



Overlap of atopic, eosinophilic, and T_H2-high asthma phenotypes in a general population with current asthma

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ABSTRACT

Background: Atopic, eosinophilic, and T_H2-high asthma phenotypes may overlap, but the extent is unknown. Understanding the overlap across these phenotypes may be useful in guiding asthma patient care.

Objective: To examine the frequency and overlap of atopic, eosinophilic, and T_H2-high asthma phenotypes.

Methods: We analyzed 2005 to 2006 data from the National Health and Nutrition Examination Survey. Patients with asthma were identified based on the participant self-report. Eosinophilic asthma was defined as a blood eosinophil cutoff point of ≥ 150 , 300, or 400/ μ L. Atopic asthma was defined as having an allergen-specific IgE level of ≥ 0.35 IU/mL for any of the 9 perennial allergens tested. T_H2-high asthma was defined as a total serum IgE of ≥ 100 IU/mL and a blood eosinophil count of ≥ 140 / μ L.

Results: The study included 269 children and 310 adults. Depending on the eosinophil cutoff used, 31% to 78% of children and 21% to 69% of adults with asthma were classified as having eosinophilic asthma. In addition, 63% of children and 61% of adults were classified as having atopic disease and 48% of children and 37% of adults as having T_H2-high asthma. At a higher eosinophil cutoff point, a greater proportion of eosinophilic asthma can be classified as atopic or T_H2 high, but a lower proportion of atopic or T_H2-high asthma can be classified as eosinophilic. Approximately 70% or more of children and adults with asthma were 1 of these 3 phenotypes.

Conclusion: A considerable overlap among eosinophilic, atopic, and T_H2-high asthma phenotypes exists in a general asthma population.

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Introduction

Asthma is a complex and heterogeneous disease with a wide range of clinical characteristics, varying disease progression, and response to treatment.^{1–3} Although various categorization approaches have been used to define asthma phenotypes, allergic and nonallergic are historically the most widely recognized.¹ Phenotypic heterogeneity and clusters of asthma have also been defined

based on clinical and physiologic characteristics, including sex, age at onset, degree of airflow obstruction, atopic status, degree of obesity, and corticosteroid use.^{2–4} The coupling of clinical characteristics with inflammatory status has helped further refine the phenotypic clustering.^{2,5}

Allergic asthma is thought to result from aeroallergen-induced inflammation driven by T_H2 cytokines, including interleukin (IL) 4, IL-5, and IL-13. Release of these cytokines leads to recruitment of immune cells, such as eosinophils and basophils.⁶ Basic research in asthma has focused intensely on understanding how T_H2 cytokines cause asthma-like pathologic and physiologic findings.⁷ The term *allergic asthma* has been further divided into atopic, eosinophilic, and T_H2-high inflammatory phenotypes. It has been assumed that these phenotypes overlap with one another, but the extent of their overlap is not well understood. Although atopy has been associated with any age at asthma onset, it commonly begins in early childhood. Eosinophilic inflammation in asthma has been associated with increased asthma severity, atopy, and late-onset disease.^{8,9}

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Asthmatic patients with T_H2 -high inflammation have a greater degree of bronchial hyperresponsiveness, greater serum IgE concentrations, and increased blood and airway eosinophils.¹⁰ Although there is a link between atopy with T_H2 cytokines and eosinophilic inflammation, there are also indications that high eosinophilic inflammation is not always associated with atopy,² and allergic asthmatic patients treated with anti-IgE therapy do not always respond to this treatment.¹

Given that biologic therapies that target these specific asthma phenotypes are either currently available or in development^{11–14} and that some newer medications may be directed at more than one phenotype, an understanding of the overlap across these phenotypes may be useful in guiding treatment decisions, optimization, and overall care. The present study was conducted to evaluate the distribution and overlap of atopic, eosinophilic, and T_H2 -high asthma phenotypes in a general asthma population in the United States. We hypothesized that there would be significant overlap of these phenotypes among asthmatic patients.

