

Trends in Omalizumab Utilization for Asthma: Evidence of Suboptimal Patient Selection



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What is already known about this topic? Omalizumab has been available as a treatment for asthma in the United States for 14 years.

What does this article add to our knowledge? Many omalizumab users have low or very low adherence to inhaled corticosteroid and/or inhaled corticosteroid-long-acting β -agonist inhalers in the 12 months before omalizumab initiation.

How does this study impact current management guidelines? The study findings highlight the need for control, risk, and adherence assessments when considering omalizumab for patients with asthma.

BACKGROUND: Utilization trends of omalizumab, a first-in-its-class asthma biologic approved in 2003 for individuals not controlled by inhaled corticosteroids (ICSs), may reveal lessons in patient selection.

OBJECTIVE: To describe utilization patterns for omalizumab since its introduction in 2003, with a focus on patient-level characteristics of patients for whom omalizumab was initiated.

METHODS: Using a large US database of administrative claims, we identified privately insured and Medicare Advantage

beneficiaries with asthma between 2003 and 2015.

Characteristics of incident (no omalizumab use in the previous 12 months) and prevalent users of omalizumab for asthma were described and omalizumab use trends graphed. A comparison cohort (1:5 matching proportion) of nonomalizumab users was compared with incident omalizumab users on demographic characteristics, medication adherence (medication possession ratio [MPR]) for ICSs and/or ICS/long-acting β -agonist (ICS-LABA), exacerbation frequency, and asthma control in the 6 months before omalizumab initiation.

RESULTS: We identified 7,658 prevalent and 3,399 incident omalizumab users. Omalizumab incidence peaked in the second quarter of 2004 at 0.65 per 1,000 individuals with asthma, whereas prevalence peaked in the fourth quarter of 2006 at 3.22; as of fourth quarter 2015, rates were 0.14 and 1.96, respectively. In the 12 months before omalizumab initiation, 72.5% had low adherence (MPR $\leq$ 0.75) and 48.6% had very low adherence (MPR $\leq$ 0.5) to ICSs and/or ICS-LABA. In the period 2003 to 2015, the mean number of exacerbations in the 12 months before incident use ranged from 1.50 to 2.11 and the proportion that had poor asthma control ($\geq$ 3 rescue inhalers dispensed) ranged from 54% to 67%. Incident omalizumab users were less likely to have good asthma control than the matched cohort of nonusers (adjusted odds ratio, 0.53 [0.48-0.59]).

CONCLUSIONS: Omalizumab use for asthma has been gradually decreasing following a peak shortly after its market availability. Many omalizumab users have low or very low adherence rates for ICSs and/or ICS-LABA in the 12 months before omalizumab initiation. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1568-77)

Key words: Asthma; Omalizumab; Medication adherence; Asthma exacerbation; Asthma control

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Abbreviations used

CIU- Chronic idiopathic urticaria
COPD- Chronic obstructive pulmonary disease
ED- Emergency department
EXCELS- Evaluating Clinical Effectiveness and Long-term Safety
in Patients with Moderate-to-Severe Asthma
HEDIS- Healthcare Effectiveness Dataset Information Set
ICS- Inhaled corticosteroid
ICS-LABA- Inhaled corticosteroid/long-acting β -agonist
MPR- Medication possession ratio
OLDW- OptumLabs Data Warehouse

corticosteroids (ICSs) in 2003.¹ Recently, 2 additional asthma biologics have been approved, both targeting IL-5: mepolizumab in 2015² and reslizumab in 2016.³ In addition, in 2016 an indication for asthma in 5- to 11-year-olds has been added for omalizumab.⁴ A systematic review and meta-analysis of 25 clinical trials concluded that omalizumab reduces asthma exacerbations when used as an adjunctive therapy to ICSs.⁵ Given the findings from clinical trials and the drug's label, one would expect to find individuals who start omalizumab to have frequent asthma exacerbations despite being highly adherent to ICSs and/or inhaled corticosteroid/long-acting β -agonist (ICS-LABA). However, trial conditions may be different than real-world clinical practice in important ways, including patient selection.⁶ Evidence from secondary data sources such as administrative claims can be useful to understand patient-level factors associated with medication use in clinical practice settings.⁷ The objective of this study was to describe utilization patterns for omalizumab since its introduction in 2003, with a focus on patient-level characteristics of patients for whom omalizumab was initiated.

METHODS

Data source

We conducted a retrospective cohort analysis using administrative claims from OptumLabs Data Warehouse (OLDW), which includes more than 110 million privately insured and Medicare Advantage enrollees throughout the United States, with highest representation from the South and Midwest.⁸ This study was deemed exempt from institutional board review because only deidentified data were used.

Cohort selection

Population. We identified all beneficiaries in OLDW with at least 12 months of continuous enrollment in both medical and pharmacy coverage between 2003 and 2015; 55 million unique individuals contributed 590 million person-quarters of coverage to the population denominator. Medicare Advantage beneficiaries accounted for 9% of person-quarters of coverage in the OLDW population (17.5% of person-quarters for people with asthma).

Asthma population. From the population, we identified 14,634,621 people with at least 1 asthma diagnosis code. We applied a modified version of the Healthcare Effectiveness Dataset Information Set (HEDIS) criteria for persistent asthma (described in more detail in this article's Online Repository available at www.jaci-inpractice.org) to yield a population of 1,702,300 people with asthma.⁹

Prevalent cohort. From the total population we identified 17,327 individuals who had a claim for omalizumab in pharmacy claims or medical claims (using Healthcare Common Procedure Coding System [HCPCS] codes C2917, S0107, and J2357). Among these omalizumab users, we applied the same modified HEDIS definition of asthma described above to create a cohort of 7,658 prevalent users of omalizumab.

The only other current clinical indication for omalizumab use is for treatment of chronic idiopathic urticaria (CIU). To avoid describing trends related to the treatment of CIU, we excluded all patients who had a CIU diagnosis (*International Classification of Diseases, Ninth Revision* code 708.1 and *International Classification of Diseases, Tenth Revision* code L50.1) after January 1, 2013, the year when the new indication was approved.

Incident cohort. To create the omalizumab incident cohort, we selected individuals from the prevalent cohort who had continuous medical and pharmacy insurance coverage for at least 12 months before the first recorded omalizumab use; this requirement ensures that we do not capture individuals who may have switched insurance and were continuing omalizumab use (and therefore reduces contamination of the cohort with prevalent users). There were 3399 incident users of omalizumab.

