Original Article

Factors Related to Biologic Adherence and Outcomes Among Moderate-to-Severe Asthma Patients

Oyomoare L. Osazuwa-Peters, PhD[a], Melissa A. Greiner, MS[a], Amber Oberle, MD[b], Megan Oakes, MS[a], Sheila M. Thomas, PharmD, RPh[c], and Hayden Bosworth, PhD[a,d,e] *Durham, NC; and Bridgewater, NJ*

What is already known about this topic? Asthma biologic adherence rate appears to be relatively high among patients with moderate-to-severe asthma.

What does this article add to our knowledge? Asthma biologic adherence varies with administration setting, with lowest rates in the Clinic setting, whereas racial and ethnic as well as insurance-related disparities were apparent among patients who self-administer.

How does this study impact current management guidelines? Biologic adherence may be improved through specialist access before initiation of therapy and allowing for self-administration when feasible.

BACKGROUND: Adherence barriers to asthma biologics may not be uniform across administration settings for patients with moderate-to-severe asthma.
OBJECTIVE: To examine differences in asthma biologic adherence and associated factors, as well as association with a 1-year all-cause emergency department (ED) visit, across administration settings.
METHODS: A retrospective study of biologic naïve moderate-to-severe asthma patients with initial biologic therapy between January 1, 2016, and April 30, 2020, in the Optum Clinformatics Data Mart was performed. Three administration settings were identified: Clinic-only (outpatient office/infusion center), Home (self-administration), and Hybrid setting (mixture of clinic and self-administration). Asthma biologic adherence was the proportion of observed over expected biologic dose administrations received within 6 months from initial therapy. Factors associated with adherence were identified by administration setting, using Poisson regression analyses. A relationship between a 1-year all-cause ED visit and adherence was assessed for each administration setting using Cox regression analyses.
RESULTS: The study cohort was 3932 patients. Biologics adherence was 0.75 [0.5, 1] in Clinic setting, the most common administration setting, and 0.83 [0.5, 1] in both Home and Hybrid settings. Specialist access was consistently associated with better biologic adherence, whereas Black race, Hispanic ethnicity, lower education, Medicare only insurance, and higher patient out-of-pocket cost were associated with worse biologic adherence in some settings. In the Hybrid setting, hazard for a 1-year all-cause ED visit decreased with biologic adherence.
CONCLUSIONS: Asthma biologic adherence varied by administration setting. Efforts to improve asthma biologic adherence should consider promoting self-administration when beneficial, improving prior specialist access, and targeting patients with higher risk of suboptimal adherence particularly Black and Hispanic patients. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2355-66)

Key words: *Administration setting; Asthma biologics; Medication adherence; Health care use; Social determinants*

Targeted biologic therapy has become an increasingly important treatment alternative for patients with moderate-to-severe asthma.[1] Because patients with moderate-to-severe asthma may be relatively unresponsive to high-dose inhaled corticosteroids and effective oral corticosteroids often exert unacceptable adverse effects,[2] biologic therapy is a critical alternative treatment. Moreover, despite only accounting for ≤10% of the asthma population in the United States, moderate-to-severe

[a]Department of Population Health Sciences, Duke University School of Medicine, Durham, NC
[b]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, Duke University School of Medicine, Durham, NC
[c]Patient Informed Development and Health Value Translation, Research & Development, Sanofi, Bridgewater, NJ
[d]Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC
[e]Center of Innovation to Accelerate Discovery and Practice Transformation (ADAPT), Durham, NC
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Corresponding author: Hayden Bosworth, PhD, Department of Population Health Sciences, Duke University School of Medicine, 215 Morris St, Durham, NC 27701. E-mail: boswo001@duke.edu.
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Abbreviations used
aHR- Adjusted hazard ratio
aRR- Adjusted rate ratio
CI- Confidence interval
ED- Emergency department
HCPCS- Health care Common Procedure Coding System
ICD- International Classification of Diseases
ICD-9-CM- International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM- International Classification of Diseases, Tenth Revision, Clinical Modification
IND- Indemnity
NDC- National Drug Code

asthma is responsible for >80% of total asthma-related health care costs,[3] as well as significant indirect costs due to productivity loss and reduced quality of life.[4] Currently, there are 5 biologic therapies approved by the United States Food and Drug Administration for the treatment of moderate-to-severe asthma: omalizumab (targeting IgE), mepolizumab and reslizumab (targeting IL-5), benralizumab (targeting IL-5Rα), and dupilumab (targeting IL-4Rα). Evidence from randomized control trials shows that these therapies can effectively reduce asthma exacerbations by as much as 50% to 60%.[3]

Despite some evidence of relatively higher levels of biologic adherence, fundamental details of asthma biologic adherence remain unclear. Biologics differ in multiple ways from typical asthma medications (eg, relatively higher cost, injectable or intravenous infusion with differing administration settings, frequency of administration, and greater asthma severity). Therefore, adherence barriers may not be uniform for patients on asthma biologics. Specifically, although some asthma biologics can be self-administered at home by patients after receipt from a pharmacy (eg, dupilumab, mepolizumab, and benralizumab), others must be regularly administered at a provider facility (eg, reslizumab), such as an infusion center or at the doctor's office. Furthermore, other patients get administered at a provider facility, but receive their asthma biologics directly from the specialty pharmacy (brown bagging practice) or have the asthma biologic supplied directly to the clinic ahead of their visit (white bagging practice). This fundamental variation in asthma biologic administration setting suggests that patients who differ in how they receive asthma biologics might also differ in characteristics and in barriers experienced that translate to nonadherence.

Our 3 aims are as follows: First, we probe a large database to describe differences in the characteristics of patients with moderate-to-severe asthma on biologic therapy, stratifying patients by biologic therapy administration setting (Home, Clinic-only, and Hybrid). Second, we examine factors associated with asthma biologic adherence by administration setting. Lastly, we assess whether a 1-year all-cause emergency department (ED) visit, a health care utilization outcome, is associated with biologic adherence in the study population.

METHODS

We accessed data from the Optum Clinformatics Data Mart, a database of commercially and publicly insured enrollees from January 1, 2015, to April 30, 2020. Approval for this study was given by the Duke Health Institutional Review Board.

Adult patients (≥18 years) were included in the cohort if within the specified period they had at least 1 pharmacy claim with asthma biologics National Drug Codes or 1 medical claim with asthma biologics Health care Common Procedure Coding System (HCPCS) codes, indicating asthma biologic therapy or dispensing of asthma biologics (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). To limit the cohort to asthma biologic naive patients only, we excluded patients with the first qualifying biologic claim date in year 2015. Date of the first observed biologic fill, injection, or infusion was selected as the index date. To exclude patients with nonasthma or off-label applications of asthma biologics (eg, idiopathic urticaria, atopic dermatitis, and allergic rhinitis), we restricted to patients who had a diagnosis of moderate-to-severe asthma using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 493.00, 493.01, 493.02, 493.10, 493.11, 493.12, or ICD, Tenth Revision, Clinical Modification (ICD-10-CM) codes J45.x or J45.5x listed in any position within 3 months before the index date. Patients were required to have continuous medical and prescription insurance coverage 6 months before and after index. Lastly, we included only patients who were on a single biologic therapy during the 6-month follow-up period.