Methods

Study Population and Setting

We analyzed data from the National Health and Nutrition Examination Survey (NHANES), an annual survey of a nationally representative sample of the noninstitutionalized United States population. NHANES is conducted by the National Center for Health Statistics of the Centers for Disease Prevention and Control.¹⁵ Each survey consists of a combination of an in-home interview, an examination at a mobile examination center, and laboratory tests. In each survey, participants were selected using a complex stratified multistage cluster sampling scheme. The NHANES's medical conditions file contains questions related to the medical history of participants. Asthma patients aged 6 to 64 years were identified based on the participant's self-report or parental reports of a child's current asthma, defined as answering yes to the question, "Has a doctor or other health professional ever told you that you have asthma?" and answering that they still had asthma at the time of their interviews. Participants with a prior diagnosis of asthma but responding that they no longer had asthma were excluded from the analysis. Persons younger than 6 years were not studied because the diagnosis of asthma is difficult to establish in early childhood. Persons older than 64 years were also excluded to avoid the potential misdiagnosis with chronic obstructive pulmonary disease.

Definition of Eosinophilic, Atopic, and T_H2 -High Asthma Phenotype

In all survey years, NHANES participants had their complete blood cell count data recorded, which included absolute cell counts (cells per microliter) of eosinophils derived from the eosinophil percentage of the total white blood cells per microliter.¹⁵ Eosinophilic phenotype was defined using 3 different blood eosinophil cutoff points: 150, 300, and 400/ μ L. In the 2005 and 2006 survey years, serum IgE was tested, including total serum IgE and allergen-specific IgE for 19 allergens for those 6 years or older. We defined atopic asthma as current asthmatic patients with an allergen-specific IgE level of ≥ 0.35 IU/mL to any of the 9 tested perennial allergens, including *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat epithelium and dander, dog dander, German cockroach, *Alternaria alternata*, *Aspergillus fumigatus*, and rat and mouse urine proteins.¹⁵ T_H2 -high status was defined according to a previously developed algorithm requiring a total serum IgE level of ≥ 100 IU/mL and a blood eosinophil count of ≥ 140 / μ L.^{10,16} We included only survey years 2005 and 2006 in the final study sample because this is the timeframe during which IgE data were collected.

Other Characteristics

Background characteristics, including age, sex, race/ethnicity, and educational level, were extracted from the demographic variables file in NHANES. Smoking history was extracted from smoking cigarettes use file, and a participant was defined as a nonsmoker if the participant reported "ever smoked fewer than 100 cigarettes in life." Survey participants who smoked at least 100 cigarettes were classified as current or ex-smokers. Children were considered nonsmokers.¹⁷ Body mass index (BMI; a measure of weight in kilograms divided by height in meters squared) data from the body measurements file were used to define obesity status. In children, obesity was defined as a BMI in the ≥ 95 th percentile, and overweight was defined as a BMI between the 85th and 95th percentiles of the corresponding age and sex reference groups.¹⁸ In adults, study participants with a BMI of ≥ 30 were considered obese and those with a BMI of 25 to <30 were considered overweight.

Asthma attack (ie, worsening of asthma symptoms) was identified by an affirmative response of patients with asthma to the question, "In the past year, did you have an asthma attack?"

Statistical Analysis

We measured the proportion of eosinophilic, atopic, and T_H2 -high asthma among current asthmatic patients and determined the cross-distribution among these phenotypes. The frequency of each asthma phenotype was compared between children and adults using the Rao-Scott χ^2 test. Statistical significance was set at $P \leq .05$. Analyses were performed separately for children and adults. In a sensitivity analysis, we repeated the analyses for patients who reported at least one asthma attack in the year before the interviews as a proxy for exacerbations and potentially uncontrolled asthma. All analyses considered the complex multistage sampling using the sampling weights provided by NHANES.¹⁵ Analyses were conducted using SAS statistical software, version 9.3 (SAS Institute Inc, Cary, North Carolina).

