rituximab therapy and routinely check immunoglobulin levels before initiation of therapy because these patients may be at an increased risk for prolonged hypogammaglobulinemia requiring IgG replacement therapy.

Most important, there was a subset of 5 patients (highlighted in Table I) who had recovery of peripheral B cells, but prolonged hypogammaglobulinemia and sustained absence or decreased switched or unswitched memory B-cell compartments. This subset of patients had an average duration of IgG replacement therapy of 83 months compared with 24 months for the other patients. There did not seem to be a correlation with the amount of cumulative rituximab received because this subset of patients had received an average cumulative dose of 4.8 g of rituximab compared with 6.3 g for the other patients. In patients with hypogammaglobulinemia after rituximab therapy, we recommend monitoring switched memory B cells in flow cytometry. This, in conjunction with recovery of other immunoglobulins (IgM and IgA), may be a possible indication for tapering and discontinuing IgG replacement therapy.

Of note, only 3 of the 17 patients in our cohort had undergone splenectomy. In patients who have undergone splenectomy, memory B cells, IgM memory B cells, and switched B cells have been found to be significantly reduced than in controls,[9] which may account for why this subset of patients was unable to produce switched memory B cells.

In conclusion, given the increasing number of reports of hypogammaglobulinemia detected after rituximab therapy, we recommend evaluating immunoglobulin levels and flow cytometry before initiation of therapy. In hypogammaglobulinemia noted after rituximab therapy, there appear to be 2 subsets of patients, one of which recovers and one with persistent hypogammaglobulinemia with long-lasting low or absent memory B cells. To determine the treatment length in patients, it is potentially important to trend the B-cell subsets by flow cytometry in addition to IgA and IgM levels.

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Measuring the effect of asthma control on exacerbations and health resource use

To the Editor:

Previous studies have documented the significant negative effect of asthma and poor control on health care resource use (HRU).[1,2] The extent of the effect is associated with the degree of asthma control. Standardized tools, such as the Asthma Control Questionnaire (ACQ),[3] have been shown to be valid measures of control. Previous studies examining HRU using validated control measures have typically been conducted in clinical trials or specialty or severe populations not generalizable to the broader persistent asthma population.[4,5] Other studies conducted in real-world settings have used surrogate markers of control (eg, β-agonist use or exacerbations).[2,6,7] Our study aimed to bridge this gap by using a validated measure of asthma control (ACQ-5) in a real-world setting in a general population with persistent asthma.

The Observational Study of Asthma Control and Outcomes included a prospective survey and retrospective claims of patients with asthma enrolled in Kaiser Permanente of Colorado (KPCO). Eligible patients received 3 rounds of the same survey during 1 year: April through August 2011, September through December 2011, and March through June 2012. Study variables for this analysis included asthma control measured by using the ACQ-5, exacerbations, HRU, self-reported adherence, and sociodemographic characteristics. In adjusted analyses HRU measures were regressed on ACQ-5 scores (as a continuous variable) by using negative binomial models controlling for fixed effects, age, sex, family income level, race, educational attainment, ethnicity, and smoking status. A more complete description of the methods is available in the Methods section in this article's Online Repository at www.jacionline.org.

Fig E1 and Table E1 in this article's Online Repository at www.jacionline.org present the sample disposition and descriptive characteristics. One thousand seven hundred ninety-nine subjects completed all 3 surveys, 387 completed only 2 surveys, and 495 completed only 1 survey. Self-reported adherence to controller medications was substantial (77%). Nineteen percent of subjects reported having an exacerbation requiring the use of oral corticosteroids in the previous 6 weeks. Most ACQ-5 scores in this general population with persistent asthma fell between 0 and 1 (55%) or 1 and 2 (30%, Table I and Fig E2 in this article's Online Repository at www.jacionline.org). Only 10% of subjects with ACQ-5 scores of 0 to 1 reported having an exacerbation compared with 62% of those with ACQ-5 scores of 4 to 5 (Table I and see Fig E3 in this article's Online Repository at www.jacionline.org). Mean unadjusted HRU generally increased with increasing ACQ-5 scores. Inhaled corticosteroid (ICS) prescriptions were higher for higher ACQ-5 scores, whereas adherence was slightly higher.