Comparison cohort. To better understand how incident omalizumab users may differ from other people with asthma, we created a comparison group of 1.7 million nonomalizumab users with asthma: (1) For each incident omalizumab user i , we calculated S_i : the number of days from meeting the modified HEDIS definition for asthma to the first use of omalizumab. (2) Then, each omalizumab user was matched to all nonomalizumab users who met the modified HEDIS definition for asthma in the same year and quarter and were still covered S_i days after meeting the modified HEDIS definition for asthma. (3) An anchor date was defined for each omalizumab user to be the date of first use and for each nonomalizumab user to be that user's asthma definition date plus the matched omalizumab user's value of S_i . (4) We calculated the number of asthma exacerbations (defined below) for each incident omalizumab user and matched nonomalizumab user in the 12 months before the anchor date. (5) Finally, where possible, we selected 5 nonuser matches for each omalizumab user with the same number of asthma exacerbations in the 12 months before the anchor date of omalizumab use. A single nonuser could be matched to multiple users of omalizumab, and therefore be included in the comparison analysis multiple times over different time periods. We did not follow a similar matching procedure for prevalent omalizumab users because we are unable to determine key information about these users' initiation of the drug and therefore cannot create a suitable comparison sample.

Variable definitions

Medication possession ratio. Asthma medications were identified using National Drug Codes (NDCs) from the HEDIS definition criteria as we have previously described using OLDW data.^{10,11} Medication adherence was assessed using medication possession ratio (MPR) and was calculated using the HEDIS asthma criteria to define medication dispensing events.¹⁰ The MPR is a measure of a patient's adherence to prescribed medication. It is equal to the sum of the number of days of medication the patient has from prescription fills divided by the number of days in the period. For example, a patient filling one 30-day prescription over a period of 60

days would have an MPR of 0.50. Because patients often fill their asthma medications with a 90-day supply each time, we looked back an additional 90 days beyond the 12 months for which we calculated the MPR and counted any medication that would be available as of 12 months before the anchor date. Using this rule, a patient filling a 90-day supply 14 months before the anchor date would start the 12-month MPR measurement period with 30-day medication supply.

The MPR was determined for ICS and ICS-LABA products, selected because of the indication of omalizumab for individuals with asthma not controlled by ICSs. A cutoff value of 0.75 or more for MPR for ICSs and/or ICS-LABA was selected as the threshold associated with decreased asthma exacerbations.¹² Another study, defining regular use as at least 1 ICS fill each quarter for a 1-year period, found evidence of decreased hospitalization for asthma and implies that thresholds lower than 0.75 may also lead to reduced exacerbations (as compared with low adherence).¹³ For the purposes of this study, given that the primary outcome for omalizumab studies was asthma exacerbations, we therefore defined low adherence to ICSs and/or ICS-LABA as an MPR of less than 0.75 but also reported less than 0.50 as very low adherence.

Asthma exacerbations. Asthma exacerbations were defined by hospitalization with asthma as the primary diagnosis, or emergency department (ED) visit with asthma as the primary diagnosis, or oral steroid within 1 month of an outpatient visit with asthma.^{14,15} We allowed no more than 1 asthma exacerbation to be counted in any 30-day period to avoid double or triple counting exacerbations that met all 3 criteria and but represented only 1 exacerbation episode.

Asthma control. To estimate asthma control¹⁶ in our omalizumab incident cohort and comparison cohort, we counted rescue inhaler pharmacy fills, noting that fewer than 3 rescue inhaler fills in a year have been validated against patient-reported good asthma control in a previous study.¹⁷

Specialist access and *high deductible health plan* variables are defined in the Methods section of this article's Online Repository at www.jaci-inpractice.org.

Statistical analysis

Prevalence and incidence trends of omalizumab use were described per 1,000 individuals with asthma and graphed on a quarterly basis. Omalizumab and nonomalizumab users were compared using chi-square tests with unadjusted proportions to present the observed demographic characteristics of omalizumab users.

To analyze incident omalizumab users, we present both unadjusted proportions and adjusted rate ratios. Conditional (fixed effects) logistic regression with robust SEs was used to produce an adjusted comparison of demographic characteristics in the incident omalizumab user group and the matched nonuser cohort. We present adjusted odds ratios from this analysis. An adjusted odds ratio of greater than 1 indicates that people with the characteristic had higher odds of being omalizumab users than people without the characteristic (or people with the base-level characteristic). All demographic variables were included in the regression to allow direct comparison on each characteristic while holding constant all other characteristics. The MPR was described as mean proportion, asthma exacerbations as mean total and also in ED and hospitalization subcategories, and asthma control as mean rescue inhaler fills and as proportion that had 3 or more in the previous 6 months. Population's demographic characteristics (sex, race/ethnicity, annual household income, age at entry to cohort, use of specialists, MPRs, asthma control, geography,

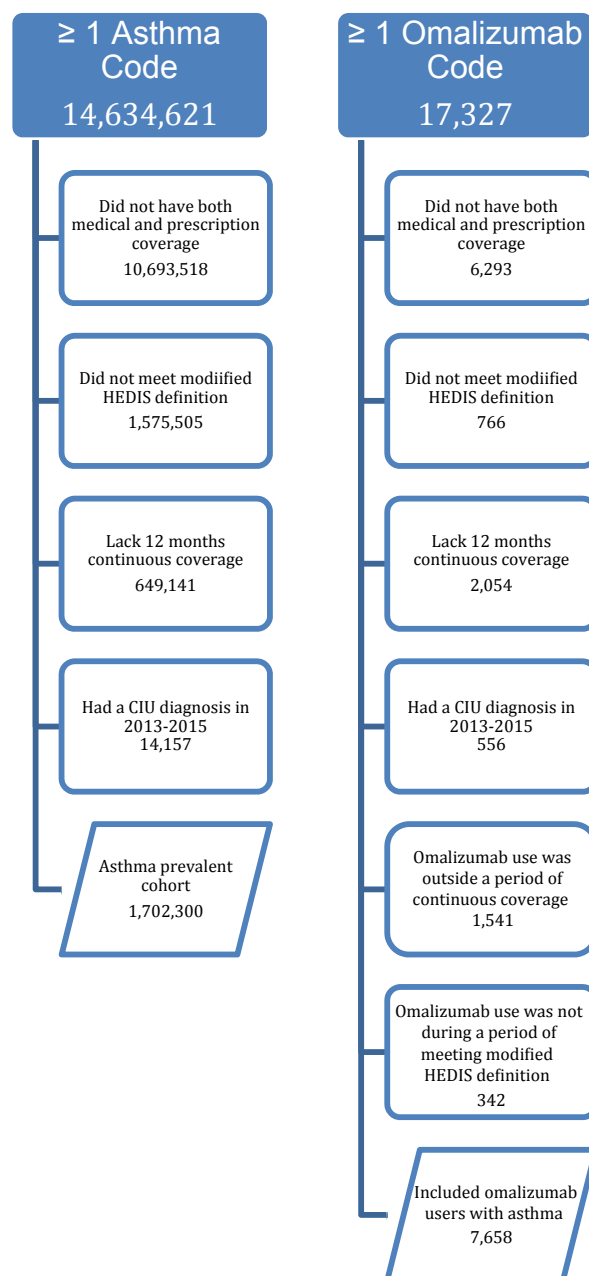


FIGURE 1. Asthma and prevalent omalizumab cohorts.

and insurance plan eligibility for a Health Savings Account/Health care Reimbursement Account) were categorized and compared using Pearson chi-square tests and Stuart-Maxwell tests of marginal homogeneity.¹⁸ Statistical analysis was performed using Stata version 14 software (StataCorp LLC, College Station, Texas).

