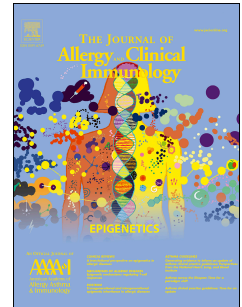


# Journal Pre-proof

Severe Asthma in the US Population and Eligibility for Monoclonal Antibody Therapy

Ayobami Akenroye, MD MPH, Meredith McCormack, MD MHS, Corinne Keet, MD PhD



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Severe Asthma in the US Population and Eligibility for Monoclonal Antibody Therapy

Ayobami Akenroye MD MPH<sup>1</sup>, Meredith McCormack MD MHS<sup>2</sup>, Corinne Keet MD PhD<sup>1</sup>

<sup>1</sup>Division of Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287

<sup>2</sup>Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 1830 E. Monument St., Baltimore, MD 21205

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**ADDRESS CORRESPONDENCE TO:**

Ayobami T. Akenroye  
Division of Allergy and Clinical Immunology  
Johns Hopkins University School of Medicine  
600 N. Wolfe Street  
Baltimore, MD 21287  
Email: [aakenroye@jhmi.edu](mailto:aakenroye@jhmi.edu)  
Telephone: 8572223661

32 ***Capsule summary***

33 This study shows that while about 80% of subjects with severe asthma may qualify for  
34 one or more of the currently available biologics, less than 10% of these patients will be  
35 eligible for all five.

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To the Editor,

Asthma is a disease with high morbidity. In the US, about 26 million individuals have asthma, accounting for 1.7 million emergency department visits and 440,000 hospitalizations annually.<sup>1</sup> Most patients with severe asthma respond to inhaled corticosteroids (ICS) therapy combined with short-acting beta agonists (SABA) or long-acting beta agonists (LABA), however, about 3.6-10% of subjects with asthma have severe disease refractory to maintenance therapy with ICS and account for a disproportionate percentage of asthma-related costs.<sup>2,3</sup> The development of monoclonal antibodies for the treatment of asthma has revolutionized the care of these patients with severe asthma.

At the time of this writing, the Food and Drug Administration (FDA) has approved five biologics for the treatment of severe asthma. These include, omalizumab, an anti-immunoglobulin E (IgE) antibody for allergic asthma, three anti-interleukin 5 or receptor antagonists (anti-IL5; mepolizumab, reslizumab, and benralizumab) for severe eosinophilic asthma, and dupilumab, an interleukin-4 receptor alpha antagonist approved for the treatment of moderate to severe eosinophilic asthma or corticosteroid-dependent asthma.<sup>4</sup> Our goal was to evaluate the percentage of patients with asthma in the U.S. who met criteria for eligibility for any of these monoclonal antibodies and to assess the degree of overlap of participants eligible for these biologics.

We identified participants with severe asthma from the 2005-2012 National Health and Nutrition Examination Survey (NHANES) to generate a nationally representative sample. Participants with severe asthma were aged  $\geq 6$  years with current asthma; on ICS combined with LABA or an anticholinergic for at least a year, or on oral corticosteroids for at least 3 months at the time of interview; and had  $\geq 1$  exacerbation in the prior year requiring an emergency room or urgent care center visit. We determined if subjects were eligible for a biologic based on the FDA-approved indications. For omalizumab, this included age, weight, IgE, and perennial sensitivity. Since only NHANES 2005-2006 had IgE and perennial sensitivity data available, we imputed these for 2007-2012. For the anti-IL5s and dupilumab, eligibility included age and eosinophil count. For dupilumab, eligibility also included patients on oral steroid for at least 90 days at the time of the interview. We conducted sensitivity analyses to evaluate the impact of varying duration of ICS/LABA use and oral corticosteroid use on proportion of patients classified as having severe asthma. Full details of methods can be found in the *Supplementary Appendix*.

There were 3039 survey participants with current asthma. There was a female preponderance (63 [60-66] %). Almost a quarter (22 [19-27] %) had an emergency room or urgent care visit for asthma in the prior year. 99 (3.1 [2.3-4.2] %) participants met criteria for severe asthma. [eTable 1, eFigure 1] This proportion was robust to various definitions of severity based on duration of ICS/LABA or oral corticosteroid use. [eFigure2]. 76% of participants aged  $<18$  had eosinophil counts  $>150$  cells/mm<sup>3</sup> and 40 % of these participants had eosinophil counts  $\geq 400$  cells/mm<sup>3</sup>, compared to 67 % and 25%, respectively, of those  $\geq 18$ . [Table 1] eTable2 in *Supplementary appendix* shows results of imputation of IgE and perennial sensitivity.