In adjusted analyses each 1-point increase in ACQ-5 score was associated with an odds ratio of 2.14 of having an asthma exacerbation (Table II). In addition, each 1-point increase in

TABLE I. Unadjusted mean exacerbations and HRU by ACQ-5 score (per 4 months)

	ACQ-5 score = 0-1.0, n = 3654 (55.2%)	ACQ-5 score = 1.0-2.0, n = 1984 (30.0%)	ACQ-5 score = 2.0-3.0, n = 759 (11.5%)	ACQ-5 score = 3.0-4.0, n = 191 (2.9%)	ACQ-5 score = 4.0-5.0, n = 29 (0.4%)	ACQ-5 score = 5.0-6.0, n = 5 (0.1%)	Total n = 6622
No. of exacerbations*	0.10 (0.30)	0.24 (0.43)	0.32 (0.47)	0.46 (0.50)	0.62 (0.49)	0.40 (0.55)	0.18 (0.38)
Self-reported adherence*	77.0 (35.1)	75.8 (32.9)	75.7 (32.2)	78.2 (30.5)	87.3 (25.6)	76.0 (25.1)	76.6 (34.0)
HRU†							
No. of prescriptions							
All cause	5.72 (5.47)	7.11 (6.80)	8.56 (7.41)	10.70 (9.75)	11.41 (6.51)	12.60 (3.44)	6.64 (6.41)
Asthma-specific							
Oral prednisone	0.11 (0.42)	0.17 (0.51)	0.25 (0.64)	0.52 (0.90)	0.69 (0.97)	0.40 (0.55)	0.16 (0.50)
SABA	0.37 (0.65)	0.66 (0.95)	0.82 (1.07)	1.26 (1.29)	1.28 (1.22)	1.80 (0.84)	0.54 (0.86)
ICS	0.88 (0.85)	0.92 (0.95)	0.98 (0.98)	1.12 (1.12)	1.28 (1.16)	0.80 (0.84)	0.91 (0.91)
No. of visits							
All cause							
ED	0.05 (0.26)	0.09 (0.43)	0.12 (0.42)	0.12 (0.36)	0.21 (0.56)	0.00 (0.00)	0.07 (0.34)
Inpatient	0.02 (0.15)	0.02 (0.16)	0.03 (0.22)	0.07 (0.34)	0.10 (0.31)	0.00 (0.00)	0.02 (0.17)
Outpatient	2.05 (2.76)	2.20 (3.34)	2.59 (4.13)	2.87 (5.07)	2.93 (3.46)	4.80 (2.59)	2.19 (3.22)
Telephone/E-mail	2.76 (4.35)	2.90 (4.39)	3.37 (4.56)	4.18 (6.38)	4.90 (5.62)	9.80 (9.88)	2.93 (4.48)
Asthma specific							
ED	0.02 (0.17)	0.05 (0.33)	0.08 (0.33)	0.08 (0.29)	0.17 (0.54)	0.00 (0.00)	0.04 (0.25)
Inpatient	0.02 (0.14)	0.02 (0.15)	0.03 (0.22)	0.06 (0.33)	0.07 (0.26)	0.00 (0.00)	0.02 (0.16)
Outpatient	0.35 (0.65)	0.43 (0.76)	0.53 (0.89)	0.79 (1.12)	1.00 (1.31)	0.60 (0.55)	0.41 (0.74)
Telephone/E-mail	0.09 (0.35)	0.12 (0.38)	0.15 (0.47)	0.31 (0.83)	0.34 (0.81)	0.40 (0.55)	0.11 (0.40)

*In previous 6 weeks; collected by patient survey.
†All HRU measures collected from claims data over 4 months (2 months before and 2 months after survey completion).