RESULTS

Prevalent cohort

Starting with 14,634,621 individuals in the data set with at least 1 asthma diagnosis code, a cohort of 1,702,300 included individuals with asthma was identified after excluding 10,693,518 who lacked both medical and prescription coverage, 1,575,505 who failed to meet the modified HEDIS criteria, and

TABLE I. Descriptive statistics: Prevalent cohort demographic characteristics

Demographic characteristic (%)	Unadjusted percentages		P value (Pearson χ^2)
	Asthma prevalent cohort excluding omalizumab users (n = 1,694,642)	Omalizumab prevalent cohort (n = 7,658)	
Female	54.9	61.7	<.001
Race/ethnicity			.062
White	72.4	73.5	
Black	10.1	10.1	
Hispanic	8.4	8.3	
Asian	2.9	2.6	
Unknown	6.2	5.5	
Annual household income			<.001
<\$40,000	14.9	12.1	
\$40,000-50,000	5.3	5.0	
\$50,000-59,000	5.2	5.5	
\$60,000-74,000	7.3	8.3	
\$75,000-99,000	10.5	12.6	
>\$100,000	27.8	32.5	
Unknown	29.1	24.1	
Age at entry into cohort (y)			<.001
0-9	20.7	2.4	
10-17	10.4	7.1	
18-34	12.7	17.0	
35-44	12.0	22.2	
45-54	14.6	25.7	
55-64	13.4	18.1	
≥65	16.1	7.5	
Geography (census division)			<.001
East North Central	17.3	12.2	
East South Central	4.4	3.7	
Mid Atlantic	8.5	6.7	
Mountain	8.3	10.7	
New England	4.7	3.1	
Pacific	5.8	5.0	
South Atlantic	26.5	28.6	
West North Central	11.4	8.9	
West South Central	13.1	13.1	
Unknown/other	0.1	8.1	
High deductible health plan	7.0	7.9	.003

smaller groups who failed to have 12 months of continuous coverage or had a CIU diagnosis after 2013. A cohort of omalizumab users yielded 17,327 individuals with at least 1 billing code for omalizumab. The exclusion criteria for coverage, asthma HEDIS definition, and CIU diagnosis were applied to yield a final prevalent cohort of 7,658 individuals. [Figure 1](#) summarizes the prevalent omalizumab cohort and asthma cohort using a flow diagram. Prevalent omalizumab users were those with any omalizumab use during the time we observed them.

The following demographic characteristics of the omalizumab prevalent cohort were different than those of the asthma cohort that did not use omalizumab: sex (61.7% females in omalizumab users vs 54.9% in nonusers; $P < .001$), annual household income (higher income in the omalizumab group; $P < .001$), age (less likely to be younger than 18 years or older than 65 years in the omalizumab group; $P < .001$), geography (census division: higher South Atlantic, Mountain, and unknown/other in the

omalizumab group; $P < .001$), and in proportion covered by a high deductible health plan (8.5% in the omalizumab group vs 7.5%; $P = .003$) ([Table I](#)).

Trends in prevalent omalizumab use from 2003 to 2015 illustrate that the peak prevalence of omalizumab use occurred in the fourth quarter of 2006 at 3.22 of 1,000 individuals with asthma (n = 1,311 of 407,531 person-quarters) ([Figure 2](#)). Prevalence declined beginning in 2007 until 2014 after which a trend of increasing prevalence was observed until the final quarter in 2015 when the rate was 1.96 per 1,000 individuals with asthma (n = 834 of 424,956 person-quarters).

Incident cohort

Incident omalizumab users were those from the prevalence cohort who had at least 12 months between cohort entry and first omalizumab use, resulting in 3,399 individuals in the omalizumab incidence cohort. A parallel comparison cohort of individuals was

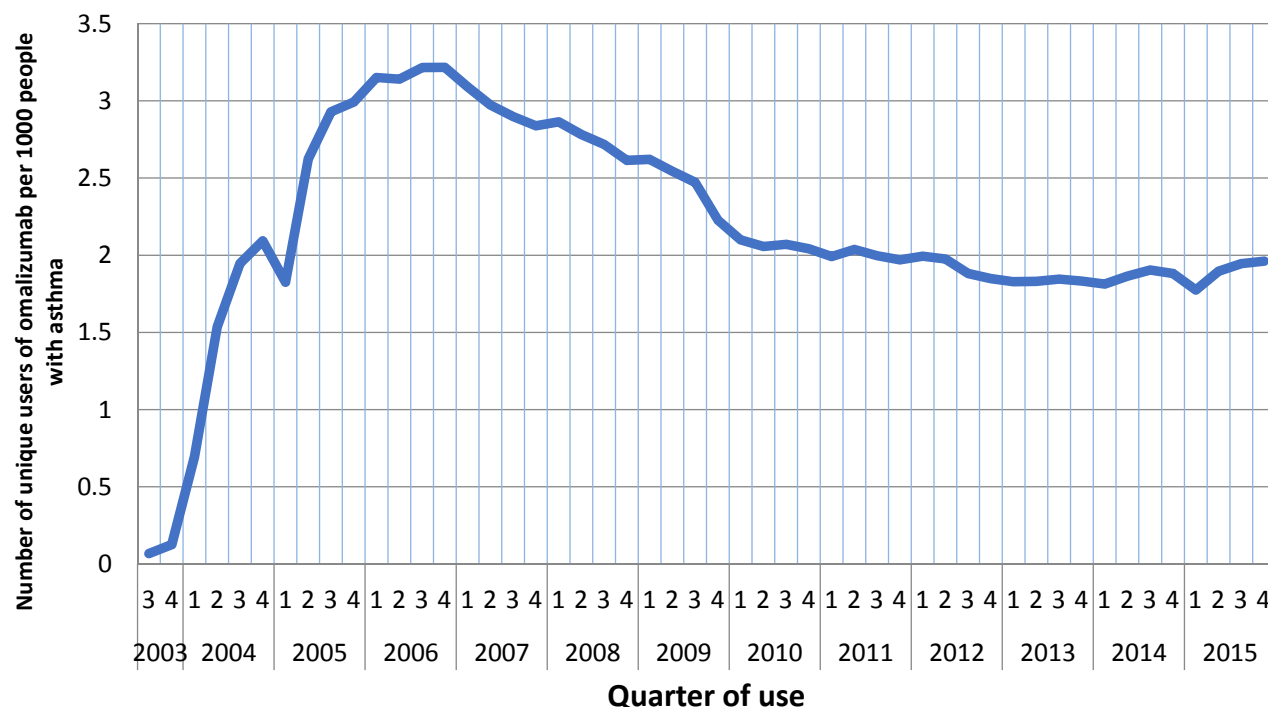


FIGURE 2. Unique, prevalent omalizumab users, 2003-2015 (N = 7,658 prevalent omalizumab users).

created by applying the matching criteria described in the Methods section, eliminating 96,934 of the 1,694,642 prevalent asthma patients who did not use omalizumab, and randomly selected 5 matched controls for each incident omalizumab user as described in the Methods section, resulting in 16,579 in the matched nonomalizumab incident cohort. Figure 3 displays the incident cohort development in flow diagram format. Of 3,399 incident omalizumab users, 40 could not be matched to non-omalizumab users. These nonmatched individuals had much higher rates of exacerbations in the 12 months leading up to their first use of omalizumab: mean 8.33 ± 1.75 exacerbations for the unmatched incident users versus 1.72 ± 1.77 exacerbations for users who were matched to nonusers. The conditional logit analysis necessarily omits the unmatched users.