Of those with asthma, 2.4% were dupilumab-eligible, 2.2% mepolizumab-eligible, 1.6% omalizumab-eligible, 1.3% benralizumab-eligible, and 0.5% reslizumab-eligible. Among those with severe asthma, 73% were dupilumab-eligible, 72% mepolizumab-eligible, 41% omalizumab-eligible, 40% benralizumab-eligible, and 15% reslizumab-eligible. [Table 1] 2.8% of participants with asthma and 85% of those with severe asthma were eligible for at least one biologic. Every anti-IL5-eligible participant was also dupilumab-eligible except for participants aged 6-11 who were eligible for mepolizumab (7% of mepolizumab-eligible participants) but not for dupilumab. 91%, 55%, and 22% of dupilumab-eligible participants were eligible for mepolizumab, benralizumab, and reslizumab respectively. Over 70% of omalizumab-eligible participants were dupilumab- or mepolizumab-eligible. Conversely, about 40% of dupilumab- or anti-IL5-eligible participants were omalizumab-eligible. [Figure 1A and B] Overall, based on these eligibility criteria, 702,000 (95% CI: 468,000 – 962,000) people in the U.S. would be eligible for at least one biologic as a treatment for asthma.

In a nationally-representative sample of the U.S. population, we found that over 80% of participants with severe asthma and 2.8% of participants with asthma may be eligible for one of the currently available biologics. To our knowledge, this is the first study to date providing an estimate of Americans eligible for asthma biologics. These levels of eligibility are similar to a study of 69 patients with uncontrolled asthma in which 43.5% were eligible for omalizumab, but higher than a retrospective study of mepolizumab eligibility among patients referred to a tertiary center for severe asthma that found 49% were eligible for mepolizumab.<sup>5,6</sup> These results are also consistent with prior studies on asthma phenotypes including one using NHANES to generate clusters of asthma phenotype,<sup>7</sup> which showed that 78% of children and 69% of adults had eosinophilic asthma. This distribution of eosinophilic asthma is likely related to the percentage of participants we have found as eligible to one of these biologics given that four of the five currently available biologics are indicated for eosinophilic asthma.

The proportion of omalizumab-eligible participants eligible for mepolizumab in this study is slightly higher than previously reported. IDEAL,<sup>8</sup> an observational study of severe asthma patients showed that 53% of omalizumab-eligible patients from Australia and North America were anti-IL5 eligible. Another study showed that 47% of omalizumab-eligible patients were eligible for anti-IL5.<sup>5</sup> However, our results of the proportion of anti-IL5 or mepolizumab-eligible patients who were omalizumab-eligible are similar to the 37% and 36% reported by IDEAL<sup>8</sup> and Lee et al<sup>5</sup> respectively. Switches between these biologics are possible due to the overlap although proportion of eligible participants dropped significantly as eligibility criteria became stricter based on age and eosinophil count. This was most notable for reslizumab, approved for those aged  $\geq 18$  and with eosinophil counts over 400 cells/mm<sup>3</sup>. [Table E3 in *Supplementary Appendix*]. Only a quarter of adults with severe asthma in this study had eosinophil count  $\geq 400$  cells/mm<sup>3</sup> and just two out of ten mepolizumab-eligible participants were reslizumab-eligible. This is similar to the 18% of mepolizumab-eligible patients eligible for reslizumab in IDEAL.<sup>8</sup>

Because the study design was cross-sectional, we are unable to make inferences about how disease severity or treatment changed over time. We could have also misclassified participants' disease severity. Our estimates of omalizumab eligibility are imprecise because of the small number of subjects with IgE data. Questionnaire data are self-reported and the definition of asthma severity may be influenced by healthcare utilization patterns and medication adherence. However, these are real-life challenges that clinicians face when defining asthma severity in practice. Also, we have not addressed comparative effectiveness or costs of these biologics and this will be important for future research. Regardless of eligibility, providers may need to incorporate other factors such as insurance, costs, and route of administration into their decision to prescribe these biologics. For instance, dupilumab and mepolizumab are approved for home administration while reslizumab is given intravenously. Furthermore, annual costs of these biologics, the wholesale acquisition costs, range from \$27,950 for reslizumab, to \$48,472 for the first year on benralizumab.<sup>9</sup> Despite these limitations, however, this study provides important insights into available treatments options for patients with severe asthma for clinicians in real-world settings.

In summary, using a nationally-representative sample, we were able to show that 80% of participants with severe asthma, and about 700,000 Americans, would meet criteria for one of the currently available biologics. These results could help inform therapeutic choices for providers caring for patients with asthma who may be considering initiating therapy with a biologic agent or switching to an alternative agent.

*Ayobami Akenroye, MD MPH<sup>1</sup>*

*Meredith McCormack MD MHS<sup>2</sup>*

*Corinne Keet, MD PhD<sup>1</sup>*

Author Affiliations: <sup>1</sup>Department of Pediatric Allergy and Immunology, Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287

<sup>2</sup>Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 1830 E. Monument St., Baltimore, MD 21205

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200

201 **FIGURE LEGEND**

202 Figure 1A and B. For the heat map, the value in the cell reflects what percentage of  
203 participants eligible for the biologic in the row (A-E) was eligible for the biologics in the  
204 column. For instance, 73% of participants eligible for omalizumab were eligible for  
205 mepolizumab but only 44% of those eligible for mepolizumab were eligible for  
206 omalizumab.