We measured adherence for 6 months starting from index date. We categorized patients by their biologic administration setting based on (a) solely medical claims (Clinic-only), (b) pharmacy claims only (Home), or (c) both medical and pharmacy claims (Hybrid). The Clinic-only group was composed of patients who received biologic infusions and/or injections in a clinic or hospital setting. For this Clinic-only subgroup, we retained distinct medical claims per service date with an asthma biologics HCPCS code. We further limited per beneficiary to 1 distinct biologic claim record per 8-day window based on a minimum 14-day dose frequency across brands.

Patients with a Home administration setting received their asthma biologics from a specialty pharmacy and self-administered at home or elsewhere, but not at the clinic (ie, no medical claims). For each biologic fill, fill end date was determined as fill start date + days supply − 1. For overlapping fills (ie, fill start date occurred before previous fill was exhausted), we shifted fill start date forward to the next day after fill end date of the previous fill.[5] We further excluded adjusted fill dates that were beyond patient last follow-up date and truncated any oversupply for fill end dates beyond last follow-up date. Then we calculated true days supply per pharmacy claim as the difference between fill end date and adjusted fill date.

The Hybrid administration setting subgroup was composed of patients who (a) switched from one administration setting to the other over the 6-month follow-up period, (b) received their asthma biologics directly from the specialty pharmacy with administration in clinic, or (c) had the specialty pharmacy deliver the biologic to the clinic with administration in clinic (white bagging).[6] See this article's Online Repository text at www.jaci-inpractice.org for details of how double counting was avoided.

For a few patients (<11) on the provider-delivered biologic reslizumab who had pharmacy claim records found, we included them in descriptive analyses but excluded them from all other statistical analyses.

Outcome variables

We considered 2 main outcomes. First, we estimated biologic adherence as the number of observed biologic doses administered divided by the number of brand-specific expected biologic dose

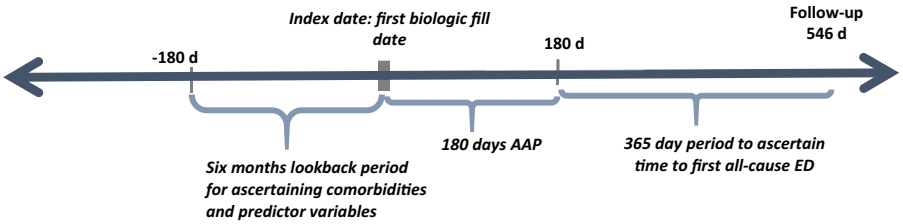

FIGURE 1. Study design. *AAP,* Adherence ascertainment period; *ED,* emergency department.

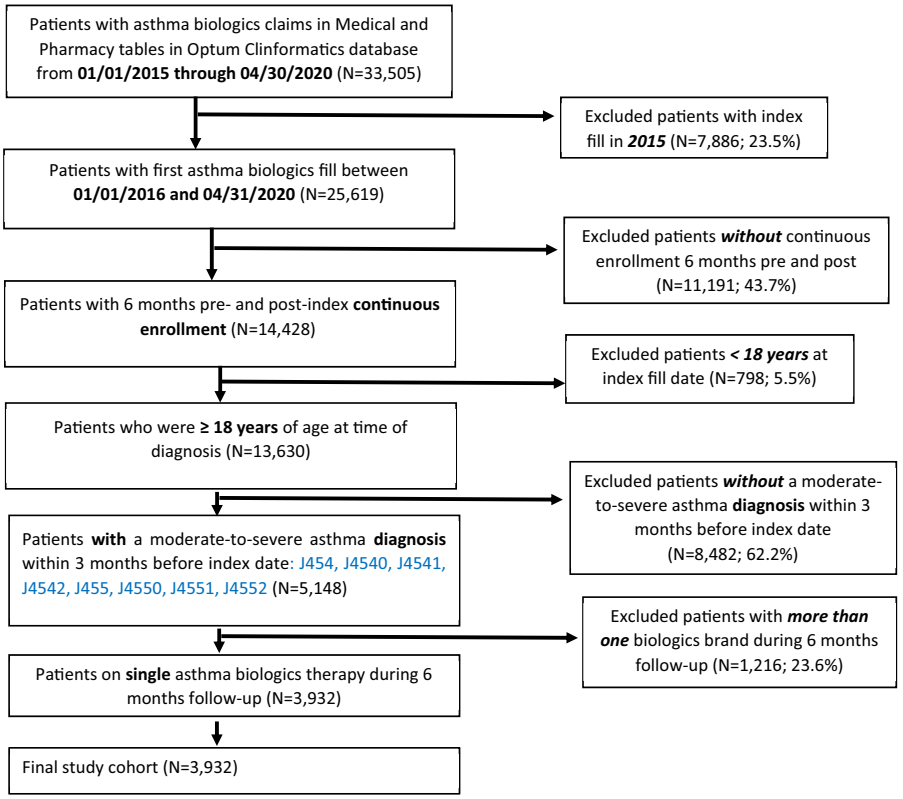

FIGURE 2. Flow chart showing sample sizes as inclusion/exclusion criteria were applied to get the final sample size. International Classification of Diseases, Tenth Revision, Clinical Modification moderate-to-severe asthma diagnosis codes in blue font.

administrations within the follow-up period. The number of observed biologic doses (adherence numerator) within the 6 months of follow-up was determined for each administration setting as follows:

- *Clinic-only*: number of distinct medical claim records for asthma biologics
- *Home*: days supply divided by brand-specific dose frequency
- *Hybrid*: combined information from pharmacy and medical claim records by obtaining: (i) number of observed biologic doses based on pharmacy claim records, (ii) number of observed biologic doses for medical claims for asthma biologics most likely supplied by clinic and/or doctor's office (exclusion algorithm in this article's Online Repository text at www.jaci-inpractice.org), (iii) total number of observed doses (sum of i and ii).

We then rounded the calculated total observed number of fills to integers. We determined the prescribed asthma biologic regimen for each patient as the expected number of biologic dose administrations based on brand-specific dosing schedules reported in the literature[7] (see Table E1 and Online Repository text at www.jaci-inpractice.org). Omalizumab has a variable dosing schedule of every 2 or 4 weeks depending on patient weight and IgE levels. Because patient weight and IgE levels were unavailable, a patient was assumed to be on a 2-week dosing schedule when there was at least 1 record of a refill within 3 weeks of previous fill, and/or if there were more than 6 fills observed within the 6-month follow-up period; otherwise, a 4-week schedule was assigned. Also, dosing schedule changes for benralizumab, depending on the number of doses taken; it goes from an every 4-week schedule for the first 3 doses, followed by an 8-week dosing schedule. For approximately 15% of patients where the number observed was greater than the number of expected biologic administrations (eg, related to differing weeks per month, rounding of fractional fills, etc.), we capped adherence at a maximum of 1 (or 100%).

