 0.4 $\pm$ 0.8        | <.001    |
| $\geq 1$                                           | 2,100 (23.0)                                                              | 328 (76.5)                           | 2,428 (25.4)         | <.001    |
| $\geq 2$                                           | 487 (5.3)                                                                 | 264 (61.5)                           | 751 (7.9)            | <.001    |
| $\geq 1$ ED visit                                  | 517 (5.7)                                                                 | 103 (24.0)                           | 620 (6.5)            | <.001    |
| $\geq 1$ Hospitalization                           | 80 (0.9)                                                                  | 46 (10.7)                            | 126 (1.3)            | <.001    |
| $\geq 1$ ED visit or hospitalization               | 527 (5.8)                                                                 | 105 (24.5)                           | 632 (6.6)            | <.001    |
| OCS average cumulative daily dosage (mg/d)         |                                                                           |                                      |                      | <.001    |
| None                                               | 5,756 (63.1)                                                              | 0                                    | 5,756 (60.3)         |          |
| >0-<2.5 mg/d                                       | 2,956 (32.4)                                                              | 52 (12.1)                            | 3,008 (31.5)         |          |
| $\geq 2.5$ mg/d                                    | 405 (4.4)                                                                 | 377 (87.9)                           | 782 (8.2)            |          |
| OCS dosage (mg/d)                                  | 0.5 $\pm$ 1.2                                                             | 5.9 $\pm$ 4.3                        | 0.7 $\pm$ 1.8        | <.001    |
| Eosinophil count determined                        | N = 2,194                                                                 | N = 198                              | N = 2,392            |          |
| cells/mm <sup>3</sup>                              | 259 $\pm$ 262                                                             | 318 $\pm$ 427                        | 263 $\pm$ 280        | .42      |
| $\geq 150$ cells/mm <sup>3</sup>                   | 1,383 (63.0)                                                              | 112 (56.6)                           | 1,495 (62.5)         | .07      |
| $\geq 300$ cells/mm <sup>3</sup>                   | 645 (29.4)                                                                | 74 (37.4)                            | 719 (30.1)           | .02      |
| $\geq 400$ cells/mm <sup>3</sup>                   | 384 (17.5)                                                                | 53 (26.8)                            | 437 (18.3)           | .001     |
| Asthma-related comorbidities                       |                                                                           |                                      |                      |          |
| Charlson comorbidity index                         | 1.0 $\pm$ 0.8                                                             | 1.3 $\pm$ 0.7                        | 1.1 $\pm$ 0.8        | <.001    |
| Body mass index (kg/m <sup>2</sup> )               | 31.2 $\pm$ 7.7                                                            | 32.5 $\pm$ 8.5                       | 31.3 $\pm$ 7.7       | .001     |
| Obesity $\geq 30$ kg/m <sup>2</sup>                | 4,399 (48.3)                                                              | 242 (56.4)                           | 4,641 (48.6)         | <.001    |
| Missing                                            | 216 (2.4)                                                                 | 1 (0.2)                              | 217 (2.3)            |          |
| Gastroesophageal reflux disease                    | 1,307 (14.3)                                                              | 139 (32.4)                           | 1,446 (15.1)         | <.001    |
| Pneumonia                                          | 266 (2.9)                                                                 | 43 (10.0)                            | 309 (3.2)            | <.001    |
| Rhinitis                                           | 2,639 (28.9)                                                              | 247 (57.6)                           | 2,886 (30.2)         | <.001    |
| Chronic sinusitis                                  | 1,225 (13.4)                                                              | 151 (35.2)                           | 1,376 (14.4)         | <.001    |
| Acute upper respiratory tract infections           | 1,218 (13.4)                                                              | 126 (29.4)                           | 1,344 (14.1)         | <.001    |
| Nasal polyps                                       | 121 (1.3)                                                                 | 40 (9.3)                             | 161 (1.7)            | <.001    |
| Eczema                                             | 165 (1.8)                                                                 | 24 (5.6)                             | 189 (2.0)            | <.001    |
| Urticaria                                          | 168 (1.8)                                                                 | 16 (3.7)                             | 184 (1.9)            | .006     |
| Corticosteroid-related comorbidities               |                                                                           |                                      |                      |          |
| Poisoning by adrenal corticosteroids               | 18 (0.2)                                                                  | 5 (1.2)                              | 23 (0.2)             | <.001    |
| Cataracts                                          | 376 (4.1)                                                                 | 32 (7.5)                             | 408 (4.3)            | <.001    |
| Glaucoma                                           | 192 (2.1)                                                                 | 11 (2.6)                             | 203 (2.1)            | .52      |
| Osteoporosis                                       | 275 (3.0)                                                                 | 23 (5.4)                             | 298 (3.1)            | .006     |
| Fractures                                          | 446 (4.9)                                                                 | 32 (7.5)                             | 478 (5.0)            | .02      |
| Hypertension                                       | 2,705 (29.7)                                                              | 159 (37.1)                           | 2,864 (30.0)         | .001     |
| Infections                                         | 1,526 (16.7)                                                              | 117 (27.3)                           | 1,643 (17.2)         | <.001    |
| Anxiety                                            | 995 (10.9)                                                                | 60 (14.0)                            | 1,055 (11.1)         | .047     |
| Depression                                         | 1,130 (12.4)                                                              | 54 (12.6)                            | 1,184 (12.4)         | .91      |
| Diabetes                                           | 999 (11.0)                                                                | 52 (12.1)                            | 1,051 (11.0)         | .45      |
| Ulcer disease                                      | 21 (0.2)                                                                  | 4 (0.9)                              | 25 (0.3)             | .01      |