TABLE II. Regression results: exacerbations and HRU (incremental effect for a 1-point change in ACQ-5 score per 4 months)

	Incidence rate ratio	SE	95% CI	*P* value
Self-reported exacerbations (yes/no)*	2.141†	0.082	1.99-2.31	<.001
HRU‡				
No. of prescriptions				
All cause	1.208	0.015	1.18-1.24	<.001
Asthma specific	1.247	0.017	1.22-1.28	<.001
Oral prednisone	1.617	0.067	1.49-1.75	<.001
SABA	1.466	0.029	1.41-1.52	<.001
ICS	1.072	0.016	1.04-1.10	<.001
No. of visits/encounters				
All cause				
ED	1.356	0.083	1.20-1.53	<.001
Inpatient	1.245	0.115	1.043-1.49	.02
Outpatient	1.129	0.020	1.09-1.17	<.001
Telephone/E-mail encounters	1.121	0.022	1.08-1.16	<.001
Asthma specific				
ED	1.586	0.125	1.36-1.85	<.001
Inpatient	1.242	0.123	1.02-1.51	.03
Outpatient	1.277	0.030	1.22-1.34	<.001
Telephone/E-mail encounters	1.441	0.066	1.32-1.58	<.001

Controlling for round and group, age, sex, family income level, race, educational attainment, ethnicity, and smoking status.
*Self-reported exacerbations in previous 6 weeks.
†Odds ratio.
‡All HRU measures collected from claims data over 4 months (2 months before and 2 months after survey completion).

ACQ-5 score was associated with a 21% increase in the expected number of prescriptions (all cause), a 36% and 59% increase in expected emergency department (ED) visits (all cause and asthma related, respectively), a 24% increase in expected inpatient visits, a 13% and 27% increase in expected outpatient visits, and a 62%, 47%, and 7% increase in the expected number of oral prednisone, short-acting β-agonist (SABA), and ICS prescriptions, respectively.

The results of this study provide a clear indication of the deleterious effect of poor asthma control on exacerbations and HRU. Consistent with other reports, the number of exacerbations and HRU were higher when asthma was poorly controlled.[2,4-8] Our study furthers knowledge of the relationship between asthma control and these outcomes by assessing a broad range of asthma control in a general population sample and by providing detailed quantification of how each 1-point difference in ACQ-5 score is associated with increasing exacerbations and HRU. The ACQ-5 score distribution in this study reflects a general population of patients with persistent asthma (mean, 0.99; median, 0.80). The percentage of subjects experiencing an exacerbation requiring oral corticosteroid use increased significantly as the ACQ-5 score increased, reaching 62% for those with ACQ-5 scores of between 4 and 5. HRU followed a similar pattern, with increasing ED visits, inpatient and outpatient visits, and SABA and prednisone prescriptions associated with increasing ACQ-5 scores.

The findings of this study are strengthened by use of a validated measure of asthma control in a real-world setting in a general community population of patients with persistent asthma. This is in contrast to most other studies using validated measures of asthma control, which have typically been conducted in clinical trials of specialty or severe populations not generalizable to the broader asthmatic population or to studies in real-world settings that used surrogate markers of control (eg, β-agonist use or exacerbations).[2,4-6,8]

Potential limitations of the study include selection bias (subjects who were willing to participate in this study might differ from other subjects with asthma), the small proportion of

subjects with ACQ scores of greater than 4.0, and recall bias associated with self-reported medication adherence and exacerbations. A more complete discussion of the limitations and ramifications of the results is provided in the Discussion section in this article's Online Repository at www.jacionline.org.

Overall, the results of this study demonstrate a strong association between suboptimal asthma control and deleterious outcomes, such as more frequent exacerbations and higher HRU. The results also suggest that validated measures of control, such as the 5-question ACQ-5, can provide beneficial information for routine clinical care without undue respondent or clinical burden. The results of this analysis might also support close monitoring of asthma control in clinical practice and use of a validated control questionnaire to guide ongoing treatment decisions. Furthermore, estimates of the specific relationship between the ACQ score and exacerbations and HRU might be beneficial for population health and future applications, such as modeling the effect of disease interventions that improve asthma control through an estimation of the effect on ACQ-5 scores and subsequent HRU and exacerbations.