After adjusting for all observed characteristics as described in the Methods section, the incident omalizumab cohort differs from the matched nonomalizumab controls in sex (less likely to be female in the omalizumab group), household income (more likely to have income of \$50-59K or income above \$100,000), age (less likely to be 0-17 and 55 years or older in the omalizumab group), specialist care (more likely to have allergist or pulmonologist care in the omalizumab group), medication possession (less likely to have an MPR of 0), asthma control (less likely to have fewer than 3 rescue inhaler fills), and geography (more likely to be East South Central, Mountain, Pacific, South Atlantic, and West South Central), but not in race/ethnicity, or coverage via high deductible health plan (Table II). The major effect of adjusting for other characteristics was to demonstrate that once we adjust for age, specialist care, MPR, asthma control, region of the country, income, race, and high deductible health plan, women are less likely than men to receive omalizumab. See this article's Online Repository at www.jaci-inpractice.org for a description of the cohort after excluding chronic obstructive

pulmonary disease (COPD) and other respiratory disease diagnoses.

Trends in incident omalizumab use from 2003 to 2015 reveal a peak incidence in the second quarter of 2004 of 0.65 per 1,000 individuals with asthma ($n = 192$ out of 295,361 person-quarters), with a steady decline in incident use until 2012, and perhaps an increase from 2013 to 2015 (see Figure 4); incident omalizumab use at the end of 2015 was 0.14 per 1,000 individuals with asthma ($n = 61$ out of 424,956 person-quarters).

ICS and/or ICS-LABA adherence and asthma exacerbations in the 12 months before omalizumab initiation

There was no observed trend in adherence rates for ICSs and/or ICS-LABA between 2003 and 2015 (Figure 5, A). Among incident omalizumab users with at least 15 months of insurance coverage before first omalizumab use, 72.5% had low adherence ($MPR \leq 0.75$) and 48.6% had very low adherence ($MPR \leq 0.5$) to ICSs and/or ICS-LABA in the 12 months before first use (Figure 5, B).

There was a slight upward trend in the number of asthma exacerbations in the 12 months before omalizumab initiation from 2005 to 2013 (Figure 6, A), with little trend seen when looking at hospitalizations and ED visits separately (Figure 6, B), suggesting that the growth in exacerbations may have been driven by outpatient exacerbations. These data also demonstrate that most of the exacerbations measured in the study were not defined by hospitalization or ED visits. The mean number of exacerbations in the previous 12 months ranged from 1.50 to 2.11 in the period 2003 to 2015. There were no clear trends for the number of rescue inhaler claims in this period; the proportion of omalizumab incident users who had 3 or more rescue inhalers dispensed ranged from 54% to 67% in this period.

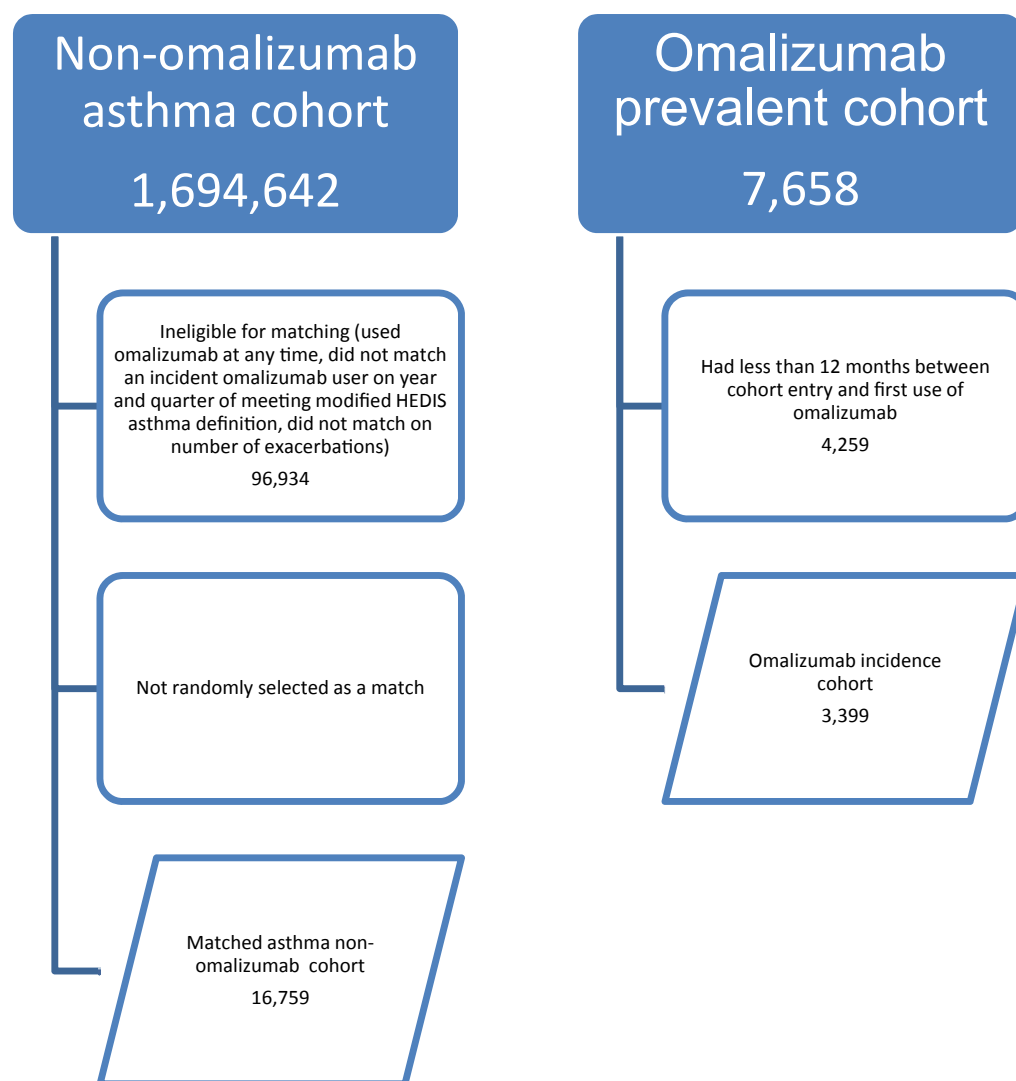


FIGURE 3. Incident cohorts.