TABLE I. Patient baseline characteristics by asthma biologic administration setting*

	Administration setting			
Variable	**Clinic only**	**Home**	**Hybrid**	***P***
N	2898	786	248	
Brand, n (%)				<.001
Omalizumab	1484 (51.2)	175 (22.3)	117 (47.2)	
Mepolizumab	717 (24.7)	196 (24.9)	79 (31.9)	
Benralizumab	639 (22.0)	>11	>11	
Dupilumab	0 (0.0)	242 (30.8)	0 (0.0)	
Reslizumab	58 (2.0)	<11	<11	
Age at diagnosis (y)	58.00 [47.00, 68.00]	66.00 [52.00, 72.00]	68.00 [61.00, 74.00]	<.001
Sex: male, n (%)	1062 (36.6)	266 (33.8)	76 (30.6)	.079
Race and ethnicity, n (%)				<.001
Asian	99 (3.4)	35 (4.45)	<11	
Black	296 (10.2)	72 (9.2)	34 (13.7)	
Hispanic	240 (8.3)	88 (11.2)	23 (9.3)	
White	1909 (65.9)	452 (57.5)	156 (62.9)	
Unknown	354 (12.2)	139 (17.7)	>11	
Region, n (%)				<.001
South	1329 (45.9)	368 (46.8)	126 (50.8)	
Midwest	684 (23.6)	136 (17.3)	34 (13.7)	
Northeast	281 (9.7)	89 (11.3)	37 (14.9)	
West	604 (20.8)	193 (24.6)	51 (20.6)	
Education, n (%)				<.001
High school or less	600 (20.7)	159 (20.2)	64 (25.8)	
Less than bachelor	1443 (49.8)	375 (47.7)	122 (49.2)	
Bachelor+	564 (19.5)	127 (16.2)	35 (14.1)	
Unknown	291 (10.0)	125 (15.9)	27 (10.9)	
FPL: below 400% FPL/unknown, n (%)	576 (19.9)	199 (25.3)	50 (20.2)	.004
Homeownership, n (%)				.065
Probable homeowner	1871 (64.6)	466 (59.3)	157 (63.3)	
Probable renter	223 (7.7)	66 (8.4)	15 (6.0)	
Unknown	804 (27.7)	254 (32.3)	76 (30.6)	
Household income, n (%)				<.001
<$40K	507 (17.5)	167 (21.2)	66 (26.6)	
$40K-$99K	948 (32.7)	249 (31.7)	84 (33.9)	
$100K+	867 (29.9)	173 (22.0)	48 (19.4)	
Unknown	576 (19.9)	197 (25.1)	50 (20.2)	
Net-worth, n (%)				.045
<$25K	600 (20.7)	177 (22.5)	61 (24.6)	
$25K-$149K	470 (16.2)	118 (15.0)	32 (12.9)	
$150K-$249K	229 (7.9)	45 (5.7)	22 (8.9)	
$250K-$499K	348 (12.0)	92 (11.7)	29 (11.7)	
$500K+	678 (23.4)	160 (20.4)	54 (21.8)	
Unknown	573 (19.8)	194 (24.7)	50 (20.2)	
Occupation type, n (%)				.21
Employed	421 (14.5)	99 (12.6)	38 (15.3)	
Unemployed	183 (6.3)	57 (7.3)	23 (9.3)	
Unknown	2294 (79.2)	630 (80.2)	187 (75.4)	
Insurance type, n (%)				<.001
Commercial	1824 (62.9)	239 (30.4)	30 (12.1)	
Medicare DUAL/LIS	205 (7.1)	177 (22.5)	62 (25.0)	
Medicare only	869 (30.0)	370 (47.1)	156 (62.9)	
Health plan type, n (%)				<.001
EPO	220 (7.6)	>11	<11	
HMO	379 (13.1)	160 (20.4)	53 (21.4)	

(continued)

TABLE I. *(Continued)*

Variable	Administration setting			P
	Clinic only	Home	Hybrid	
IND	15 (0.5)	<11	<11	
OTH	779 (26.9)	361 (45.9)	149 (60.1)	
POS	1387 (47.9)	184 (23.4)	24 (9.7)	
PPO	118 (4.1)	61 (7.8)	>11	
Obstructive sleep apnea, n (%)	706 (24.4)	227 (28.9)	71 (28.6)	.019
Obesity, n (%)	676 (23.3)	224 (28.5)	70 (28.2)	.005
Chronic sinusitis, n (%)	757 (26.1)	196 (24.9)	56 (22.6)	.412
Acute sinusitis, n (%)	511 (17.6)	122 (15.5)	40 (16.1)	.346
Atopic dermatitis, n (%)	99 (3.4)	86 (10.9)	<11	<.001
Congestive heart failure, n (%)	164 (5.7)	77 (9.8)	21 (8.5)	<.001
Glottic dysfunction, n (%)	71 (2.4)	13 (1.7)	<11	.412
Gastroesophageal reflux, n (%)	924 (31.9)	287 (36.5)	107 (43.1)	<.001
Dementia, n (%)	12 (0.4)	<11	<11	.018
Depression, n (%)	526 (18.2)	166 (21.1)	47 (19.0)	.167
Drug abuse, n (%)	76 (2.6)	42 (5.3)	12 (4.8)	<.001
Anxiety disorder, n (%)	559 (19.3)	189 (24.0)	43 (17.3)	.007
Bronchiectasis, n (%)	192 (6.6)	57 (7.3)	23 (9.3)	.264
Respiratory infection, n (%)	883 (30.5)	267 (34.0)	80 (32.3)	.162
Nasal polyps, n (%)	293 (10.1)	82 (10.4)	21 (8.5)	.663
Frequency of short-acting asthma medications in prior 6 mo	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	1.00 [0.00, 2.00]	.019
Complex asthma medication regimen, n (%)	1971 (68.0)	626 (79.6)	210 (84.7)	<.001
Any communication barrier, n (%)	995 (34.3)	323 (41.1)	93 (37.5)	.002
Any ED visits in prior 6 mo, n (%)	648 (22.4)	249 (31.7)	87 (35.1)	<.001
Any urgent care visit in prior 6 mo, n (%)	115 (4.0)	66 (8.4)	28 (11.3)	<.001
Any inpatient hospital in prior 6 mo, n (%)	471 (16.3)	171 (21.8)	53 (21.4)	<.001
Any specialist visit in prior 6 mo, n (%)	2563 (88.4)	687 (87.4)	226 (91.1)	.277
No. of distinct medications in prior 6 mo	10.00 [6.00, 15.00]	13.00 [9.00, 18.00]	15.00 [10.00, 19.00]	<.001
Patient cost for index biologic ($)	60.00 [0.00, 640.49]	80.00 [8.35, 366.52]	60.00 [0.00, 442.78]	.019
Total medication cost in prior 6 mo ($)	340.35 [111.45, 634.30]	385.70 [159.62, 682.86]	370.11 [166.45, 729.08]	<.001
Season of index biologic fill, n (%)				.05
Spring	831 (28.7)	234 (29.8)	51 (20.6)	
Summer	637 (22.0)	173 (22.0)	56 (22.6)	
Fall	630 (21.7)	166 (21.1)	73 (29.4)	
Winter	800 (27.6)	213 (27.1)	68 (27.4)	
Year of index biologic fill, n (%)				<.001
2016	362 (12.5)	49 (6.2)	14 (5.6)	
2017	622 (21.5)	114 (14.5)	53 (21.4)	
2018	604 (20.8)	171 (21.8)	58 (23.4)	
2019	1022 (35.3)	322 (41.0)	102 (41.1)	
2020	288 (9.9)	130 (16.5)	21 (8.5)	

ED, Emergency department; *EPO*, Exclusive Provider Organization; *FPL*, Federal Poverty Level; *HMO*, Health Maintenance Organization; *IND*, indemnity; *LIS*, low income subsidy; *OTH*, Other; *POS*, point of service; *PPO*, Preferred Provider Organization.
*Cells are masked using <11 (when cell values are within 1-10) or >11 (for neighboring cells). This is so as to follow the Centers for Medicare and Medicaid cell size suppression policy, as required by the data source.