\*P values determined by chi-square test or Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

†Patients may have more than 1 insurance plan.

**TABLE E4.** Unadjusted analysis of association of baseline variables in 2010 and number of OCS courses in 2011 in adults with persistent asthma (N = 9,546)

| Baseline variables (2010)                                 | Number of OCS courses dispensed in 2011<br>Data as N (%) or mean $\pm$ SD |                                     | P value* |
|-----------------------------------------------------------|---------------------------------------------------------------------------|-------------------------------------|----------|
|                                                           | OCS<br>0-3 courses/y (N = 9,136)                                          | OCS<br>$\geq 4$ courses/y (N = 410) |          |
|                                                           |                                                                           |                                     |          |
| Age (y)                                                   | 45.9 $\pm$ 12.8                                                           | 49.0 $\pm$ 10.9                     | <.001    |
| Sex: female                                               | 5,604 (61.3)                                                              | 288 (70.2)                          | <.001    |
| Ethnicity                                                 |                                                                           |                                     | <.001    |
| White                                                     | 4,195 (45.9)                                                              | 161 (39.3)                          |          |
| Black                                                     | 1,235 (13.5)                                                              | 79 (19.3)                           |          |
| Hispanic                                                  | 2,271 (24.9)                                                              | 118 (28.8)                          |          |
| Asian/Pacific Islanders                                   | 712 (7.8)                                                                 | 40 (9.8)                            |          |
| Others/unknown                                            | 723 (7.9)                                                                 | 12 (2.9)                            |          |
| Estimated education level up to grade 12 by geocoding (%) | 22.4 $\pm$ 17.3                                                           | 24.9 $\pm$ 18.8                     | .006     |
| Enrollment duration (y)                                   | 16.3 $\pm$ 10.4                                                           | 17.4 $\pm$ 10.5                     | .03      |
| Private insurance                                         | 522 (5.7)                                                                 | 15 (3.7)                            | .08      |
| Current smoking                                           | 665 (7.3)                                                                 | 14 (3.4)                            | <.001    |
| Missing                                                   | 590 (6.5)                                                                 | 8 (2.0)                             |          |
| Charlson comorbidity index                                | 1.0 $\pm$ 0.8                                                             | 1.3 $\pm$ 0.8                       | <.001    |
| Obesity, $\geq 30$ kg/m <sup>2</sup>                      | 4,416 (48.3)                                                              | 225 (54.9)                          | .004     |
| Missing                                                   | 215 (2.4)                                                                 | 2 (0.5)                             |          |
| Gastroesophageal reflux disease                           | 1,346 (14.7)                                                              | 100 (24.4)                          | <.001    |
| Rhinitis                                                  | 2,679 (29.3)                                                              | 207 (50.5)                          | <.001    |
| Chronic sinusitis                                         | 1,247 (13.6)                                                              | 129 (31.5)                          | <.001    |
| Nasal polyp disease                                       | 134 (1.5)                                                                 | 27 (6.6)                            | <.001    |
| Eczema                                                    | 172 (1.9)                                                                 | 17 (4.1)                            | .001     |
| Asthma specialist visit                                   | 1,881 (20.6)                                                              | 186 (45.4)                          | <.001    |