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Endemic mycoses in patients with *STAT3*-mutated hyper-IgE (Job) syndrome

To the Editor:

STAT3-mutated hyper-IgE (Job) syndrome (*STAT3* HIES) is characterized by highly elevated serum IgE level, recurrent episodes of pneumonia, eczema, skin abscesses, mucocutaneous candidiasis, and dental, vascular, and skeletal abnormalities.[1] STAT3 also promotes CD4 T_H17 differentiation and expression of the associated cytokines IL17 and IL22.[2] T_H17 cells are believed to enhance mucosal immunity through antimicrobial peptides, impairment of which may explain the typical epithelial infections in patients with *STAT3* HIES.

Cryptococcus, *Histoplasma*, and *Coccidioides* are endemic fungi that may cause disseminated infection involving the brain or the gastrointestinal (GI) tract in patients with *STAT3* HIES, a pattern distinct from other primary immunodeficiences.[3-5] We report 5 cases and review the literature on endemic fungal infections complicating HIES (see Table E1 in this article's Online Repository at www.jacionline.org). The patients described in these clinical cases were enrolled in protocols approved by the institutional review board of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health. The patients and/or their families provided written informed consent.

Histoplasmosis (H) 1: STAT3 HIES was diagnosed at age 7 years in a boy with recurrent otosinopulmonary infections, skin abscesses, radial and skull fractures, eczema, and oral aphthous ulcers.

At age 10 years, he had fever, abdominal pain, and hives. Computed tomography showed bilateral lung infiltrates (Fig 1, *A* and *B*) and hepatosplenomegaly. Histoplasma was diagnosed by urine and blood antigen; Gomori-methenamine silver staining showed small yeasts in bronchial lavage. Secondary hemophagocytic lymphohistiocytosis was apparent with fever and elevated liver enzymes (5-10 times the upper limit of normal), ferritin (16.5 times the upper limit of normal), and thrombocytopenia (to 63 K/uL; reference, 206-369 K/uL). He received liposomal amphotericin B with defervescence in 3 days. C-reactive protein, hepatic, and hematologic values normalized in 7 days. Infiltrates resolved by 3 months. Liposomal amphotericin B was replaced with itraconazole at 3.5 weeks because of nephrotoxicity. Itraconazole was poorly tolerated and was changed to posaconazole. He remains well on posaconazole 12 months later.

Case H2: STAT3 HIES was diagnosed at age 5 years in a girl with *Staphylococcus aureus* skin infections, sinusitis, asthma, minimal trauma fractures, and retained primary teeth.

At age 13 years, she presented with abdominal pain, weight loss, severe iron deficiency anemia, and elevated inflammatory markers. Endoscopy showed plaques in the distal two-thirds of

METHODS

The current study was designed to expand the understanding of the relationship between control and outcomes, including exacerbations and HRU, across a broad spectrum of patients by using a valid measure of asthma control (ACQ-5). Multiple rounds of survey administration across different allergy and flu seasons increased the range of possible ACQ scores, providing more data points to estimate this relationship.

Data source

This analysis of the Observational Study of Asthma Control and Outcomes used data from a prospective survey and retrospective claims-based analysis of patients with asthma enrolled in KPCO, a group-model, closed-panel, nonprofit health maintenance organization. KPCO is the largest health care system in Colorado, providing health care services to more than 625,000 members in the Denver-Boulder metropolitan area through more than 900 physicians at 26 separate medical offices. The racial/ethnic and demographic characteristics of KPCO members are similar to those of the state as a whole. Eligible patients received surveys designed to capture information on asthma control, exacerbations, adherence, and sociodemographic characteristics during 3 rounds over the course of 1 year: between April and August 2011, between September and December 2011, and between March and June 2012. Subsequent surveys were sent to only those patients who completed the prior round. For each round, patients who did not respond after 2 attempted mailings were contacted and offered the survey by telephone.