The second outcome considered was an all-cause ED visit during follow-up (service code = 23), which extended up to 1 year from the day after the end of follow-up for adherence (see Figure 1).

Covariates

Covariates were ascertained over a 6-month lookback period from index date. For each covariate, in the presence of multiple values, we selected the value with a date nearest to the index date. Covariates considered included demographic variables, socioeconomic status, and asthma-associated comorbidities determined using validated ICD-based algorithms. Further, we ascertained the number of unique drugs dispensed, complex asthma medication regimen, prior health resource utilization, total patient cost for all medications, and any communication barrier. We also considered patient cost for index biologic and season and year of index biologic fill/service date. See Table E2 and Online Repository text at www.jaci-inpractice.org for additional details.

TABLE II. Six-month median [25th, 75th] adherence by biologic administration setting and biologic type

Biologic type	Clinic only	Home	Hybrid
Allergic asthma	0.58 [0.33, 0.83]	0.83 [0.5, 1]	0.83 [0.5, 1]
Eosinophilic asthma	1 [0.67, 1]	0.92 [0.5, 1]	1 [0.67, 1]
Overall	0.75 [0.5, 1]	0.83 [0.5, 1]	0.83 [0.5, 1]

Statistical analysis

We summarized descriptive statistics for patient baseline characteristics by biologic administration setting. Patient groups were compared using the Kruskal-Wallis test for continuous variables and the Pearson χ^2 test for categorical variables.

Outcomes were modeled separately for each administration setting subgroup due to differences in how adherence was calculated. To estimate unadjusted and adjusted associations with covariates of interest by administration setting, biologic adherence was analyzed as a proportion bounded by 0 and 1 using a Poisson regression; a biologic adherence outcome was modeled as the observed number of biologic fills (ie, a count outcome), while using the log-transformed expected number of biologic fills as an offset, which resulted in adherence rate as the outcome. Further, we computed robust standard errors for parameter estimates from Poisson regression models to control for misspecification of likelihood.[8] We assessed the goodness of fit for the Poisson regression models using the χ^2 test of deviance. We examined for multicollinearity among covariates, excluding any covariate with variance inflation factor >4.

For an all-cause ED visit, we used Kaplan-Meier to estimate cumulative incidence over a 1-year follow-up period after adherence ascertainment (Figure 1). We censored patients at the earliest of 1-year follow-up date or disenrollment date. Cumulative incidence was described overall and for each biologic administration setting stratified by quartiles of adherence percentage. We compared differences in 1-year ED visits across adherence quartiles, using log-rank tests. We used Cox proportional hazards models to assess the relationship between adherence per 10 percentage points and a 1-year ED visit in separate models for each administration setting subgroup. We performed both unadjusted models and models that adjusted for key variables found to be associated with adherence in any of the multivariable models described above. All statistical analyses were performed in R version 4.0.2.[9]

RESULTS

There were 3932 patients with moderate-to-severe asthma on asthma biologic therapy from January 1, 2016, through April 30, 2020, who met our inclusion criteria (Figure 2). Of these, almost three-quarters (N = 2898; 73.7%) were in the Clinic-only subgroup, approximately 20% (N = 786) were in the Home subgroup, and 6.3% (N = 248) were in the Hybrid subgroup. As shown in Table I, patient characteristics differed by administration location for most covariates considered. Clinic-only patients were on average relatively younger, composed of a higher proportion of males, White, from Midwest, and higher educated. Clinic-only patients had higher household income, net-worth range, commercial insurance, and mostly point-of-service health plan types relative to the other 2 subgroups. Clinic-only patients on average had better overall health as evidenced by lower frequencies for 8 comorbidities, lower median number of distinct medications during prior 6 months, lower proportion on a complex asthma medication regimen, and lower frequencies for prior health resource utilization, compared with patients in other subgroups.

Home and Hybrid patients were distinct from Clinic-only patients: being relatively older, with at least 70% on Medicare insurance types, a higher burden of comorbidities, as well as having significantly higher patient cost for either index biologics or total patient cost for all medications during prior 6 months.

As presented in Table II, the median [25th, 75th] biologic adherence was relatively lower for Clinic-only (0.75 [0.5, 1]) compared with Home (0.83 [0.5, 1]) and Hybrid (0.83 [0.5, 1]) subgroups.

Factors associated with biologic adherence differed by administration setting. In the adjusted model for the Clinic-only subgroup (Table III), a 10-year increase in age was associated with a 1% higher biologic adherence rate (adjusted rate ratio [aRR] = 1.01, 95% confidence interval [CI]: 1.00, 1.03). Only in this subgroup was geographic variation in biologic adherence rate apparent, with Midwest region (aRR = 1.06, 95% CI: 1.02-1.1) showing a 6% increase in adherence rates relative to South. Similarly, adherence differed by education with high school or less showing 5% lower adherence rates compared with less than bachelor category (aRR = 0.95, 95% CI: 0.91-0.99). Also, adherence differed marginally by household income with 5% higher adherence rates for household income <$40K compared with household income $40K to $99K (aRR = 1.05, 95% CI: 1-1.1). A number of asthma severity indicators were associated with higher biologic adherence in the Clinic-only subgroup including complex asthma regimen (aRR = 1.07, 95% CI: 1.03-1.11), any specialist visit during prior 6 months (aRR = 1.08, 95% CI: 1.02-1.14), and the presence of comorbidities such as chronic sinusitis (aRR = 1.05, 95% CI: 1.01-1.09), and depression (aRR = 1.06, 95% CI: 1-1.12). Adherence was associated with patient cost for index biologic, with a 2% decrease in adherence rates for each $1000 increase (aRR = 0.98, 95% CI: 0.96-1). Adherence was 5% lower for patients whose index season was in fall compared with spring (aRR = 0.95, 95% CI: 0.91-0.99).