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Table 1: Proportion of Participants with Asthma and Severe Asthma eligible for monoclonal antibody therapy

| *Weighted %, 95% CI                         | Overall          | ≤18              | >18              |
|---------------------------------------------|------------------|------------------|------------------|
| <b>Eligible for at least one biologic</b>   |                  |                  |                  |
| All asthma (n=3039)                         | 2.8 [1.9-3.7]    | 2.6 [1.4-3.9]    | 2.8 [1.8-3.8]    |
| Severe Asthma (n=104)                       | 84.7 [73.0-96.4] | 89.7 [74.1-97.9] | 83.9 [70.4-97.4] |
| <b>Eligible for all the five biologics</b>  |                  |                  |                  |
| All asthma                                  | 0.2 [0.0-0.5]    | 0                | 0.2 [0.0-0.6]    |
| Severe Asthma                               | 6.4 [3.1-15.9]   | 0                | 7.4 [3.5-18.3]   |
| <b>Anti-interleukin 5 therapy</b>           |                  |                  |                  |
| Mepolizumab                                 |                  |                  |                  |
| All asthma                                  | 2.2 [1.5-3.1]    | 2.5 [1.5-3.1]    | 2.1 [1.5-3.1]    |
| Severe asthma                               | 72.1 [59.6-81.8] | 88.5 [62.9-97.2] | 66.9 [53.3-78.2] |
| Benralizumab                                |                  |                  |                  |
| All asthma                                  | 1.3 [0.8-2.1]    | 1.9 [1.0-3.5]    | 1.1 [0.6-1.9]    |
| Severe asthma                               | 40.2 [26.7-55.4] | 62.8 [42.8-82.6] | 32.3 [18.7-49.7] |
| Reslizumab                                  |                  |                  |                  |
| All asthma                                  | 0.5 [0.3-1.0]    | 0                | 0.7 [0.4-1.4]    |
| Severe asthma                               | 14.8 [7.1-28.4]  | 0                | 19.5 [9.4-36.0]  |
| <b>Anti-interleukin 4/13 receptor alpha</b> |                  |                  |                  |
| Dupilumab                                   |                  |                  |                  |
| All asthma                                  | 2.4 [1.7-3.3]    | 1.9 [1.0-3.5]    | 2.5 [1.8-3.5]    |
| Severe asthma                               | 73.4 [63.4-81.4] | 67.8 [46.2-83.7] | 75.1 [64.0-83.7] |
| <b>#Anti-immunoglobulin E</b>               |                  |                  |                  |
| Omalizumab                                  |                  |                  |                  |
| All asthma                                  | 1.4 [0.6-2.1]    | 1.3 [0.2-2.4]    | 1.4 [0.5-2.2]    |
| Severe asthma                               | 41.4 [22.8-60.1] | 42.5 [10.1-75.0] | 41.3 [19.5-63.2] |
| Original data                               |                  |                  |                  |
| All asthma                                  | 1.6 [0.7-3.8]    | QNS              | QNS              |
| Severe asthma                               | 58.5 [30.7-81.8] | QNS              | QNS              |