| $\geq 7$ short-acting $\beta_2$ -agonist canisters        | 2,891 (31.6)                                                              | 171 (41.7)                          | <.001    |
| Leukotriene modifiers                                     | 1,612 (17.6)                                                              | 132 (32.2)                          | <.001    |
| Theophylline                                              | 175 (1.9)                                                                 | 16 (3.9)                            | .005     |
| Omalizumab                                                | 12 (0.1)                                                                  | 3 (0.7)                             | .02      |
| Global Initiative for Asthma step-care level              |                                                                           |                                     | <.001    |
| 1 or 2                                                    | 2,293 (25.1)                                                              | 58 (14.1)                           |          |
| 3                                                         | 3,224 (35.3)                                                              | 111 (27.1)                          |          |
| 4 or 5                                                    | 3,606 (39.5)                                                              | 240 (58.5)                          |          |
| Unclassified                                              | 13 (0.1)                                                                  | 1 (0.2)                             |          |
| Asthma Medication Ratio, $\geq 0.5$                       | 5,602 (61.3)                                                              | 258 (62.9)                          | .52      |
| Asthma exacerbations                                      |                                                                           |                                     |          |
| $\geq 1$                                                  | 2,205 (24.1)                                                              | 223 (54.4)                          | <.001    |
| $\geq 2$                                                  | 618 (6.8)                                                                 | 133 (32.4)                          | <.001    |
| $\geq 1$ ED or hospitalization                            | 571 (6.3)                                                                 | 61 (14.9)                           | <.001    |
| OCS average cumulative dosage                             |                                                                           |                                     | <.001    |
| No OCS Rx                                                 | 5,696 (62.3)                                                              | 60 (14.6)                           |          |
| $>0$ - $<2.5$ mg/d                                        | 2,853 (31.2)                                                              | 155 (37.8)                          |          |
| $\geq 2.5$ mg/d                                           | 587 (6.4)                                                                 | 195 (47.6)                          |          |
| OCS courses/y                                             |                                                                           |                                     | <.001    |
| None                                                      | 5,696 (62.3)                                                              | 60 (14.6)                           |          |
| 1-3                                                       | 3,172 (34.7)                                                              | 189 (46.1)                          |          |
| $\geq 4$                                                  | 268 (2.9)                                                                 | 161 (39.3)                          |          |
| Eosinophil count                                          | N = 2,250                                                                 | N = 142                             |          |
| cells/mm <sup>3</sup>                                     | 258 $\pm$ 263                                                             | 357 $\pm$ 465                       | .32      |
| $\geq 150$ /mm <sup>3</sup>                               | 1,403 (62.4)                                                              | 92 (64.8)                           | .56      |
| $\geq 300$ /mm <sup>3</sup>                               | 663 (29.5)                                                                | 56 (39.4)                           | .01      |
| $\geq 400$ /mm <sup>3</sup>                               | 398 (17.7)                                                                | 39 (27.5)                           | .004     |

\*P values determined by chi-square test or Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