As presented in Table IV, the Home subgroup showed race and ethnicity differences, with adherence rates being 16% lower for Black (aRR = 0.84, 95% CI: 0.72-0.99) and 13% lower for Hispanic (aRR = 0.87, 95% CI: 0.77-0.99) patients compared with White patients. Adherence rates varied by insurance type in this subgroup, with Medicare-only patients (aRR = 0.74, 95% CI: 0.66-0.83) having 26% lower adherence rates compared with commercial insurance patients. Asthma severity indicators were associated with higher adherence, including any specialist visit in prior 6 months (aRR = 1.14, 95% CI: 1-1.29), and respiratory infections (aRR = 1.09, 95% CI: 1-1.18).

Similarly, for Hybrid patients (Table V), biologic adherence differed by income, a socioeconomic status indicator, with patients in the unknown category (aRR unknown = 1.19, 95% CI: 1.01-1.4) showing 19% higher rates than patients in the $40K to $99K category. Lastly, patients with dementia (aRR = 0.67, 95% CI: 0.48-0.95) had 33% lower biologic adherence rates.

Cumulative incidence for 1-year all-cause ED visits differed by administrative setting (Figure 3) but ranged from 31% to 35% across all adherence quartiles, with no statistical difference by quartiles (Table E3, available in this article's Online Repository at www.jaci-inpractice.org). Factors associated with a 1-year all-cause ED visit differed by administration setting. In the adjusted model for the Clinic-only subgroup (Table E4, available

TABLE III. Crude rate ratio (RR) and adjusted RR estimates of adherence proportions associated with covariates of interest among a subgroup of patients in the Clinic-only administration setting (N = 2898) from a Poisson regression model*

	Unadjusted		Adjusted	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Age at diagnosis, per 10 y	**1.03 (1.01, 1.04)**	**<.001**	**1.01 (1, 1.03)**	**.038**
Sex				
Female	Reference			
Male	0.99 (0.96, 1.02)	.59	0.99 (0.96, 1.02)	.535
Race and ethnicity				
White	Reference			
Black	0.98 (0.93, 1.04)	.566	0.98 (0.93, 1.04)	.477
Hispanic	0.97 (0.91, 1.03)	.264	0.99 (0.93, 1.05)	.793
Asian	1.03 (0.94, 1.12)	.502	1.04 (0.96, 1.13)	.309
Unknown	1.03 (0.98, 1.09)	.193	1.02 (0.93, 1.13)	.654
Region				
South	Reference			
Midwest	**1.06 (1.03, 1.11)**	**<.001**	**1.06 (1.02, 1.1)**	**.001**
West	**0.95 (0.91, 1)**	**.034**	0.96 (0.92, 1)	.062
Northeast	0.98 (0.92, 1.03)	.408	0.97 (0.92, 1.03)	.33
Education				
Less than bachelor	Reference			
High school or less	**0.96 (0.92, 1)**	**.037**	**0.95 (0.91, 0.99)**	**.013**
Bachelor+	0.99 (0.95, 1.03)	.537	0.99 (0.95, 1.04)	.793
Unknown	1.03 (0.97, 1.09)	.313	0.94 (0.83, 1.05)	.268
Household income				
$40K-$99K	Reference			
<$40K	1.04 (1, 1.09)	.073	**1.05 (1, 1.1)**	**.05**
$100K+	1.02 (0.98, 1.06)	.409	1.02 (0.98, 1.07)	.297
Unknown	1.04 (1, 1.09)	.063	1.05 (0.99, 1.11)	.101
Insurance type				
Commercial	Reference			
Medicare DUAL/LIS	1.06 (0.99, 1.13)	.085	1.02 (0.95, 1.11)	.534
Medicare only	**1.06 (1.03, 1.1)**	**<.001**	1.03 (0.98, 1.08)	.216
Frequency of short-acting asthma medications	1.01 (1, 1.01)	.147	1 (0.99, 1.01)	.518
Complex asthma medication regimen	**1.09 (1.05, 1.12)**	**<.001**	**1.07 (1.03, 1.11)**	**<.001**
Any communication barrier	0.99 (0.95, 1.02)	.391	0.96 (0.9, 1.01)	.118
Any prior ED visits	**1.05 (1.01, 1.09)**	**.012**	1.02 (0.98, 1.06)	.297
Any prior urgent care visits	1.05 (0.96, 1.14)	.265	1.01 (0.93, 1.1)	.841
Any prior inpatient hospitalizations	1.02 (0.98, 1.07)	.306	0.99 (0.94, 1.04)	.633
Any prior specialist visit	**1.11 (1.05, 1.17)**	**<.001**	**1.08 (1.02, 1.14)**	**.005**
No. of distinct medications during lookback	1 (1, 1)	.054	1 (1, 1)	.311
Total medication cost to patient during lookback, per $1000	**1.02 (1.01, 1.03)**	**.003**	1.01 (0.99, 1.04)	.289
Patient cost for index biologic, per $1000	0.99 (0.97, 1.01)	.156	**0.98 (0.96, 1)**	**.017**
Index season				
Spring	Reference			
Winter	0.98 (0.94, 1.02)	.38	0.99 (0.95, 1.03)	.512
Fall	**0.93 (0.89, 0.98)**	**.002**	**0.95 (0.9, 0.99)**	**.012**
Summer	0.97 (0.93, 1.01)	.15	0.97 (0.93, 1.01)	.118
Index year				
2016	Reference			
2017	**1.19 (1.12, 1.26)**	**<.001**	**1.09 (1.03, 1.16)**	**.004**
2018	**1.19 (1.12, 1.27)**	**<.001**	**1.1 (1.04, 1.17)**	**.002**
2019	**1.2 (1.14, 1.27)**	**<.001**	**1.06 (1, 1.13)**	**.044**
2020	**1.19 (1.11, 1.28)**	**<.001**	1.07 (0.99, 1.15)	.078
Obstructive sleep apnea	1.01 (0.97, 1.05)	.565	1 (0.96, 1.04)	.895
Obesity	1.01 (0.98, 1.05)	.509	1.02 (0.98, 1.06)	.393

(continued)

TABLE III. *(Continued)*

	Unadjusted		Adjusted	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Chronic sinusitis	**1.09 (1.05, 1.12)**	**<.001**	**1.05 (1.01, 1.09)**	**.009**
Acute sinusitis	0.99 (0.95, 1.03)	.588	0.99 (0.95, 1.03)	.751
Atopic dermatitis	0.92 (0.84, 1.01)	.086	0.98 (0.9, 1.08)	.726
Chronic heart failure	1.02 (0.96, 1.09)	.545	0.98 (0.92, 1.06)	.638
Glottis dysfunction	1.04 (0.94, 1.14)	.445	1.03 (0.94, 1.13)	.515
Gastroesophageal reflux disease	1.02 (0.98, 1.05)	.286	0.99 (0.96, 1.03)	.746
Dementia	0.98 (0.73, 1.3)	.886	0.95 (0.71, 1.28)	.751
Depression	1.02 (0.98, 1.06)	.334	**1.06 (1, 1.12)**	**.034**
Drug abuse	0.9 (0.8, 1.02)	.105	0.93 (0.83, 1.04)	.188
Anxiety disorder	1 (0.97, 1.04)	.833	1.01 (0.96, 1.07)	.633
Bronchiectasis	**1.08 (1.02, 1.15)**	**.008**	1.04 (0.98, 1.1)	.196
Respiratory infections	1.02 (0.99, 1.05)	.275	1.01 (0.98, 1.05)	.468
Nasal polyps	**1.11 (1.06, 1.16)**	**<.001**	1.02 (0.97, 1.07)	.428