Results

Study Population Characteristics

The study population comprised 269 children (aged 6–17 years) and 310 adults (aged 18–64 years) with self-reported current asthma who had blood eosinophil count data (Table 1). Of these participants, most had total IgE (268 children and 309 adults) and allergen-specific IgE (267 children and 305 adults) data from the 2005 and 2006 surveys. The mean ages of the asthmatic patients were 12 and 41 in the child and adult groups, respectively. Approximately 53% of the children and 37% of the adults who participated in the study were male. Of the current asthmatic patients, 67% of children and 74% of adults reported wheezing or whistling in the prior 12 months, 64% of children and 60% of adults reported at least one asthma attack, and approximately a quarter of those with at least one asthma attack had an emergency department visit due to the attack.

Frequency of Asthma Phenotypes

The frequencies of eosinophilic (with different cutoff points), atopic, and T_H2 -high phenotypes among the asthmatic patients are presented in Table 2. The frequency of eosinophilic asthma decreased from 78% to 31% for children and from 69% to 21% for adults as the threshold definition increased from 150 to 400/ μ L. Approximately 63% of children and 61% of adults were classified as having atopic asthma and 48% and 37%, respectively, had T_H2 -high asthma. Eosinophilic and T_H2 -high phenotypes appeared to be more prevalent in children than adults. Males were more likely

Table 1
Characteristics of the study population by age group

Characteristic	Children (6–17 years old) (n = 269)	Adults (18–64 years old) (n = 310)
Age, mean (SD), y	12 (0.3)	41 (1.0)
Age at asthma onset, mean (SD), y	6 (0.3)	22 (1.1)
Sex, No. (%)		
Male	149 (53)	112 (37)
Female	120 (47)	198 (63)
Race/ethnicity, No. (%)		
Hispanic	78 (15)	54 (7)
Non-Hispanic white	78 (65)	159 (75)
Non-Hispanic black	101 (16)	86 (12)
Other	12 (4)	11 (6)
Educational level, No. (%)		
High school or higher	0	218 (88)
Less than high school	269 (100)	53 (12)
Smoking status, No. (%)		
Current smoker	0	72 (24)
Ex-smoker	0	60 (19)
Nonsmoker	268 (100)	139 (57)
Body mass index, mean (SD)	22 (0.7)	31 (0.7)
Obesity status, No. (%)		
Normal weight	159 (62)	85 (27)
Overweight	42 (15)	79 (25)
Obese	68 (23)	146 (48)
Wheezing/whistling in past year, No. (%)		
Yes	174 (67)	215 (74)
No	95 (33)	95 (26)
Any asthma attack in past year, No. (%)		
Yes	145 (64)	163 (60)
No	124 (36)	147 (40)
Any asthma ED visit in past year in those with asthma attack, No. (%)		
Yes	37 (23)	47 (26)
No	108 (77)	116 (74)

Abbreviation: ED, emergency department.

than females to be classified as having eosinophilic, atopic, or T_H2 -high asthma in both age groups.

Overlap Among Atopic, Eosinophilic, and T_H2 -High Phenotypes

Of patients with eosinophilic asthma, most could be classified as having atopic asthma, and the frequency was greater with greater eosinophil cutoffs. For children with eosinophilic asthma defined with the 150/ μ L eosinophil cutoff, 72% were also atopic (Table 3). This percentage increased to 81% and 94%, respectively, at the 300

Table 2
Frequency of eosinophilic, atopic, and T_H2 -high asthma phenotype by age and sex

Asthma phenotype	Children, % (6–17 years old)			Adults, % (18–64 years old)			P value ^a
	Male	Female	Total	Male	Female	Total	
Eosinophilic asthma							
Eosinophil cutoff of 150/ μ L	83	72	78	76	65	69	.13
Eosinophil cutoff of 300/ μ L	67	46	57	49	37	41	.02
Eosinophil cutoff of 400/ μ L	40	22	31	30	16	21	.10
Atopic asthma	72	53	63	77	51	61	.63
T_H2 -high asthma	57	36	48	47	31	37	.13