Study population

Subjects 12 years and older were identified from the KPCO database and invited to participate if they experienced persistent asthma within the previous year, as defined by clinical diagnosis and prescription drug use evidenced by 2 prescriptions of an ICS, use of omalizumab, or high use of β-agonists (>2 canisters of albuterol or equivalent within the previous 3 months). Subjects were excluded if they had a clinical diagnosis of intermittent asthma or exercise-induced asthma, but not persistent asthma, within the previous year; had a diagnosis of chronic obstructive pulmonary disease (or ≥1 prescriptions for ipratropium or tiotropium bromide and were ≥50 years of age); and lacked Kaiser prescription drug benefits or had dual insurance coverage, which would prevent accurate HRU capture in these patients. All subjects were required to have been continuously enrolled for 1 year with prescription drug benefits before the first survey date.

Study variables

Study variables for this analysis included asthma control, exacerbations, HRU, self-reported adherence, and sociodemographic characteristics. HRU was captured directly from the KPCO administrative databases. ACQ, adherence, and exacerbations were captured by the subject survey. Asthma control was assessed by using the ACQ-5, which is based on 5 symptom questions, resulting in a continuous score from 0 to 6, with lower scores representing better control. The authors of the ACQ demonstrated that the ACQ-5, ACQ-6, and ACQ-7 produce clinically equivalent results in aggregate, concluding that one can be used without preference over another; however, for individual treatment decisions, the ACQ-7 might provide more granular data.[E1] The ACQ-5 would likely be the most accessible to future users, requiring the fewest questions and making it more efficient for clinic practice. In addition, SABA use, the sixth item of the composite ACQ-6 score, was included as a discrete outcome in the current analyses. Given these factors, we chose to report results for the ACQ-5 rather than the ACQ-6.

Survey study variables included exacerbations, controller adherence, smoking status, sex, family income level, race, educational attainment, and ethnicity. Exacerbations were ascertained by asking the following question: "In the last six weeks, have you experienced serious asthma symptoms requiring you to take oral steroid medications?" Adherence was questioned as follows: "In the last six weeks, what percent of the time did you take your daily controller medications… as prescribed (such as QVAR®, Flovent®, Advair®, Singulair®)?"

HRU from the KPCO claims data was aggregated into 4-month panels (2 months before and 2 months after survey completion) with 3 rounds of surveys, resulting in three 4-month panels in 1 year. For example, total office-based visits for round 1 were calculated as the sum of all visits incurred during the 2 months preceding and 2 months after completion of the first survey.

Statistical analysis

Descriptive statistics of sociodemographic variables, clinical variables, clinical outcomes, patient-reported outcomes, and HRU were assessed. Unadjusted means and SDs for all of these variables were calculated across ACQ-5 scores. For adjusted analyses, HRU measures were regressed on ACQ-5 scores (as a continuous variable) by using negative binomial models, controlling for round and group fixed effects, age, sex, family income level, race, educational attainment, ethnicity, and smoking status. Logistic regression was used for exacerbations. A common regression approach for count outcomes would be a Poisson model. However, this approach assumes that the mean and variance of the distribution are the same. The literature and our estimates show that this assumption is violated: the data exhibit overdispersion. Negative binomial regression is a robust alternative to Poison regression. It works well with count variables, particularly in the case of overdispersed count data.

DISCUSSION

Preliminary examination of unadjusted results based on the survey administered over the course of 1 calendar year suggested that ACQ scores were worse in the winter than other seasons. After controlling for all covariates in regression analyses, season did not appear to be a statistically significant predictor of ACQ scores. However, based on the relatively small number of surveys completed in the winter, it is possible that a significant effect would be observed with a larger sample size of winter completers. Future research into the association between ACQ scores and season would be beneficial. However, the current research explicitly controlled for survey administration timing, thus controlling for any possible differences across seasons.