CI, Confidence interval; *ED*, emergency department; *LIS*, low income subsidy.
*Also adjusted for biologic generic; bold values denote statistical significance at the $P < .05$ level.

in this article's Online Repository at www.jaci-inpractice.org), biologic adherence was not significantly associated with an ED visit (adjusted hazard ratio [aHR] = 1.00, 95% CI: 0.98-1.03). However, Black race, Medicare insurance, and comorbidities such as respiratory infection and depression were associated with higher hazard of a 1-year ED visit in the multivariable model (Table E4, available in this article's Online Repository at www.jaci-inpractice.org). Similarly, in the adjusted model for the Home subgroup, the hazard for an ED visit did not differ significantly with biologic adherence (aHR = 0.98, 95% CI: 0.94-1.02) but differed significantly by race, region, insurance type, season, and comorbidities such as respiratory infection and chronic sinusitis (Table E5, available in this article's Online Repository at www.jaci-inpractice.org). Conversely, in the adjusted model for the Hybrid subgroup (Table E6, available in this article's Online Repository at www.jaci-inpractice.org), a 10 percentage point increase in biologic adherence was associated with a 9% decrease in hazard for a 1-year all-cause ED visit (aHR = 0.91, 95% CI: 0.84-0.98). In addition, each 10-year increase in age was associated with 27% lower hazard for an ED visit (aHR = 0.73, 95% CI: 0.60-0.88), a bachelor degree was associated with 58% lower ED visit risk compared with less than a bachelor degree (aHR = 0.42, 95% CI: 0.19-0.96), and depression was associated with 81% higher risk of an ED visit (aHR = 1.81, 95% CI: 1.09-3.02; Table E6, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

In a sample of patients with moderate-to-severe asthma, factors associated with biologic adherence and its association with a health care utilization outcome differed depending on the setting of biologic administration. Clinic-administered biologics tended to have lower levels of adherence compared with at-home administration or hybrid administration. A recurring theme was the importance of socioeconomic status, biologic-related financial burden, and a history of specialist access.

Biologic adherence for the Clinic-only subgroup increased with age at index and was relatively higher for Midwest compared with South, for patients with complex asthma regimen, specialist access during prior 6 months, the presence of comorbidities such as chronic sinusitis and depression, and index years 2017-2019 relative to 2016. Conversely, adherence was lower for each $1000 increase in patient cost for index biologic, for high school or less compared with less than bachelors, and for fall compared with spring index season.

Biologic adherence was relatively higher in the Home subgroup compared with Clinic-only, but similar to Hybrid subgroup. In the Home subgroup, adherence was lower for Black, Hispanic ethnicity, and unknown race relative to White race, Medicare insurance only compared with commercial insurance, and index year 2020 compared with 2016. Also, in the Home subgroup, biologic adherence was higher for patients with specialist access during prior 6 months and respiratory infection. Lastly, biologic adherence in the Hybrid subgroup was higher for unknown household income relative to $40K to $99K household income but lower for patients with dementia. Interestingly, biologic adherence was associated with lower risk of 1-year ED visits in the Hybrid subgroup but not in the Clinic-only and Home subgroups.

Only a handful of studies have previously reported on asthma biologic adherence.[10-14] The consensus has been high adherence rates for asthma biologics in a range of study populations,[10-12] and our study corroborates this finding. Despite different measures of adherence used across asthma biologic adherence studies, there generally appears to be a high level of adherence for asthma biologic therapy in patients with severe asthma.

Our study makes a novel contribution by demonstrating that although asthma biologic adherence rates may be generally high, there are differences by administration setting. We found that patients who received asthma biologics through regularly scheduled provider delivery (Clinic-only) had slightly lower adherence rates compared with those who self-administered (Home) or patients who either switched administration setting or received biologics by white/brown bagging practices (Hybrid). A plausible reason for this pattern of slightly lower adherence rates in Clinic-only patients (median: 0.75 vs 0.83) might be the inconvenience and cost of traveling to the clinic.[15,16] Also, Home and Hybrid patients were characterized by older patients with a higher comorbidity burden, greater proportion on complex

TABLE IV. Crude rate ratio (RR) and adjusted RR estimates of adherence proportions associated with covariates of interest among a subgroup of patients in the Home administration setting (N = 786 − <11 reslizumab patients) from a Poisson regression model*

	Unadjusted		Adjusted	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Age at diagnosis, per 10 y	0.98 (0.96, 1.01)	.153	1.02 (0.99, 1.05)	.162
Sex				
Female	Reference			
Male	1.04 (0.96, 1.12)	.37	1.06 (0.97, 1.15)	.18
Race and ethnicity				
White	Reference			
Black	**0.83 (0.71, 0.96)**	**.014**	**0.84 (0.72, 0.99)**	**.032**
Hispanic	0.89 (0.78, 1.01)	.072	**0.87 (0.77, 0.99)**	**.031**
Asian	0.9 (0.74, 1.09)	.278	0.87 (0.71, 1.08)	.208
Unknown	**0.86 (0.78, 0.96)**	**.007**	**0.75 (0.57, 1)**	**.05**
Region				
South	Reference			
Midwest	1.05 (0.95, 1.16)	.346	1.03 (0.93, 1.13)	.595
West	0.98 (0.9, 1.08)	.736	1.02 (0.92, 1.12)	.727
Northeast	0.99 (0.87, 1.11)	.819	1 (0.89, 1.13)	.979
Education				
Less than bachelor	Reference			
High school or less	0.97 (0.88, 1.08)	.618	0.99 (0.88, 1.1)	.786
Bachelor+	**1.12 (1.02, 1.22)**	**.016**	1.07 (0.97, 1.19)	.16
Unknown	0.95 (0.85, 1.06)	.337	1.31 (0.97, 1.75)	.075
Household income				
$40K-$99K	Reference			
<$40K	0.95 (0.85, 1.06)	.348	0.93 (0.83, 1.05)	.224
$100K+	**1.11 (1.01, 1.22)**	**.028**	1.02 (0.91, 1.13)	.778
Unknown	0.97 (0.88, 1.07)	.549	0.96 (0.84, 1.09)	.521
Insurance type				
Commercial	Reference			
Medicare DUAL/LIS	0.93 (0.85, 1.01)	.104	0.93 (0.81, 1.06)	.264
Medicare only	**0.83 (0.77, 0.9)**	**<.001**	**0.74 (0.66, 0.83)**	**<.001**
Frequency of short-acting asthma medications	1.01 (0.99, 1.02)	.533	1 (0.98, 1.02)	.83
Complex asthma medication regimen	1.02 (0.93, 1.12)	.684	0.99 (0.9, 1.09)	.878
Any communication barrier	0.99 (0.92, 1.06)	.699	0.98 (0.88, 1.1)	.789
Any prior ED visits	0.98 (0.91, 1.06)	.665	0.98 (0.89, 1.07)	.651
Any prior urgent care visits	0.95 (0.81, 1.11)	.507	1 (0.86, 1.16)	.98
Any prior inpatient hospitalizations	1.03 (0.95, 1.12)	.508	1.05 (0.95, 1.16)	.374
Any prior specialist visit	**1.2 (1.06, 1.36)**	**.005**	**1.14 (1, 1.29)**	**.044**
No. of distinct medications during lookback	1 (0.99, 1)	.692	1 (0.99, 1.01)	.724
Total medication cost to patient during lookback, per $1000	1.03 (0.98, 1.08)	.228	1.04 (0.98, 1.11)	.203
Patient cost for index biologic, per $1000	0.98 (0.93, 1.03)	.425	0.98 (0.93, 1.04)	.538
Index season				
Spring	Reference			
Winter	0.94 (0.84, 1.04)	.218	0.98 (0.89, 1.08)	.731
Fall	0.98 (0.89, 1.09)	.757	0.98 (0.88, 1.1)	.733
Summer	1.06 (0.96, 1.17)	.224	1.05 (0.95, 1.16)	.33
Index year				
2016	Reference			
2017	1.03 (0.91, 1.16)	.624	1.03 (0.89, 1.18)	.697
2018	0.98 (0.87, 1.11)	.783	1.01 (0.88, 1.16)	.879
2019	0.89 (0.79, 1)	.053	0.97 (0.84, 1.12)	.689
2020	**0.73 (0.62, 0.85)**	**<.001**	**0.76 (0.64, 0.89)**	**.001**
Obstructive sleep apnea	0.94 (0.86, 1.02)	.12	0.97 (0.89, 1.06)	.532
Obesity	0.95 (0.88, 1.03)	.255	1 (0.91, 1.09)	.967