^aRao-Scott χ^2 test comparing the frequency of phenotypes by age (ignoring sex).**Table 3**
Frequency of overlap of atopic and eosinophilic asthma phenotype

Variable	Frequency by eosinophil cutoff, %		
	150/ μ L	300/ μ L	400/ μ L
Overlap of Eosinophilic and Atopic Asthma			
Frequency of patients who were classified as having both eosinophilic and atopic asthma			
Children	56	47	29
Adults	47	31	16
Frequency of atopic asthma among those with eosinophilic asthma			
Children	72	81	94
Adults	68	74	76
Frequency of eosinophilic asthma among those with atopic asthma			
Children	89	75	46
Adults	78	51	27
Frequency of patients who can be classified as having neither eosinophilic nor atopic asthma			
Children	15	26	35
Adults	18	28	35
Overlap of Eosinophilic and T_H2-High Asthma			
Frequency of patients who were classified as having both eosinophilic and T_H2 -high asthma			
Children	48	40	25
Adults	37	25	14
Frequency of T_H2 -high asthma among those with eosinophilic asthma			
Children	62	70	81
Adults	54	61	70
Frequency of eosinophilic asthma among those with T_H2 -high asthma			
Children	100	83	52
Adults	100	68	38
Frequency of patients who can be classified as having neither eosinophilic nor T_H2 -high asthma			
Children	22	35	46
Adults	31	47	57

and 400/ μ L eosinophil cutoff. For adults, the corresponding figures were 68% at the 150/ μ L eosinophil cutoff, 74% at the 300/ μ L cutoff, and 76% at the 400/ μ L cutoff (Table 3). In contrast, for those with atopic asthma, the frequency of eosinophilic asthma decreased as eosinophilic cutoff increased. Of children classified with atopic asthma, 89%, 75%, and 46% were also classified with eosinophilic asthma at the 150, 300, and 400/ μ L cutoffs, respectively. The corresponding frequency for adults classified as having atopic asthma who also met the criteria for eosinophilic asthma were 78%, 51%, and 27%, respectively. Similarly, at greater eosinophilic cutoff points, the frequency of asthmatic patients who were classified as having both atopic and eosinophilic asthma decreased from 56% at 150/ μ L to 29% at 400/ μ L for children and from 47% at 150/ μ L to 16% at 400/ μ L for adults.

A similar pattern of overlap was also observed between eosinophilic and T_H2 -high asthma (Table 3). For those classified as having eosinophilic asthma, being classified as having T_H2 -high asthma also increased with greater eosinophil cutoff points, ranging from 62% (at 150/ μ L) to 81% (at 400/ μ L) for children and from 54% (at 150/ μ L) to 70% (at 400/ μ L) for adults. In contrast, with a greater eosinophil cutoff point, the frequency of eosinophilic asthma for those classified as having T_H2 -high asthma decreased. For children classified as having T_H2 -high asthma, the frequency of those also classified as having eosinophilic disease decreased from 100% (at 150/ μ L) to 52% (at 400/ μ L). For adults, these frequencies ranged from 100% to 38%, respectively. Similarly, at greater eosinophil cutoff points, the frequency of patients who were classified as having both T_H2 -high and eosinophilic disease decreased.

A considerable overlap was also observed between atopic and T_H2 -high asthma, which was also more pronounced for children than for adults (Table 4). For children, 68% of those classified with atopic asthma were also classified as having T_H2 -high disease, and 91% of those classified as having T_H2 -high asthma were also

Table 4
Frequency of overlap of atopic and T_H2-high asthma phenotype

Variable	Children, % (6–17 years old)	Adults, % (18–64 years old)
Frequency of patients who were classified as having both atopic and T _H 2-high asthma	43	32
Frequency of T _H 2-high asthma among those with atopic asthma	68	53
Frequency of atopic asthma among those with T _H 2-high asthma	91	86
Frequency of patients who can be classified as having neither atopic nor T _H 2-high asthma	33	35

classified as atopic. For adults, the corresponding figures were 53% and 86%, respectively.