CI, Confidence Interval; QNS, insufficient sample

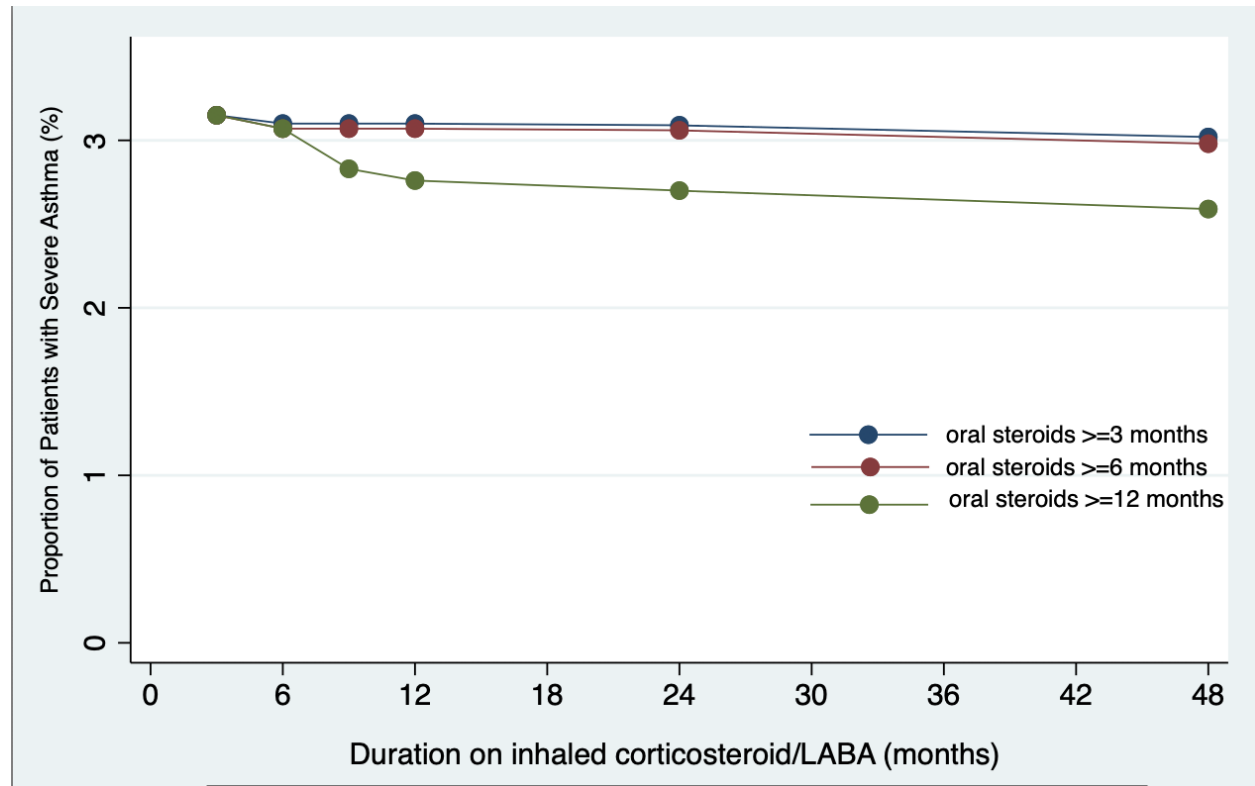
\*NHANES sample weights based on the complex sampling survey design were used in constructing estimates

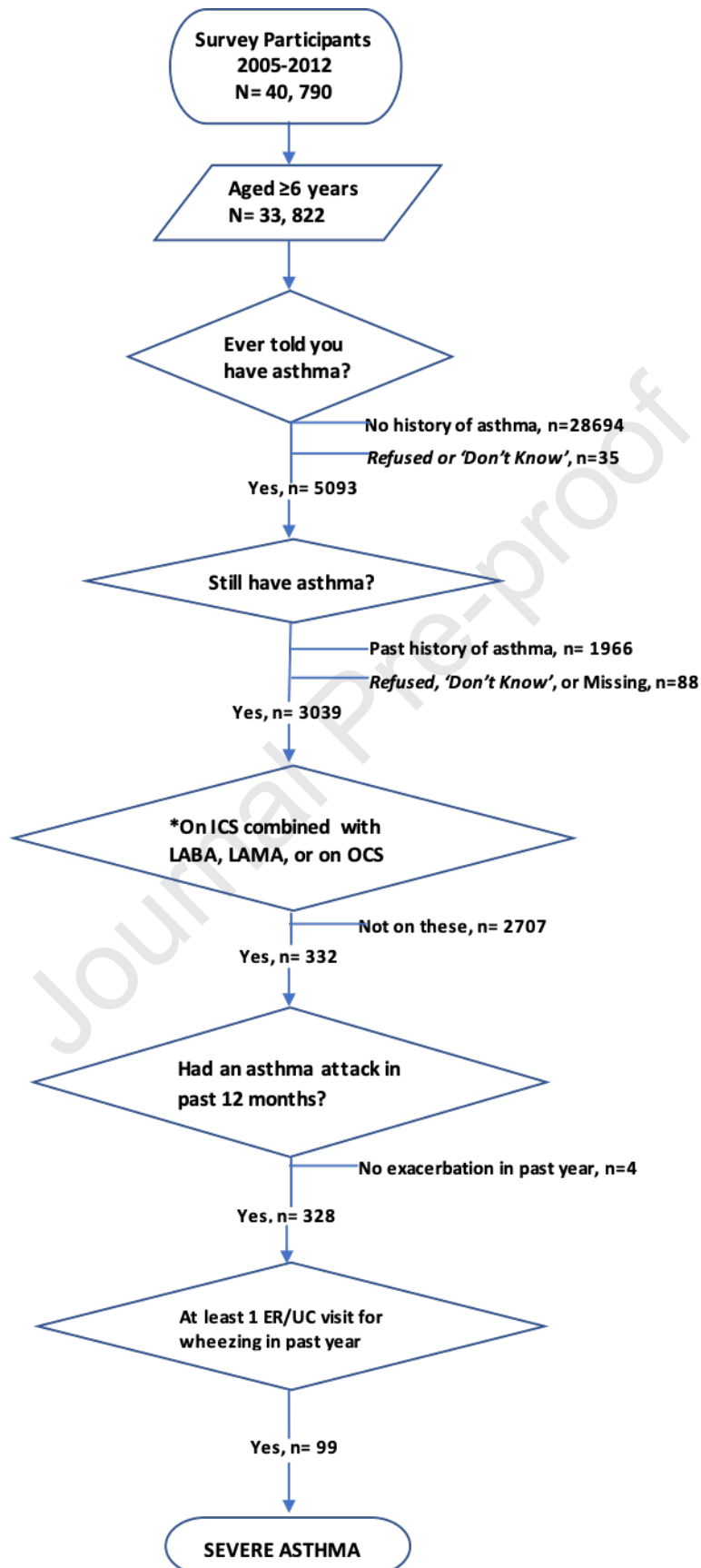
#Original data is from 2005-2006. IgE and sensitivity to perennial allergens for 2007-2012 imputed. Only 8 participants were eligible for omalizumab from 2005-2006, and only 20 had 'severe' asthma.