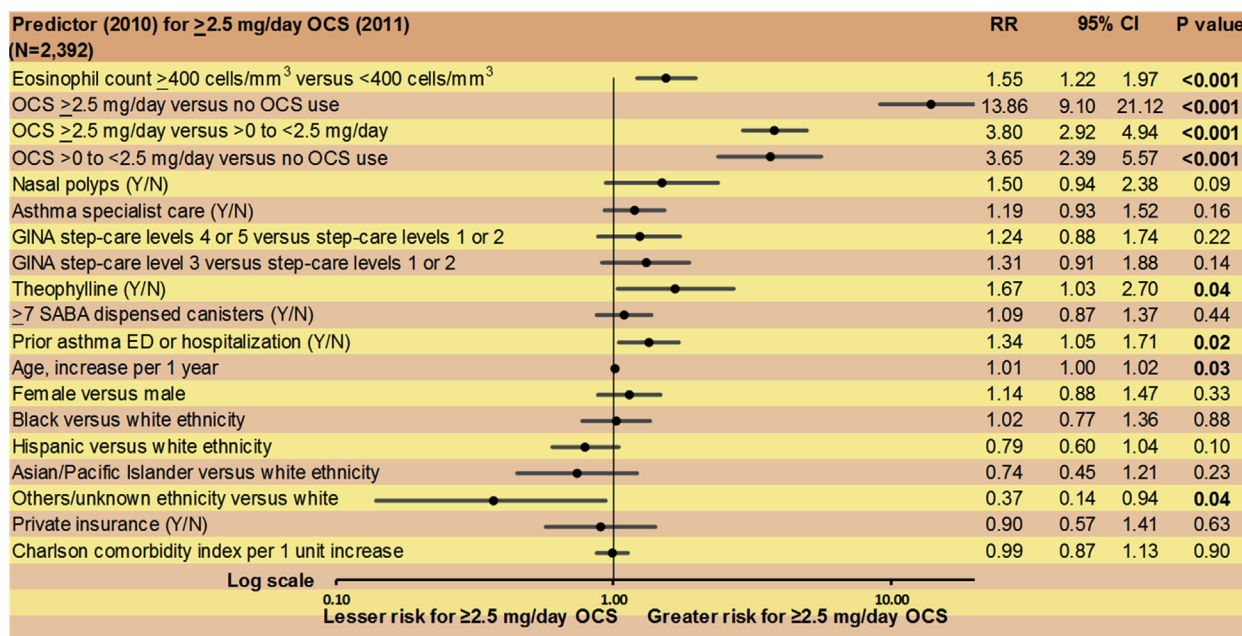


**FIGURE E1.** Adjusted RRs (95% CI) for C-OCS use defined as 2.5 mg/d or more in 2011 for each covariate (predictor) determined in 2010 in the regression model in 2,932 adult patients with persistent asthma with blood eosinophil count in 2010. Poisson regression models with robust error variance were used to estimate the adjusted RR and their 95% CIs. *N*, No; *Y*, yes.

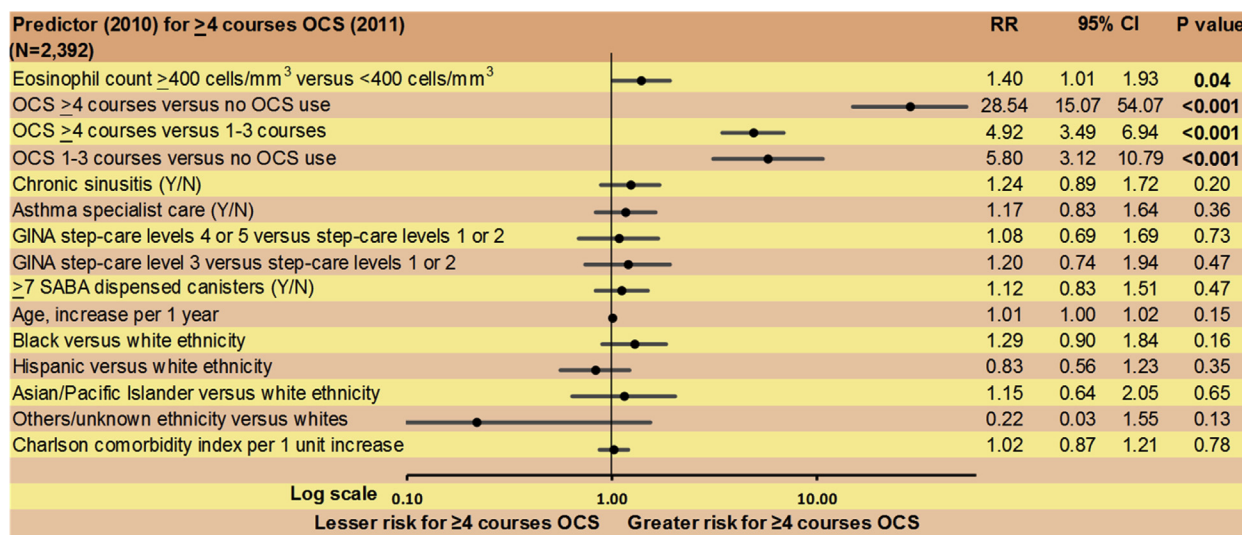


**FIGURE E2.** Adjusted RRs (95% CI) for C-OCS use defined as 4 or more courses in 2011 for each covariate (predictor) determined in 2010 in the regression model in 2,932 adult patients with persistent asthma with blood eosinophil count in 2010. Poisson regression models with robust error variance were used to estimate the adjusted RR and their 95% CIs. *N*, No; *Y*, yes.

Reproduced with permission of copyright owner.  
Further reproduction prohibited without  
permission.