At the 150/ μ L eosinophil cutoff point, 44% of children and 33% of adults were classified as having eosinophilic, atopic, or T_H2-high asthma simultaneously (Fig 1). The corresponding figures were 38% and 23% with the 300/ μ L eosinophil cutoff point and 25% and 14% with the 400/ μ L cutoff point, respectively. Most current asthmatic patients could be classified as having 1 of the 3 phenotypes, and changing the definition of eosinophilic asthma did not largely affect this frequency. Approximately 70% (at 400/ μ L) to 85% (at 150/ μ L) of children and 69% (at 400/ μ L) to 82% (at 150/ μ L) of asthmatic adults belonged to 1 of the 3 phenotypes. For adult patients between 45 and 64 years of age, the corresponding figures were 65% (at 400/ μ L) and 82% (at 150/ μ L).

The sensitivity analyses performed in patients who reported at least one asthma attack in the year before the interviews (approximately 64% of children and 60% of adult patients from Table 1) and in obese patients (23% of children and 48% of adult patients) exhibited a similar distribution and overlap among these asthma inflammatory phenotypes as observed in the overall analysis (data not shown).

Discussion

Few studies have examined the overlap among eosinophilic, atopic, and T_H2-high asthma inflammatory phenotypes in a general asthma population. Previous studies included small clinical samples or studied the general population with or without asthma.^{19–22}

We found that a high proportion of current asthmatic patients in the general population have at least 1 of these 3 phenotypes, and a significant overlap among these phenotypes exist, despite varying definitions of eosinophilic asthma.

Given the expected availability of various biologic therapies targeting atopic, eosinophilic, T_H2-high phenotypes with different mechanisms of action (eg, anti-IL-5, eosinophil depletion, anti-IL-13, anti-IgE), it is important for physicians to know who is best treated with which therapy. In addition to a drug's efficacy, safety, and specific patient phenotype based on biomarkers, an understanding of the overlapping of different asthma inflammatory phenotypes may be useful. The present study found that, at a greater eosinophil cutoff point (eg, at 400 vs 150/ μ L), a high proportion of eosinophilic asthmatic patients can also be classified as atopic or T_H2-high phenotype, making it more difficult to differentiate between these phenotypes by using biomarkers alone. Decisions on which biologics would be most appropriate to use would rest more on other factors, such as drug efficacy, safety, convenience, and access to medication. The same is true for atopic and T_H2-high asthmatic patients who are also likely to be classified with eosinophilic asthma, using a lower eosinophil cutoff point. There exists a large group of asthmatic patients (up to nearly 45% of children and one-third of adults) who can be classified with eosinophilic, atopic, and T_H2-high asthma simultaneously. This group of patients may present a challenge for physicians in deciding which treatment to choose and may require multiple factors to consider beyond relying solely on the presence of the biomarkers.

In this study cohort of current asthmatic patients, of whom approximately 15% reported an emergency department visit due to an asthma attack in the previous 12 months, the observed frequency of individual asthma phenotypes was generally in line with previous estimates. Thomson et al,¹⁹ in a small cohort of asthmatic adults, found 80% and 39% of never smokers to have atopic and T_H2-high phenotypes (using the same definition as ours) and 60% and 32% among smokers, respectively. Previous studies that measured the frequency of eosinophilic asthma mostly defined eosinophilic asthma based on elevated sputum eosinophils ($\geq 2\%$, 2.5%, or 3%). Depending on the sputum eosinophil cutoff points used, the frequency of eosinophilic asthma ranged from 42% to 79% for adult patients with severe asthma.^{23–26} Greater frequencies and degrees of overlap among eosinophilic, atopic, and T_H2-high phenotypes for