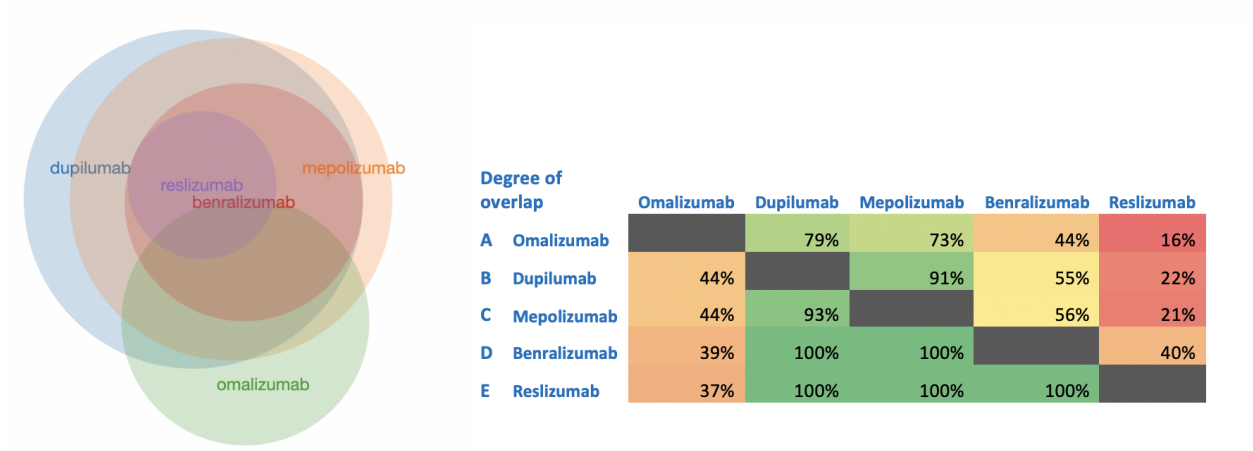
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## **SUPPLEMENTARY APPENDIX**

1. METHODS
2. TABLES/FIGURES
3. REFERENCES
4. FIGURE LEGENDS

### **1. METHODS**

#### **Data Source and Study Design**

Data for analysis were obtained from four pooled cycles (2005-2012) of the National Health and Nutrition Examination Survey (NHANES). The National Center for Health Statistics of the Centers for Disease Control and Prevention conducts the NHANES as a continuous publicly available US population-based cross-sectional survey of the noninstitutionalized civilian population.<sup>1</sup> NHANES has been conducted continuously in biennial blocks since 1999. About 10,000 individuals of all ages are sampled per biennial cycle. Sampling procedures are designed such that estimates are representative of the general noninstitutionalized U.S. population. NHANES has two phases of information gathering. The initial phase is an interview conducted in homes and subsequently, a health examination component in a mobile exam center where physical examination and laboratory evaluation takes place. Response rate for the four pooled survey cycles ranged from 71-81% for the interview portion and from 69-78% for the examination portion. In NHANES 2005-2006, low-income persons, adolescents 12-19 years, pregnant persons, persons 60 years of age and above, African Americans, and Mexican Americans were oversampled. NHANES 2007-2008 and NHANES 2009-2010 oversampled all Hispanics, persons 60 years and older, African Americans, and low-income persons were oversampled while adolescents and pregnant people were no longer oversampled. In addition, for each of the race/ethnicity domains, the 12-15 years and 16-19 years of age domains were combined while the 40-59-year age domains were split into 10-year age domains 40-49 and 50-59 years. Thus, there has been an increase in the number of participants aged 40 years and over and a decrease in the 12-19 year age group in comparison to previous cycles. In NHANES 2011-2012 and 2013-2014, non-Hispanic Asians were oversampled in addition to oversample of Hispanics, non-Hispanic blacks, older adults, and low-income whites/others. Given this complex sample

design, sample weights are assigned and analysis needs to use appropriate survey analysis methods.

### **Definitions: Asthma & Disease Severity**

#### **Patients**

Participants aged six and above were eligible. We considered a subject as having current asthma if answered the following questions in the affirmative: "Has a doctor or health professional ever told {you/study participant} that {you/s/he had} asthma?" and "Do you still have asthma?"