Subjects in this general population sample reported high adherence levels to controller medications (77%). Although not 100%, these self-reported adherence levels might be better than average[E2]; a recent systematic review reported that the mean level of adherence to ICSs was between 22% and 63%.[E3] It is possible that those who are likely to take the time to participate in a survey might be more interested in their asthma control and thus might be more likely to be adherent. However, it is also possible that there is some level of recall bias or purposeful overreporting in self-reported adherence. Adherence to ICSs is poor, and self-reported adherence is not always consistent with adherence determined through more objective measures, such as refill records.[E4]

A strength of this study is its generalizability to a general population of patients with persistent asthma. As expected for a general sample, very few subjects had an ACQ score of greater than 4.0. Subjects with this level of very poor control would likely be admitted to the hospital or ED and unable to participate in a community survey. As a result, conclusions regarding patients with ACQ-5 scores of greater than 4.0 must be made with caution.

The potential selection bias of subjects who were willing to participate in this type of study might be a limitation of the findings. Less than half of eligible members participated. Although this is a limitation, this low response is not unexpected for an uncompensated mailed survey in a general asthmatic population. The current research controlled for survey administration timing and group, as well as explicitly controlling for

sociodemographic characteristics, thereby potentially mitigating the influence of these differences. To avoid misclassifying patients with chronic obstructive pulmonary disease, we excluded patients 50 years or older who were prescribed ipratropium or tiotropium, which might have inadvertently resulted in excluding some asthmatic patients. The generalizability of the findings might also be limited by the survey response rates, as well as the geographic location of the survey. As discussed above, patients who consented to participate in the study might differ from those who declined. The extent to which these potential differences affect asthma control and outcomes is unknown but might result in underrepresentation of certain patients. The KPCO population is representative of the Colorado population, but this sample might not be generalizable to other states or regions.

Measurement of exacerbations was based on self-report and is subject to associated limitations, such as recall bias. Future analyses comparing self-reported exacerbations and oral steroid use would be beneficial but was beyond the scope of this analysis. There was a small percentage of current smokers in this sample compared with other studies, which limits its generalizability. Because some subjects completed multiple surveys over time, there was a potential for serial correlation. The regressions controlled for fixed effects, including the round of the survey, but it is possible that serial correlation affected the statistical significance of the estimates.

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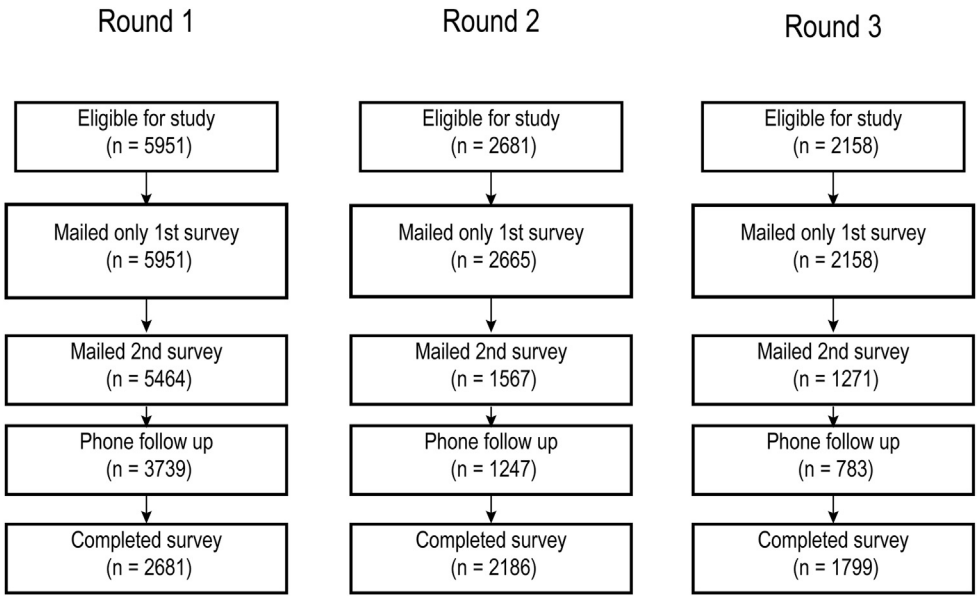

FIG E1. Patient disposition of the 3 survey rounds.