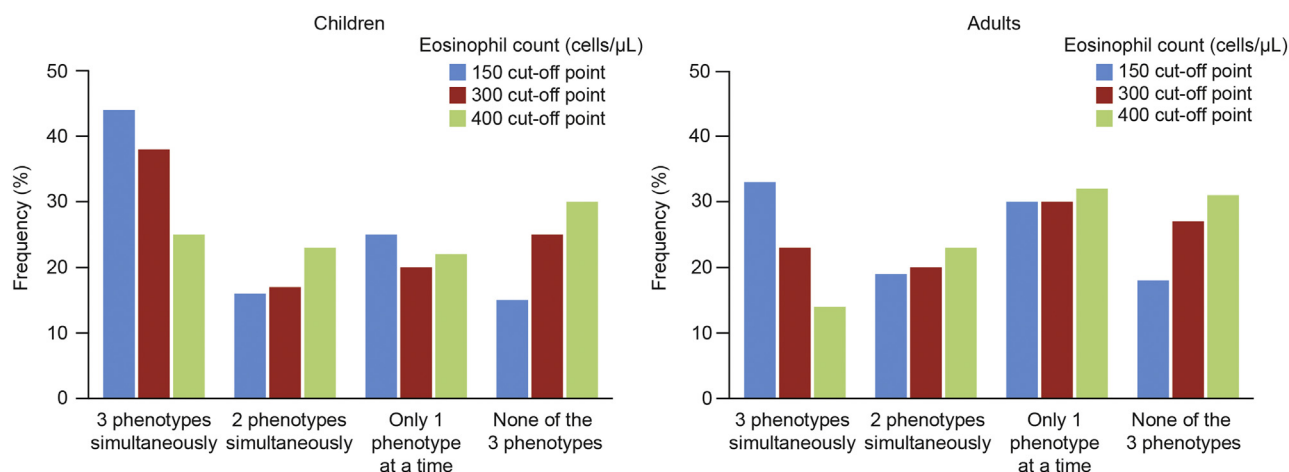


Figure 1. Overlap of atopic, eosinophilic, and T_H2-high phenotypes by eosinophil cutoff points. Left, Children (aged 6–17 years). Right, Adults (aged 18–64 years). Graphs show the percentage of patients whose asthma can be classed as 3, 2, 1, or no phenotype. Eosinophilic phenotype was defined using 3 different blood eosinophil cutoff points: 150, 300, and 400/ μ L. Atopic phenotype was defined as current asthma patients with an allergen specific IgE level of 0.35 IU/mL or higher to any of the 9 tested perennial allergens, including *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat epithelium and dander, dog dander, German cockroach, *Alternaria alternata*, *Aspergillus fumigatus*, and rat and mouse urine proteins. T_H2-high phenotype was defined as total serum IgE level of 100 IU/mL or higher and a blood eosinophil count of 140/ μ L or higher.

children vs adults confirmed the expectation that allergic asthma is associated with young age, early onset, and male sex.²⁷ Despite our findings that the frequency for each individual phenotype was somewhat lower for adults than children, we also observed an almost equally high frequency of being classified as one of these phenotypes in adults (ie, 69% to 82% of adults vs 70% to 85% of children were classified as having 1 of the 3 phenotypes). Of adults between 45 and 64 years old, 65% to 82% could be classified as having 1 of the 3 studied phenotypes, suggesting that allergy-related asthma in older adults is not uncommon and deserves more attention. The significance of these phenotypes needs further study among asthma patients 65 years and older who were not included in this study. Findings from the Swiss Study on Air Pollution and Lung Disease in Adults²⁸ within the general Swiss population (ie, with or without asthma) indicated that atopic sensitization was as high as 27% in males and 18% in females older than 60 years, which suggests allergic asthma phenotypes should not be underestimated in elderly populations.