We considered asthma to be severe if participant was on inhaled corticosteroid (ICS) therapy in combination with a long-acting beta-agonist (LABA), long-acting muscarinic antagonists (LAMA) for  $\geq 1$  year, or oral corticosteroids for  $\geq 3$  months at the time of interview, and had  $\geq 1$  exacerbation in the prior year requiring a visit to an emergency room or urgent care center.

#### **Monoclonal antibody eligibility**

For each of the definitions (I-III), we determined if subjects with severe disease were eligible for a biologic based on the Food and Drug Administration (FDA)-approved indications.

Anti-immunoglobulin E, Omalizumab: We defined subjects as eligible for omalizumab if they were aged 6 to 11, had IgE levels between 30 and 1300 kU/L, weighed 44 to 330 lbs, and had an IgE level  $\geq 0.35$  kU/L to one of the following perennial allergens (*dermatophagoides farinae*, *dermatophagoides pteronyssinus*, *cat*, *dog*, *roach*, *alternaria*, *aspergillus*, *mouse*, *rat*). For patients aged  $\geq 12$ , eligible subjects had IgE levels between 30 and 700 kU/L, weighed 66 to 330 lbs, and had an IgE level  $\geq 0.35$  kU/L to one of the perennial allergens outlined above.

Anti-interleukin 5: Subjects were eligible for mepolizumab if aged  $\geq 6$  with eosinophil count  $\geq 150$  cells/uL; for benralizumab if aged  $\geq 12$  with eosinophil count  $\geq 300$  cells/uL; for reslizumab if aged  $\geq 18$  with eosinophil count  $\geq 400$  cells/uL.

Anti-IL4/13 receptor alpha, Dupilumab: Subjects eligible for dupilumab were aged  $\geq 12$  and with eosinophil count  $\geq 0.15$  or oral corticosteroid use. We included only patients who had

been on oral steroids for at least 30 days at the time of the interview for the oral corticosteroid criterion.

### **Covariates**

Data on age, gender, race/ethnicity, insurance status, and income were from self-report. Weight, body mass index (BMI), eosinophil counts, and IgE levels were objectively measured. Only NHANES 2005-2006 included serum total immunoglobulin E (IgE) and specific IgE levels to perennial allergens. Smoking history was available for participants  $\geq 20$  years. A participant was considered a current smoker if they (1) had smoked at least 100 cigarettes in life and (2) reported currently smoking. A nonsmoker had smoked less than 100 cigarettes in life and reported not smoking at the time of the interview. A former smoker had smoked at least 100 cigarettes in life but was not currently smoking.

### **Statistical analysis**

We report weighted proportions or means. Standard errors (SE) and confidence intervals (CIs) are used as appropriate. *P* values for differences in proportions or means were calculated using chi-square test for categorical variables and Student t-test for continuous variables.

To determine omalizumab eligibility for subjects with asthma in the 2007-2012 surveys, we imputed serum IgE levels and sensitivity to perennial allergens since serum or perennial allergen IgE levels were not collected during those years. 659 (88%) and 750 (100%) of the 750 eligible participants with asthma from the 2005-06 cycle had complete serum IgE and perennial allergen testing data respectively. We used multiple imputation techniques.<sup>2-5</sup> We proceeded with fully conditional specification to decrease confounding in our estimates.<sup>6,7</sup> Thus, we included age, gender, race/ethnicity, weight, and insurance status, family to poverty level in all imputation models. Eosinophil count was also included as a possible auxiliary variable. Ten imputed data sets were developed. All analyses were done as per multiple imputation and survey data analyses in STATA (version 15.1, STATCorp, College Station, Tex). NHANES sample weights were used in all analyses to obtain unbiased national estimates. SEs, CIs, and *P* values were developed as appropriate for the complex survey design by using Taylor series linearization methods. *P* values of less than .05 were considered statistically significant.

### **Sensitivity Analyses**

We sought to evaluate the impact of using different cut-offs of duration on medication use on proportion of participants classified as having severe asthma. We assessed this proportion across varying durations of reported ICS/LABA or LAMA use ( $\geq 3$ , 6, 9, 12, 24, and 48 months) with varying oral steroid durations ( $\geq 3$ , 6, and 12 months).