(see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

An analysis of omalizumab utilization reveals an important opportunity to improve patient selection. Omalizumab use for asthma has remained steadily low since its approval in 2003, with a quarterly average incidence and prevalence of 0.2 and 2.2 omalizumab users, respectively, per 1,000 individuals with asthma. Given estimates of the uncontrolled asthma population at 5% to 10%¹⁹ and that most such patients have aeroallergen sensitivity^{20,21} and are likely to meet the labeled indications for omalizumab, our study suggests that a large group of individuals who may benefit from omalizumab are not receiving it. However, given the very small group of individuals who use omalizumab for asthma, one could expect them to be highly selected on the basis of previous asthma outcomes and failure of other asthma medications. Contrary to expectations, we found that many omalizumab users had good asthma control, few

hospitalizations and ED visits for asthma, and did not have sufficient ICS and/or ICS-LABA treatment in the 12 months before starting omalizumab. Taken together, these findings raise questions about optimal patient selection for omalizumab in real-world clinical practice settings.

Our incidence and prevalence estimates are consistent with reports about omalizumab use from the Food and Drug Administration's Sentinel database; in Sentinel, the incidence of omalizumab use ranges from about 1 to 5 per 100,000 and is very close to the 1.60 to 4.92 per 100,000 insured people in our sample (data not shown).²² However, unlike Sentinel, which includes only age and sex demographic characteristics, our study provided additional insights into omalizumab patient selection by considering asthma outcomes and medication use leading up to omalizumab initiation.

Other studies have considered ICS adherence and omalizumab use. A study in 2004-2005 using claims data found an adherence rate of 52% for asthma controller medications in 318 individuals during the year before initiating omalizumab.²³ Another interesting finding from this same study shows that

TABLE II. Descriptive statistics: Incident cohort characteristics

Demographic characteristic (%)	Unadjusted percentages			Adjusted odds ratio (95% CI) [†] (n = 20,154) [‡]
	Matched asthma nonomalizumab cohort (n = 16,795)	Omalizumab incident cohort (n = 3,399)	P value (Stuart-Maxwell marginal homogeneity test)*	
Female	56.0	61.0	.000	0.83 (0.75-0.92) [§]
Race/ethnicity			.002	
White	70.0	73.8		(base)
Black	12.1	10.8		1.07 (0.91-1.26)
Hispanic	10.0	8.2		0.95 (0.79-1.14)
Asian	3.0	2.8		0.89 (0.65-1.21)
Unknown	5.0	4.5		0.87 (0.69-1.11)
Annual household income			.000	
<\$40,000	13.3	10.8		(base)
\$40,000-50,000	5.5	4.5		0.99 (0.75-1.32)
\$50,000-59,000	5.0	5.6		1.40 (1.08-1.82) [§]
\$60,000-74,000	7.5	7.3		1.15 (0.92-1.43)
\$75,000-99,000	10.6	11.8		1.15 (0.94-1.42)
>\$100,000	27.7	33.8		1.29 (1.08-1.54) [§]
Unknown	30.4	26.2		0.99 (0.82-1.19)
Age at entry into cohort (y)			.000	
0-9	34.5	6.5		0.09 (0.07-0.11) [§]
10-17	4.7	4.2		0.56 (0.43-0.71) [§]
18-34	10.7	17.0		(base)
35-44	12.1	24.2		1.16 (0.99-1.36)
45-54	15.9	26.8		0.89 (0.76-1.04)
55-64	11.2	16.2		0.74 (0.62-0.88) [§]
>65	11.0	5.3		0.31 (0.25-0.39) [§]
Use of specialists in the 12 mo before anchor date				
At least 1 allergist visit	23.1	65.9	.000	9.89 (8.83-11.06) [§]
At least 1 pulmonologist visit	26.7	49.9	.000	4.22 (3.76-4.73) [§]
MPR (12 mo)			.000	
<15 mo coverage	5.8	4.2		0.57 (0.43-0.76) [§]
0	27.0	11.7		0.51 (0.42-0.63) [§]
>0-.25	9.2	10.4		1.18 (0.95-1.46)
>.25-.5	20.0	24.4		1.05 (0.87-1.26)
>.5-.75	22.9	22.9		0.91 (0.76-1.09)
>.75-.9	8.5	11.4		(base)
>.9-<1	5.0	6.0		0.88 (0.69-1.13)
1	5.4	9.0		1.26 (1.00-1.59) [§]
Asthma control			.000	
Good control: <3 rescue inhaler fills (12 mo)	52.4	39.1		0.53 (0.48-0.59) [§]
Poor control: 3+ rescue inhaler fills (12 mo)	47.6	60.9		(base)
Geography (census division)			.000	
East North Central	17.5	13.1		(base)
East South Central	3.9	4.2		1.35 (1.03-1.77) [§]
Mid Atlantic	8.0	7.8		1.05 (0.83-1.31)
Mountain	7.8	8.3		1.86 (1.52-2.28) [§]
New England	4.7	4.4		1.05 (0.79-1.39)
Pacific	4.8	4.9		1.52 (1.19-1.94) [§]
South Atlantic	27.4	31.7		1.56 (1.33-1.83) [§]
West North Central	12.3	10.5		1.11 (0.92-1.35)

(continued)

TABLE II. (Continued)

Demographic characteristic (%)	Unadjusted percentages			Adjusted odds ratio (95% CI) [†] (n = 20,154) [‡]
	Matched asthma nonomalizumab cohort (n = 16,795)	Omalizumab incident cohort (n = 3,399)	P value (Stuart-Maxwell marginal homogeneity test) [*]	
West South Central	13.6	14.2		1.38 (1.15-1.67) [§]
Unknown/other	—	—		0.00 (0.00-0.00)
Plan eligible for HRA or HSA	8.3	8.0	0.782	0.88 (0.73-1.07)

HRA, Health care Reimbursement Account; HSA, Health Savings Account.

^{*}Symmetry test applied to omalizumab user and 1 matched nonuser. All off-diagonal totals were greater than 20.

[†]Adjusted odds ratios using conditional (fixed effects) logistic regression with robust SEs; ratios greater than 1 indicate people with characteristic are more likely to be omalizumab users compared with those without the characteristic (or with the base level of the characteristic). All variables presented in the table were included in the regression analysis.

[‡]Conditional logit analysis excludes 40 incident omalizumab users for whom no matched nonuser could be found. These 40 users had very high exacerbation counts in the 12 mo leading up to their first use of omalizumab (mean, 8.3 ± 1.7 vs 1.7 ± 1.8 for incident omalizumab users who could be matched to nonusers).

[§] $P \leq .05$.

^{||}Cell size < 11.