The frequencies and patterns of overlap among the studied inflammatory phenotypes were likely affected by natural levels of biomarkers by age and sex and by the selected cutoff points used. For example, Klink et al²⁹ found that in a nonasthmatic study sample from the general population in Tucson, AZ, the normal serum IgE level was consistently lower for females than males. Moreover, more than 75% of females 6 years or older had a serum IgE level <90 IU/mL, which may explain the lower frequency of T_H2-high phenotypes among females than males observed in our study. Because there is no agreed standard definition for eosinophilic asthma, blood eosinophil cutoff points of 150, 300, and 400/ μ L were used to define eosinophilic asthma. These cutoffs were previously used for screening patients into clinical trials with anti-IL-5 therapies.^{11,12} Although eosinophil cutoff points significantly changed the frequency of eosinophilic asthma, the overlap between eosinophilic and atopic or T_H2-high asthma phenotypes remained substantial, and a similar pattern of overlap existed between children and adults, albeit appeared more pronounced for children. The consistent results across blood eosinophil cutoffs increased the confidence of a true finding.

Several limitations of the study should be discussed. The definition of T_H2-high asthma was not validated. It included the eosinophil count, which obviously affected the magnitude of overlap between the T_H2-high and eosinophilic phenotypes. This explains why all patients with T_H2-high asthma were also classified as having eosinophilic asthma at the lowest eosinophil cutoff point (150/ μ L). Given the lack of other assays in NHANES to measure T_H2-high status, this algorithm at best served as a practical surrogate taking advantages of 2 more widely available laboratory tests: IgE and blood eosinophil count. Because of potential variation in blood eosinophils and serum IgE, as well as the fact that blood eosinophils may be influenced by infection, antibiotic, and corticosteroid treatment, the cross-sectional nature of this study only provides a snapshot of the overlap among the phenotypes and should be interpreted with caution.

In clinical practice, to be qualified for biologic therapies, among other conditions, eligible patients will likely have more severe asthma, have already received the greatest of the step care treatments per existing guidelines, and/or have had multiple exacerbations despite high treatment adherence. NHANES did not collect data on asthma severity and did not include meaningful and reliable information on asthma medications, including corticosteroids, because they were collected only for the last month before the survey, resulting in very low frequency. This precluded stratification of patients by asthma severity. Therefore, our study population included patients with current asthma of all degrees of severity, including patients with mild asthma. Our sensitivity analysis, however, performed for those with at least an asthma attack in the

prior year, indicated a highly consistent pattern with the overall analysis. This reassures that our observations should be applicable for patients with more severe asthma.

In summary, we found that, in a general patient population with current asthma, most patients ($\geq 70\%$) can be categorized as being in one of the eosinophilic, atopic, or T_H2-high asthma inflammatory phenotypes, and a considerable overlap among these phenotypes exists. In assuming the same percentage in patients with more severe asthma (ie, those with at least Global Initiative for Asthma Step Care Level 4 and ≥ 2 exacerbations per year), we can plausibly estimate the number of adults with asthma who might be eligible for biologic treatment targeting these phenotypes in the United States. If severe asthma accounts for approximately 4.2% of total asthma patients (R.Z., unpublished data) and there are 15.8 million asthmatic patients aged 18 to 64 years in the United States,³⁰ then more than 450,000 US patients in this age group might be eligible for biologic treatments targeting these phenotypes. Future studies will need to confirm whether similar overlaps are present for patients with more severe asthma who may be the target of biologics and new asthma therapies.