**2: TABLES****Table E1: Baseline Characteristics of Survey Participants with Current Asthma**

|                                                                | <b>Overall</b>   | <b>&lt;18</b>    | <b>≥18</b>       |
|----------------------------------------------------------------|------------------|------------------|------------------|
| <b>N</b>                                                       | <b>3039</b>      | <b>1186</b>      | <b>1853</b>      |
| Gender, female (%)                                             | 58.8 [56.4-61.2] | 46.5 [42.7-50.3] | 63.1 [60.1-66.0] |
| <b>RACE/ETHNICITY</b>                                          |                  |                  |                  |
| Non-Hispanic White                                             | 67.8 [63.4-71.9] | 56.5 [51.1-61.8] | 71.8 [67.5-75.8] |
| Non-Hispanic Black                                             | 15.8 [13.0-18.9] | 20.5 [16.6-25.0] | 14.1 [11.6-17.1] |
| Hispanic                                                       | 10.6 [8.6-13.0]  | 16.2 [13.2-19.7] | 8.6 [6.7-10.9]   |
| Asian and other Non-Hispanic races                             | 5.9 [4.7-7.3]    | 6.8 [5.1-9.1]    | 5.5 [4.2-7.2]    |
| BMI (kg/m <sup>2</sup> ), mean (SE)                            | 28.5 [0.23]      | 22.4 [0.27]      | 30.6 [0.25]      |
| *Poverty to income ratio, mean (SE)                            | 2.6 [0.08]       | 2.4 [0.09]       | 2.7 [0.09]       |
| <b>HEALTH INSURANCE, % [CI]</b>                                |                  |                  |                  |
| No coverage                                                    | 13.2 [11.1-15.6] | 6.9 [4.7-10.1]   | 15.4 [12.9-18.3] |
| <i>Of those insured:</i>                                       |                  |                  |                  |
| Private insurance, %                                           | 65.9 [62.7-68.9] | 58.7 [65.3-71.9] | 68.7 [65.3-71.9] |
| Public insurance, %                                            | 34.0 [31.0-37.1] | 41.2 [35.1-47.6] | 31.2 [28.0-34.6] |
| Other insurance                                                | 0.1 [0.0-0.4]    | 0.03 [0.0-0.2]   | 0.1 [0.03-0.5]   |
| <b>ASTHMA-RELATED QUESTIONS</b>                                |                  |                  |                  |
| ΨSevere asthma                                                 | 3.1 [2.3-4.2]    | 2.8 [1.8-4.5]    | 3.2 [2.3-4.5]    |
| Emergency room or urgent care visit for asthma, past 12 months | 21.6 [18.8-24.8] | 22.4 [18.6-26.6] | 21.4 [18.1-25.0] |
| On inhaled corticosteroids (ICS)                               | 8.3 [6.9-9.8]    | 11.1 [9.2-13.3]  | 7.3 [5.7-9.3]    |
| On ICS/LABA                                                    | 15.3 [13.4-17.5] | 9.9 [7.9-12.5]   | 17.2 [14.7-20.1] |
| ^On oral corticosteroids                                       | 2.5 [1.9-3.3]    | 2.9 [1.8-4.7]    | 2.3 [1.7-3.2]    |
| <b>SMOKING STATUS</b>                                          |                  |                  |                  |
| Current smoker                                                 | 25.3 [22.1-28.6] | N/A              | 25.3 [22.1-28.6] |
| Former smoker                                                  | 25.5 [23.3-28.0] | N/A              | 25.5 [23.3-28.0] |
| Non-smoker                                                     | 49.2 [45.7-52.7] | N/A              | 49.2 [45.7-52.7] |
| <b>HEMATOLOGICAL INDICES</b>                                   |                  |                  |                  |

|                                                       |                  |                  |                  |
|-------------------------------------------------------|------------------|------------------|------------------|
| Eosinophil count, mean (SE)                           | 272 [6.4]        | 336 [16.2]       | 251 [5.9]        |
| Eosinophil count <150 cells/mm <sup>3</sup> , %       | 30.4 [28.4-32.5] | 24.0 [20.6-27.7] | 32.7 [30.3-35.3] |
| Eosinophil count ≥150- 300 cells/mm <sup>3</sup> , %  | 25.0 [23.1-27.0] | 18.2 [15.2-21.7] | 27.4 [25.1-30.0] |
| Eosinophil count ≥300 - 400 cells/mm <sup>3</sup> , % | 14.9 [13.4-16.5] | 15.5 [12.4-19.2] | 14.7 [12.9-16.8] |
| Eosinophil count ≥400 cells/mm <sup>3</sup> , %       | 29.6 [27.7-31.6] | 42.3 [38.4-46.3] | 25.1 [23.1-27.3] |

**Total serum IgE**

|                  |                  |                  |                  |
|------------------|------------------|------------------|------------------|
| IgE <30          | 29.3 [24.1-34.6] | 17.0 [10.6-23.3] | 31.4 [25.2-37.5] |
| IgE 30-700 mg/dl | 63.6 [59.2-68.1] | 68.6 [62.3-75.8] | 62.8 [57.2-68.4] |
| IgE >700-1300    | 3.8 [2.0-5.7]    | 8.3 [5.5-11.1]   | 3.1 [1.1-5.2]    |
| IgE >1300        | 3.2 [1.8-4.6]    | 6.1 [1.9-10.4]   | 2.7 [1.3-4.2]    |

|                                          |                  |                  |                  |
|------------------------------------------|------------------|------------------|------------------|
| Sensitivity to Perennial aeroallergens,% | 59.4 [49.7-69.1] | 67.2 [56.2-79.2] | 56.3 [45.1-62.1] |
|------------------------------------------|------------------|------------------|------------------|