(continued)

TABLE IV. *(Continued)*

	Unadjusted		Adjusted	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Chronic sinusitis	0.99 (0.91, 1.08)	.85	0.98 (0.89, 1.07)	.603
Acute sinusitis	1.07 (0.97, 1.17)	.169	1.05 (0.96, 1.16)	.274
Atopic dermatitis	1.02 (0.91, 1.13)	.739	1.05 (0.92, 1.21)	.446
Chronic heart failure	**0.88 (0.77, 1)**	**.045**	0.92 (0.81, 1.04)	.193
Glottis dysfunction	0.97 (0.7, 1.35)	.852	0.98 (0.74, 1.29)	.878
Gastroesophageal reflux disease	**0.92 (0.85, 1)**	**.046**	0.94 (0.87, 1.02)	.147
Dementia	1.02 (0.81, 1.27)	.884	1.02 (0.78, 1.32)	.895
Depression	1 (0.91, 1.08)	.911	1.02 (0.91, 1.13)	.752
Drug abuse	**0.82 (0.67, 0.99)**	**.044**	0.84 (0.7, 1.01)	.07
Anxiety disorder	1 (0.92, 1.08)	.979	0.97 (0.87, 1.09)	.596
Bronchiectasis	0.93 (0.81, 1.08)	.363	0.95 (0.83, 1.09)	.45
Respiratory infections	1.07 (0.99, 1.15)	.074	**1.09 (1, 1.18)**	**.039**
Nasal polyps	0.98 (0.86, 1.11)	.735	0.98 (0.85, 1.12)	.766

CI, Confidence interval; *ED*, emergency department; *LIS*, low income subsidy.
*Also adjusted for biologic generic; bold values denote statistical significance at the $P < .05$ level.

asthma regimens, and higher cumulative incidence for ED visits, all of which indicate worse asthma severity. Greater levels of asthma severity, as implied by these indicators for Home and Hybrid patients, may have motivated higher rates of adherence to biologics coupled with the convenience of self-administration, especially given that biologic adherence can result in improved outcomes as was seen in Hybrid patients, and reported elsewhere.[14]

Our study identifies the multifaceted manifestation of financial burden and racial disparities for patients with asthma who receive biologic therapy across different administration settings. Specifically, racial and ethnic differences in adherence rates were apparent in the Home administration setting, with Black and Hispanic patients showing 16% and 13% lower adherence rates than White patients, respectively. Also, Home patients on Medicare only, who were without additional subsidies or supplemental insurance, showed a 25% lower adherence rates relative to commercially insured Home patients. In addition, Clinic-only patients showed a 2% decrease in adherence rates for each $1000 increase in index biologic cost. Therefore, patient financial burden for asthma biologics appears to be a major barrier to adherence irrespective of administration setting, which highlights a critical need for policies and strategies that will increase patient access to biologic therapy regardless of race or socioeconomic status.

Our study has limitations. First, we operationalized adherence using a different approach for each administration setting, due to inherent differences in pharmacy versus medical claims data. Moreover, to operationalize our definition of adherence, we used claims-based algorithms shaped by deductions. However, these assumptions allow us to leverage administrative claims data for research, despite inherent limitations of administrative claims intended for billing purposes. Second, for Home and Hybrid setting patients, a pharmacy claim for an asthma biologic fill does not guarantee actual administration of the biologic. Third, some key variables that may have provided useful insight had very high missing rates or were entirely missing (eg, objective measures of asthma severity, distance to nearest clinic). Fourth, our study only considered a 6-month follow-up period, a snapshot over the duration for long-term application of asthma biologic therapy. This is a tradeoff whereby considering a longer follow-up period would have necessitated requiring continuous insurance enrollment over longer time frames, which would have led to greater sample attrition and limited power for comparisons by administration setting.

The strengths of our study include using a large, US representative sample of commercially and publicly insured patients, explicit consideration of different administration settings, inclusion of all approved asthma biologics in the United States, and inclusion of important socioeconomic variables.

Clinical implications/recommendations

Our study highlights some important clinical implications for improving biologic adherence among moderate-to-severe asthma. First, our results showed that a subspecialist visit in the prior 6 months before the onset of biologic therapy corresponded to 8% to 25% increased adherence rates across administration settings. Specialists may play a key role through effective communication in preparing patients with information on their condition and treatment options before the initiation of biologic therapy.[12] Moreover, results from our study suggest that considering factors such as setting of administration and comorbidity burden may be important to the overall level of adherence. Also, clinicians can confidently prescribe biologics for at-home use in patients deemed capable of self-medicating as we see that there is a positive association with adherence. Such an option has increasing value in the face of the COVID-19 pandemic, which saw a drop of up to 70% in outpatient visits at its peak, largely because patients were avoiding regular outpatient care as a precaution to reduce the risk of contracting the coronavirus.[17]

CONCLUSIONS

Overall, we found that asthma biologic adherence was generally high for patients with moderate-to-severe asthma on biologic therapy but lowest for patients in the clinic setting, the most common setting of administration. Specialist access was consistently associated with better biologic adherence, whereas factors associated with race, education, and patient financial burden were associated with worse biologic adherence in some settings. Further, efforts to improve asthma biologic adherence

TABLE V. Crude rate ratio (RR) and adjusted RR estimates of adherence proportions associated with covariates of interest among a subgroup of patients in the Hybrid administration setting (N = 248 − <11 reslizumab patients) from a Poisson regression model*