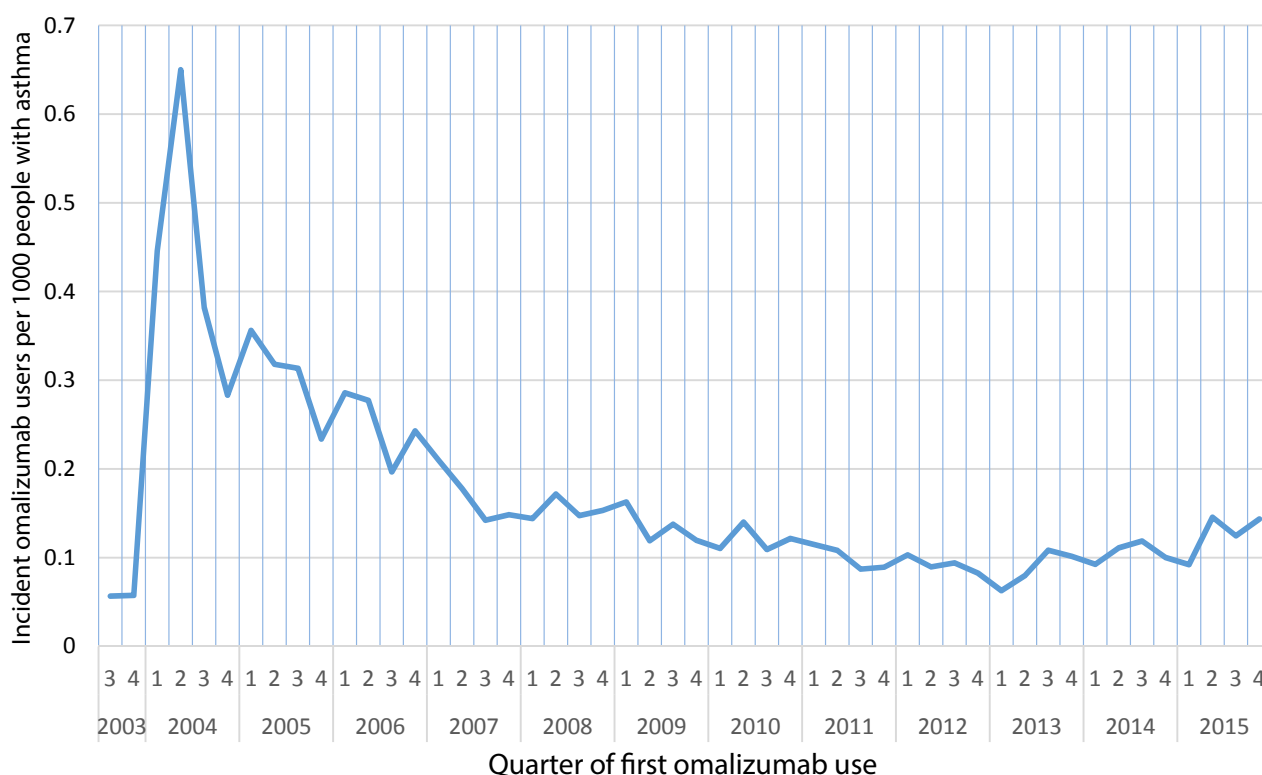


FIGURE 4. Unique incident omalizumab users, 2003-2015 (N = 3,399 incident omalizumab users).

adherence to ICSs or ICS/LABA decreases after omalizumab is started; over the long-term, treatment persistence with omalizumab is far higher (54%) than with ICSs or ICS/LABA (19%).²³ Adherence to ICSs and ICS/LABA should be considered in the context of overall low adherence rates in multiple asthma studies.²⁴ The “Evaluating Clinical Effectiveness and Long-term Safety in Patients with Moderate-to-Severe Asthma (EXCELS)” was a 5-year prospective study that enrolled 5041 omalizumab users and 2886 who were not using omalizumab.²⁵ In EXCELS, 25% of new omalizumab users had good asthma control, as measured by the Asthma Control Test, which is lower than the 33% to 46% we estimated using a validated claims data definition of asthma control in the present study.²⁶ These differences may be related to patient selection (registry enrolled vs

passively collected in claims data) or the difference in asthma control assessment (direct patient report based on 4-week recall vs claims data based on 12 months of rescue inhaler refills). Like in EXCELS, we identified a group of patients who start omalizumab with good asthma control. It is hypothesized that these patients have high risk based on previous asthma exacerbations, though additional studies are needed to better understand this group of patients. In EXCELS, the investigators categorized exacerbation frequency into very frequent, rare, and so forth, so it is difficult to directly compare our findings of an average of 1.5 to 2.1 asthma exacerbations in the previous 12 months with their findings. Notably, both studies identified a group of patients who have no recent asthma exacerbations leading up to omalizumab initiation. This group is of particular interest given that the

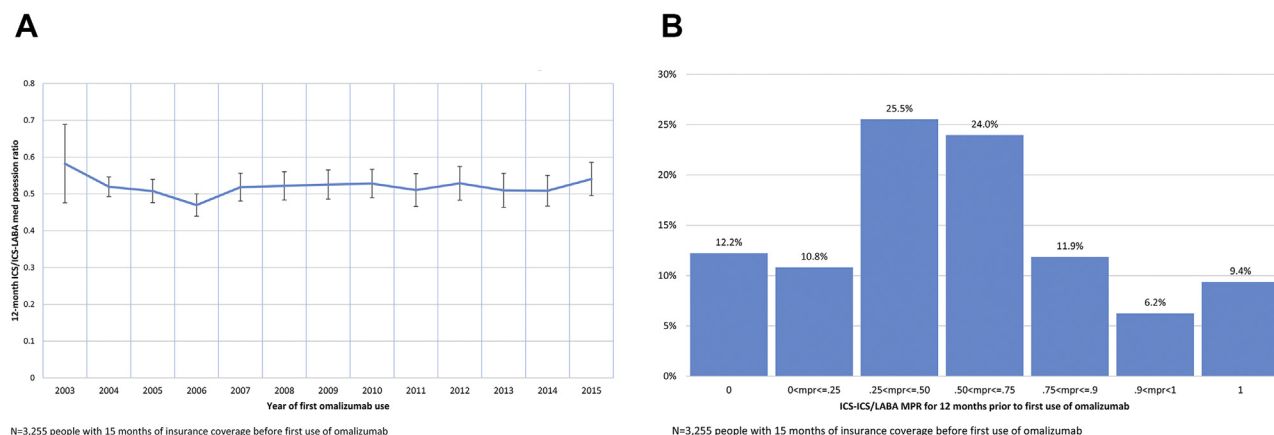


FIGURE 5. A, Mean MPR of ICSs and/or ICS-LABA 12 months before incident omalizumab use, 2003-2015. Bars represent 95% CIs. **B,** MPR of ICSs and/or ICS-LABA 12 months before incident omalizumab use, 2003-2015, by percentage. Bars represent 95% CIs.