101 SE, standard error; CI, confidence interval, IQR interquartile range

102 \*Family income to poverty level as per the Department of Health and Human Services annual  
103 poverty guidelines

104 ΨSevere asthma defined as current asthma and on inhaled corticosteroid combined with long  
105 acting beta agonist (LABA) or anticholinergic agent and with ≥1 exacerbation requiring  
106 emergency room or urgent care visit in prior 12 months

107

108

**Table E2: Imputation Results: Immunoglobulin E and Sensitivity to Perennial Allergens**

|                                                  | Original data    | Imputed data     |  |
|--------------------------------------------------|------------------|------------------|--|
| <b>Total serum IgE</b>                           |                  |                  |  |
| IgE <30                                          | 27.2 [21.8-33.4] | 30.1 [22.9-37.3] |  |
| IgE 30-700 mg/dl                                 | 65.2 [58.2-71.6] | 63.1 [57.3-68.8] |  |
| IgE >700-1300                                    | 4.4 [2.6-7.3]    | 3.6 [1.1-6.2]    |  |
| IgE >1300                                        | 3.2 [1.5-6.5]    | 3.2 [1.4-5.1]    |  |
| <b>Sensitivity to Perennial aeroallergens, %</b> | 60.3 [55.6-64.9] | 58.2 [47.2-69.3] |  |

**Table E3: Eligibility for Monoclonal Antibodies Based on Current Drug Labeling**

**I. PATIENTS 6 to <12 YEARS OF AGE**

|                                        | SERUM IGE (IU/ml) |             |                            |             |
|----------------------------------------|-------------------|-------------|----------------------------|-------------|
|                                        |                   | <30         | 30-1300                    | >1300       |
| <b>Eosinophil count (cells/cu. mm)</b> | < 150             | none        | *Omalizumab                | none        |
|                                        | ≥150              | Mepolizumab | *Omalizumab<br>Mepolizumab | Mepolizumab |

*Patients <6 years of age are not eligible for any of the currently approved biologics*

**II. PATIENTS 12 to <18 YEARS OF AGE**

|                                        | SERUM IGE (IU/ml) |                                            |                                                           |                                            |
|----------------------------------------|-------------------|--------------------------------------------|-----------------------------------------------------------|--------------------------------------------|
|                                        |                   | <30                                        | 30-700                                                    | >700                                       |
| <b>Eosinophil count (cells/cu. mm)</b> | < 150             | none                                       | *Omalizumab                                               | none                                       |
|                                        | 150-<300          | Dupilumab,<br>Mepolizumab                  | Omalizumab,<br>Dupilumab,<br>Mepolizumab                  | Dupilumab,<br>Mepolizumab                  |
|                                        | ≥300              | Dupilumab,<br>Mepolizumab,<br>Benralizumab | Omalizumab,<br>Dupilumab,<br>Mepolizumab,<br>Benralizumab | Dupilumab,<br>Mepolizumab,<br>Benralizumab |

**III. PATIENTS ≥18 YEARS OF AGE**

|                                        | SERUM IGE (IU/ml) |                                                           |                                                                          |                                                           |
|----------------------------------------|-------------------|-----------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------|
|                                        |                   | <30                                                       | 30-700                                                                   | >700                                                      |
| <b>Eosinophil count (cells/cu. mm)</b> | < 150             | none                                                      | *Omalizumab                                                              | none                                                      |
|                                        | 150-<300          | Dupilumab,<br>Mepolizumab                                 | Omalizumab,<br>Dupilumab,<br>Mepolizumab                                 | Dupilumab,<br>Mepolizumab                                 |
|                                        | 300-<400          | Dupilumab,<br>Mepolizumab,<br>Benralizumab                | Omalizumab,<br>Dupilumab,<br>Mepolizumab,<br>Benralizumab                | Dupilumab,<br>Mepolizumab,<br>Benralizumab                |
|                                        | ≥400              | Dupilumab,<br>Mepolizumab,<br>Benralizumab,<br>Reslizumab | Omalizumab,<br>Dupilumab,<br>Mepolizumab,<br>Benralizumab,<br>Reslizumab | Dupilumab,<br>Mepolizumab,<br>Benralizumab,<br>Reslizumab |

\*To be eligible for omalizumab, patients also need to demonstrate sensitivity to a perennial allergen, and weigh 44-330 lbs if <12 years of age or 66-330 lbs if ≥12 years

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#### 4. FIGURE LEGENDS

##### **FIGURE E1: Flow chart of definition of severe asthma**

\*Had to have been on ICS with LABA/LAMA for at least a year, or OCS for at least 3 months at the time of the interview. ICS, inhaled corticosteroid; OCS, oral corticosteroid; LABA, long acting beta agonist; LAMA, long acting muscarinic antagonist

**FIGURE E2:** Percentage of Participants with Severe Asthma (by varying durations of medication use). *Percentage of participants with severe asthma was ~3% regardless of duration of medication use.*