	Unadjusted		Adjusted	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Age at diagnosis, per 10 y	0.98 (0.95, 1.02)	.297	0.98 (0.93, 1.02)	.287
Sex				
Female	Reference			
Male	0.97 (0.87, 1.08)	.548	0.96 (0.85, 1.08)	.464
Race and ethnicity				
White	Reference			
Black	1.1 (0.98, 1.23)	.12	1.04 (0.9, 1.19)	.625
Hispanic	0.93 (0.77, 1.13)	.449	0.9 (0.71, 1.14)	.395
Asian	0.79 (0.59, 1.06)	.113	0.88 (0.57, 1.37)	.577
Unknown	0.97 (0.84, 1.12)	.683	1.14 (0.82, 1.58)	.426
Region				
South	Reference			
Midwest	0.91 (0.81, 1.04)	.161	0.9 (0.77, 1.05)	.188
West	0.89 (0.78, 1.01)	.062	0.92 (0.8, 1.06)	.236
Northeast	0.86 (0.73, 1.02)	.089	0.84 (0.7, 1.01)	.059
Education				
Less than bachelor	Reference			
High school or less	1.03 (0.92, 1.15)	.65	1.02 (0.88, 1.18)	.802
Bachelor+	0.96 (0.82, 1.12)	.588	0.94 (0.79, 1.12)	.478
Unknown	0.96 (0.83, 1.13)	.643	0.7 (0.46, 1.05)	.081
Household income				
$40K-$99K	Reference			
<$40K	1 (0.88, 1.13)	.956	1.01 (0.87, 1.17)	.893
$100K+	1.01 (0.87, 1.16)	.939	1.04 (0.88, 1.24)	.635
Unknown	1.05 (0.93, 1.18)	.427	**1.19 (1.01, 1.4)**	**.035**
Insurance type				
Commercial	Reference			
Medicare DUAL/LIS	1 (0.86, 1.16)	.961	0.95 (0.77, 1.18)	.653
Medicare only	1.01 (0.87, 1.16)	.942	1.1 (0.91, 1.34)	.314
Frequency of short-acting asthma medications	1.01 (0.98, 1.03)	.569	1.02 (0.99, 1.05)	.219
Complex asthma medication regimen	1.08 (0.94, 1.25)	.28	1.17 (0.99, 1.37)	.06
Any communication barrier	1.03 (0.94, 1.14)	.498	1.09 (0.93, 1.28)	.293
Any prior ED visits	1.05 (0.95, 1.16)	.315	1.02 (0.9, 1.16)	.717
Any prior urgent care visits	0.98 (0.84, 1.14)	.774	1 (0.83, 1.21)	.97
Any prior inpatient hospitalizations	1.03 (0.92, 1.15)	.637	1 (0.87, 1.16)	.965
Any prior specialist visit	1.22 (0.99, 1.51)	.066	1.25 (0.98, 1.6)	.07
No. of distinct medications during lookback	1 (0.99, 1.01)	.797	1 (0.99, 1.01)	.71
Total medication cost to patient during lookback, per $1000	0.97 (0.89, 1.06)	.518	0.95 (0.85, 1.06)	.385
Patient cost for index biologic, per $1000	1.02 (0.94, 1.1)	.669	1.03 (0.95, 1.13)	.465
Index season				
Spring	Reference			
Winter	1.01 (0.89, 1.15)	.882	0.95 (0.83, 1.09)	.456
Fall	0.91 (0.79, 1.05)	.208	0.84 (0.71, 1)	.056
Summer	1.03 (0.89, 1.18)	.693	0.96 (0.82, 1.13)	.631
Index year				
2016	Reference			
2017	1.02 (0.79, 1.31)	.899	1.04 (0.77, 1.41)	.809
2018	1 (0.78, 1.29)	.974	1 (0.74, 1.36)	.987
2019	1.02 (0.8, 1.3)	.87	1.01 (0.73, 1.38)	.97
2020	1 (0.75, 1.34)	.976	0.92 (0.65, 1.32)	.665
Obstructive sleep apnea	0.95 (0.85, 1.07)	.409	0.88 (0.77, 1.01)	.062
Obesity	1.04 (0.93, 1.15)	.524	1.05 (0.9, 1.21)	.551

(continued)

TABLE V. *(Continued)*

	Unadjusted		Adjusted	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Chronic sinusitis	0.93 (0.81, 1.05)	.238	0.91 (0.77, 1.06)	.219
Acute sinusitis	0.97 (0.84, 1.12)	.666	1.02 (0.87, 1.2)	.808
Atopic dermatitis	1.14 (0.9, 1.44)	.265	1.03 (0.78, 1.37)	.815
Chronic heart failure	1 (0.83, 1.21)	.992	1.05 (0.83, 1.32)	.695
Glottis dysfunction	0.9 (0.74, 1.08)	.256	0.84 (0.58, 1.22)	.369
Gastroesophageal reflux disease	0.97 (0.88, 1.07)	.592	0.95 (0.85, 1.07)	.401
Dementia	**0.65 (0.62, 0.68)**	**<.001**	**0.67 (0.48, 0.95)**	**.024**
Depression	0.98 (0.86, 1.1)	.692	0.93 (0.78, 1.1)	.385
Drug abuse	1.04 (0.86, 1.26)	.693	1.09 (0.86, 1.37)	.491
Anxiety disorder	1.04 (0.92, 1.17)	.508	1.02 (0.86, 1.21)	.794
Bronchiectasis	1.03 (0.89, 1.19)	.717	1.02 (0.87, 1.21)	.777
Respiratory infections	0.98 (0.89, 1.09)	.728	1 (0.89, 1.13)	.993
Nasal polyps	1.04 (0.89, 1.21)	.64	1.1 (0.91, 1.33)	.338

CI, Confidence interval; *ED*, emergency department; *LIS*, low income subsidy.
*Also adjusted for biologic generic; bold values denote statistical significance at the $P < .05$ level.

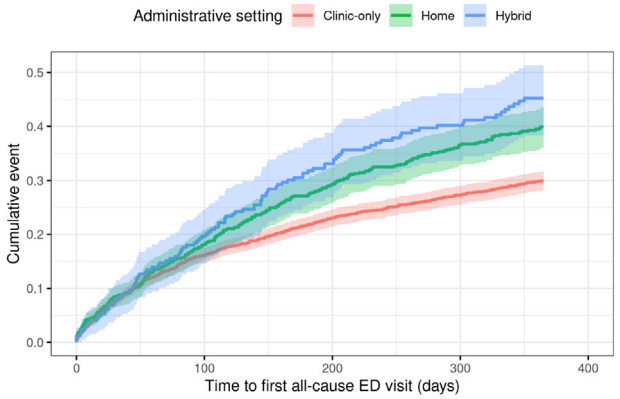

FIGURE 3. Kaplan-Meier curve by administrative setting, showing cumulative incidence of emergency department visits over 1 year from the day after the end of 6-month follow-up for adherence.

should consider improving specialist access and targeting patient subgroups with higher risk of suboptimal adherence.

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