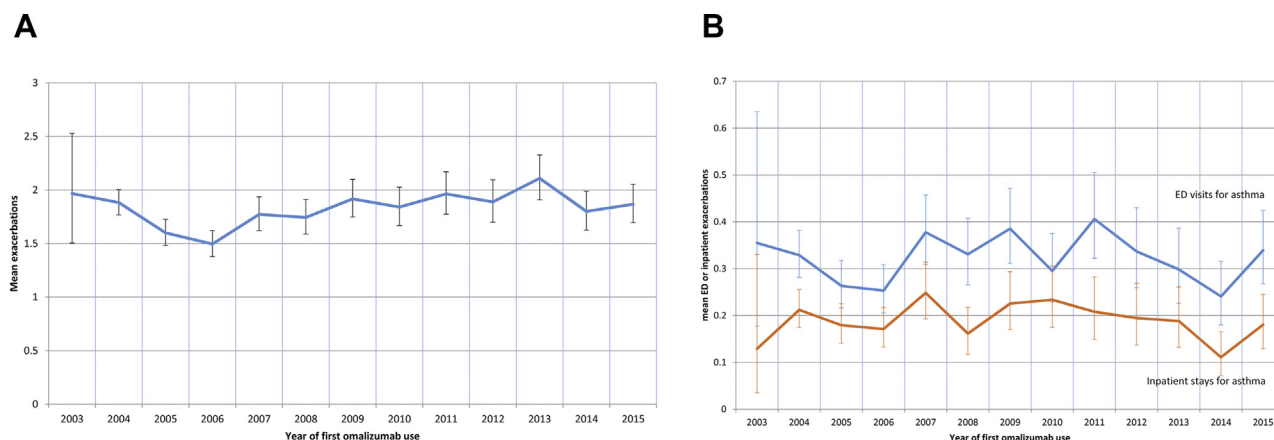


FIGURE 6. A, Mean number of asthma exacerbations 12 months before incident omalizumab use. Bars represent 95% CIs. **B,** Mean number of ED and inpatient hospitalizations for asthma in 12 months before first omalizumab use. Bars represent 95% CIs.

primary expected outcome, based on data from multiple prospective clinical trials, is reduced asthma exacerbations.⁵

There are several important limitations when considering the findings from this study. First, omalizumab is recommended for individuals with asthma not controlled on ICSs who have a serum IgE level between 30 and 700/1500 IU/mL and who have a positive allergy test result to a perennial allergen. In this study, we did not link laboratory or allergy test results to individuals, preventing additional judgments of individual suitability for omalizumab. In addition, we included children younger than 12 years in the study even though omalizumab was not approved for children 6 to 11 years old until 2016 in the United States. Second, the OLDW sample includes data from a major insurer, and the utilization patterns may be influenced by insurer coverage policies. However, on review of coverage policies, which are available for the time periods we studied, they are consistent with the labeling of the drug.²⁷ Enforcement or approval processes nonetheless may vary by payer, and this remains a limitation of this study. Third, using claims data has inherent limitations, which require some key assumptions. For example, we used rescue inhaler pharmacy fills as a marker for asthma control, which was previously validated in a different population¹⁷ but may not work the best for a cohort of patients

using omalizumab. Also, pharmacy filling of an asthma medication is only an estimate for adherence, which requires not only acquiring the medication from the pharmacy but also using the medication on schedule with good technique. Pharmacy filling also does not capture medication samples that may be given directly to patients, and we were unable to identify an estimate of medication sampling frequency in this population. Another example is using claims for ED and hospitalization and restricting for first diagnostic position for asthma; it is possible that asthma exacerbations are undercounted using these methods. However, many events would be captured also by a prescription for an oral corticosteroid and the total count for exacerbations is less likely to be undercounted.

The limitations of the study are balanced by its strengths. First, we used definitions and outcomes that were previously validated, and our findings were consistent with other reports. Second, the size of the population included in OLDW allowed us to identify a large sample of omalizumab users and similar nonomalizumab users. Third, we showed trend data for 13 years, whereas previous studies were limited to shorter follow-up periods. Fourth, the OLDW contained many important demographic variables and included individuals from all regions of the United States, increasing the generalizability of the findings.

Finally, these data are derived from real-world clinical settings, also increasing the generalizability of the findings.⁷

Future research will provide additional context for these findings. For example, linking data for IgE, allergy tests, blood eosinophil counts, and lung function tests to the claims data could provide important detail about current patient selection for omalizumab. In such a study with links to additional clinical/laboratory data, analysis of individuals who did not receive omalizumab but otherwise appeared to meet the criteria for using omalizumab would shed light on potential underuse of omalizumab. Our demographic data suggest that age, sex, and geographic disparities for omalizumab use may not be explained by the epidemiology of allergic asthma (ie, patient selection influenced by factors not known to influence omalizumab response). Further research is needed to better understand these disparities. Also, individuals with a comorbid diagnosis of COPD may respond differently to omalizumab and represent a surprisingly high fraction of the omalizumab users in this study, and merit further investigation. It is unclear from clinical trial data whether omalizumab is effective for COPD or for the asthma-COPD overlap syndrome. Finally, our findings raise questions about ICS and/or ICS-LABA use during omalizumab treatment. Of the 25 studies identified in a recent systematic review and meta-analysis of omalizumab for asthma, only 2 studies assessed outcomes in subjects not on either inhaled or oral steroids.⁵ In one study, no difference was found in FEV₁ (only outcome reported) and in another no difference in bronchial hyperresponsiveness (only outcome reported).⁵ A recent systematic review of real-life effectiveness studies for omalizumab in adults with asthma²⁸ found only 2 relevant studies, one of which had a run-in period to select for adherence²⁹ and another of which excluded nearly 50% of individuals because of study selection criteria.³⁰ These findings, along with the description of omalizumab users in OLDW, raise the question about outcomes for those who use omalizumab while having low adherence to ICSs and/or ICS-LABA.

In summary, this study suggests that a large number of patients have not had adequate treatment with ICSs and/or ICS-LABA in the 12 months leading up to omalizumab initiation. In addition, many who start omalizumab appear to have good asthma control and few asthma exacerbations. However, use of omalizumab remains very low among individuals with asthma, and many individuals who may benefit from omalizumab are not being selected for initiation. Our findings support the need for the development and testing of innovative solutions to optimally identify individuals most likely to benefit from omalizumab.

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METHODS

Modified HEDIS definition

The HEDIS definition for persistent asthma was met if 1 of the following conditions was met: (1) 4 or more asthma medications dispensed, (2) 1 or more ED or hospitalization with primary diagnosis of asthma, or (3) 4 or more asthma outpatient visits with 2 or more asthma medications dispensed over a 1-year period.^{E1} Our modifications were as follows: (1) we used a rolling 1-year time period rather than a calendar year; (2) we required only 1 year of meeting the asthma criteria instead of at least 2 years to reduce bias from requiring long periods of continuous enrollment in our sample; and (3) we did not apply the following diagnosis exclusion criteria: COPD/emphysema (other emphysema)/obstructive chronic bronchitis, chronic respiratory conditions due to fumes/vapors, cystic fibrosis, and acute respiratory failure. We included COPD and other respiratory disease codes in the cohort because the only labeled indication for omalizumab among these disorders is asthma. We provide a sensitivity analysis describing the cohort with and without excluding COPD and other respiratory disease codes listed in HEDIS exclusion to allow comparisons with the HEDIS asthma population.