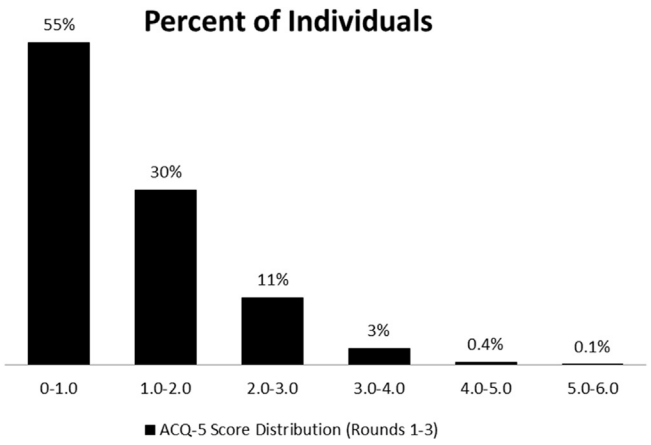

FIG E2. Distribution of ACQ-5 scores for the study population.

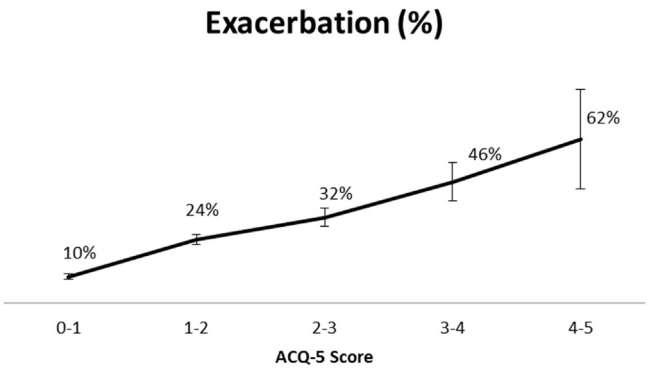

FIG E3. Exacerbation rates by ACQ-5 scores.

TABLE E1. Sample disposition and baseline demographics

Sample disposition	
No. of surveys completed	
Round 1	2681
Round 2	2186
Round 3	1799
All rounds	6666
Baseline demographics	n = 2681
Sex (female)	0.65
Mean age (y)	47.9
Age group	
12-24 y	0.13
25-34 y	0.11
35-44 y	0.16
45-54 y	0.22
55-64 y	0.26
65-74 y	0.09
75-84 y	0.03
>85 y	0.01
Race	
White	0.85
Asian	0.02
African American	0.04
American Indian	0.04
Native Hawaiian	0.01
Multiple race	0.00
NA	0.04
Ethnicity	
Hispanic	0.13
Non-Hispanic	0.86
NA	0.01
Income (US dollars/y)	
<$10,000	0.02
$10,000-$30,000	0.08
$30,000-$50,000	0.16
$50,000-$70,000	0.15
$70,000-$90,000	0.16
>$90,000	0.31
NA	0.04
No answer	0.08
Education	
Less than eighth grade	0.03
High school but did not graduate	0.05
High school graduate or GED	0.14
Some college	0.27
College graduate	0.25
Postgraduate	0.25
NA	0.01
Smoking history	
Never smoked	0.66
Current smoker	0.05
Previous smoker	0.28
Allergies*	0.74
Employed	0.69
Exacerbation†	0.19
Controller adherence*	0.77

Data represent proportion of patients, unless otherwise indicated. *NA,* Subject did not select an answer for the question; *No answer,* subject selected "I do not want to answer this question."

*In the previous 6 weeks.

†Exacerbation of asthma requiring the use of oral corticosteroids in the previous 6 weeks.