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References

- Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet*. 2006; 368:804–813.
- Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med*. 2008;178:218–224.
- Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med*. 2010;181:315–323.
- Newby C, Heaney LG, Menzies-Gow A, et al. Statistical cluster analysis of the British Thoracic Society Severe refractory Asthma Registry: clinical outcomes and phenotype stability. *PLoS One*. 2014;9:e102987.
- Moore WC, Hastie AT, Li X, et al. Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis. *J Allergy Clin Immunol*. 2014;133:1557–1563.
- Chung KF. Asthma phenotyping: a necessity for improved therapeutic precision and new targeted therapies [published online June 15, 2015]. *J Intern Med*. <http://dx.doi.org/10.1111/joim.12382>.
- Barnes PJ. The cytokine network in asthma and chronic obstructive pulmonary disease. *J Clin Invest*. 2008;118:3546–3556.
- Wener RR, Bel EH. Severe refractory asthma: an update. *Eur Respir Rev*. 2013; 22:227–235.
- Walford HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. *J Asthma Allergy*. 2014;7:53–65.
- Woodruff PG, Modrek B, Choy DF, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med*. 2009;180: 388–395.
- Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371:1198–1207.
- Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3:355–366.
- Hanania NA, Noonan M, Corren J, et al. Lebrikizumab in moderate-to-severe asthma: pooled data from two randomised placebo-controlled studies. *Thorax*. 2015;70:748–756.
- Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med*. 2014; 2:879–890.
- Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). *National Health and Nutrition Examination Survey Data 2015*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. Accessed August 11, 2015. <http://www.cdc.gov/nchs/nhanes.htm>.
- Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med*. 2011;365:1088–1098.
- Tran TN, Khatry DB, Ke X, Ward CK, Gossage D. High blood eosinophil count is associated with more frequent asthma attacks in asthma patients. *Ann Allergy Asthma Immunol*. 2014;113:19–24.

- [18] Barlow SE; Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007;120(suppl 4):S164–S192.
- [19] Thomson NC, Chaudhuri R, Spears M, Haughney J, McSharry C. Serum periostin in smokers and never smokers with asthma. *Respir Med*. 2015;109:708–715.
- [20] Kelley CF, Mannino DM, Homa DM, Savage-Brown A, Holguin F. Asthma phenotypes, risk factors, and measures of severity in a national sample of US children. *Pediatrics*. 2005;115:726–731.
- [21] Arbes SJ Jr, Calatroni A, Mitchell HE, Gergen PJ. Age-dependent interaction between atopy and eosinophils in asthma cases: results from NHANES 2005–2006. *Clin Exp Allergy*. 2013;43:544–551.
- [22] Pekkanen J, Lampi J, Genuweit J, Hartikainen AL, Järvelin MR. Analyzing atopic and non-atopic asthma. *Eur J Epidemiol*. 2012;27:281–286.
- [23] Lemiere C, Ernst P, Olivenstein R, et al. Airway inflammation assessed by invasive and noninvasive means in severe asthma: eosinophilic and non-eosinophilic phenotypes. *J Allergy Clin Immunol*. 2006;118:1033–1039.
- [24] Dente FL, Bacci E, Bartoli ML, et al. Effects of oral prednisone on sputum eosinophils and cytokines in patients with severe refractory asthma. *Ann Allergy Asthma Immunol*. 2010;104:464–470.
- [25] Fleming L, Wilson N, Regamey N, Bush A. Use of sputum eosinophil counts to guide management in children with severe asthma. *Thorax*. 2012;67:193–198.
- [26] de Carvalho-Pinto RM, Cukier A, Angelini L, et al. Clinical characteristics and possible phenotypes of an adult severe asthma population. *Respir Med*. 2012;106:47–56.
- [27] Nieves A, Magnan A, Boniface S, et al. Phenotypes of asthma revisited upon the presence of atopy. *Respir Med*. 2005;99:347–354.
- [28] Wüthrich B, Schmid-Grendelmeier P, Schindler C, et al. Prevalence of atopy and respiratory allergic diseases in the elderly SAPALDIA population. *Int Arch Allergy Immunol*. 2013;162:143–148.
- [29] Klink M, Cline MG, Halonen M, Burrows B. Problems in defining normal limits for serum IgE. *J Allergy Clin Immunol*. 1990;85:440–444.
- [30] Blackwell DL, Lucas JW, Clarke TC. Summary health statistics for US adults: National Health Interview Survey, 2012. *Vital Health Stat 10*. 2014;(260):1–161.