Variable definitions

Specialist access. Because specialist physicians are more likely than primary care physicians to prescribe omalizumab, we measured whether each patient in the incident and matched

cohort had seen a pulmonologist and/or an allergist in the 6 months before the anchor date.

High deductible health plan. Some beneficiaries in the sample had high deductible health plans; they are identified by a variable indicating whether their health plan qualifies for a Health care Reimbursement Account or a Health Savings Account. As of 2016, Health Savings Account–linked high deductible health plans are required to have a limit of \$1,300 for single coverage or \$2,600 for family coverage. There is no specific deductible requirement for Health care Reimbursement Accounts, but they are frequently offered with high deductible health plans.^{E2}

RESULTS

Because of concerns about modifying HEDIS criteria to allow for COPD and other respiratory disease diagnoses, we also described our incident cohort after applying these exclusion criteria, finding similar differences as those described when comparing incident omalizumab users to a matched cohort except that excluding COPD and other respiratory disease diagnoses yielded a younger cohort (Table E1). Most of the exclusions were for a diagnosis of COPD and not for other respiratory diseases (Table E2). The number of reliever fills in 12 months are higher in the omalizumab incident cohort compared to the matched cohort of nonomalizumab users (Table E3).

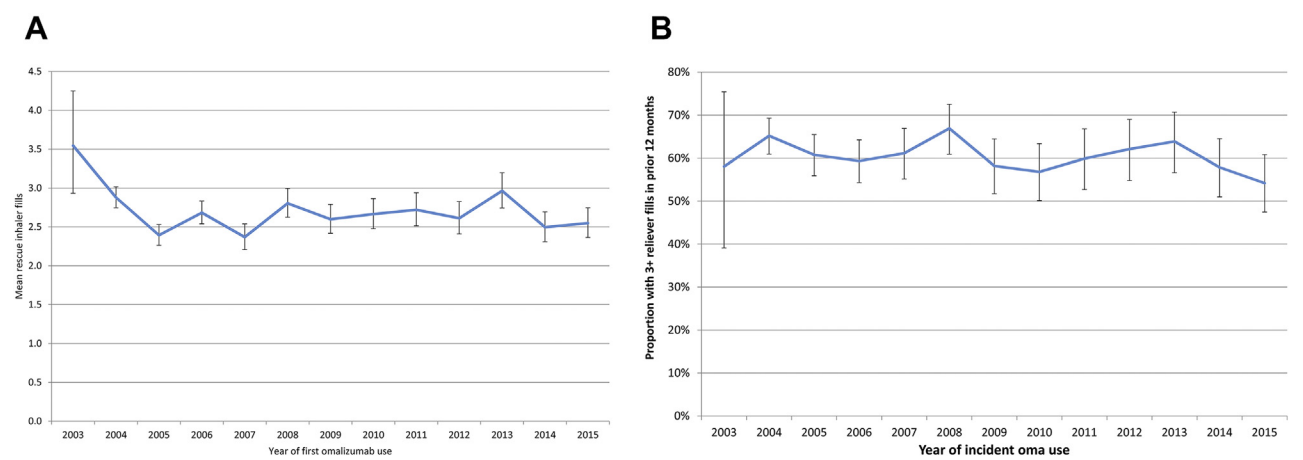


FIGURE E1. A, Mean number of rescue inhaler claims 6 months before first omalizumab use. Bars represent 95% CIs. **B,** Percentage of individuals with at least 3 rescue inhaler claims 6 months before first omalizumab use. Bars represent 95% CIs. *Oma*, Omalizumab.

TABLE E1. Sensitivity analysis using HEDIS exclusion diagnosis codes

Demographic characteristic (%)	Matched asthma nonomalizumab cohort (n = 7,130)	Omalizumab incident cohort (n = 1,461)	P value (Stuart-Maxwell test of marginal homogeneity)
Female	50.9%	58.9%	<.001
Race/ethnicity			.011
White	70.4	75.1	
Black	11.1	8.2	
Hispanic	9.5	8.7	
Asian	3.4	3.3	
Unknown	5.6	4.8	
Annual household income			.101
<\$40,000	8.2	7.3	
\$40,000-50,000	4.2	3.1	
\$50,000-59,000	4.6	5.1	
\$60,000-74,000	7.4	7.1	
\$75,000-99,000	11.0	10.3	
>\$100,000	33.6	38.0	
Unknown	31.1	29.2	
Age at entry into cohort (y)			<.001
0-9	46.1	10.5	
10-17	6.4	7.3	
18-34	12.9	22.9	
35-44	12.1	26.8	
45-54	12.1	21.8	
55-64	7.0	9.1	
≥65	3.4	1.6	
Geography (census division)			<.001
East North Central	16.9	11.6	
East South Central	2.9	4.0	
Mid Atlantic	8.4	7.2	
Mountain	8.0	11.7	
New England	4.0	2.3	
Pacific	5.1	6.4	
South Atlantic	25.7	29.2	
West North Central	13.0	11.6	
West South Central	15.9	16.1	
Unknown/other	X*	X*	
High deductible health plan			.074
Plan eligible for HRA or HSA	9.7	8.6	

HRA, Health care Reimbursement Account; HSA, Health Savings Account.

*Values 10 or less are not allowed to be reported in OLDW for the overall purpose of maintaining deidentified data.

TABLE E2. COPD and other respiratory disease exclusion cohorts

HEDIS Exclusion	Total asthma cohort	Prevalent omalizumab cohort	Incident omalizumab cohort
COPD	455,598 (27)	3,618 (47)	1,725 (51)
Obstructive chronic bronchitis	248,447 (15)	1,683 (22)	838 (25)
Emphysema/other emphysema	130,271 (8)	592 (8)	296 (9)
Acute respiratory failure	111,197 (7)	748 (10)	383 (11)
Cystic fibrosis	5,871 (0)	66 (1)	30 (1)
Chronic respiratory conditions due to fumes/vapors	623 (0)	<11* (0)	<11* (0)
Number with at least 1 exclusion diagnosis	518,555 (30)	4,068 (53)	1,938 (57)

Values represent n (%).

*Values 10 or less are not allowed to be reported in OLDW for the overall purpose of maintaining deidentified data.

TABLE E3. Reliever fills in 12 mo before the anchor date

Measure	Matched cohort	Incident omalizumab users	P value*
Mean (SE)	3.99 (0.039)	5.48 (0.100)	.0001
Median (IQR)	2 (1-5)	4 (1-8)	
No reliever fills in 12 mo (%)	20.2	14.4	.0001

IQR, Interquartile range.

*P value from test of equality of means/proportions.

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