

ORIGINAL ARTICLE

Asthma and Rhinitis

Overlap of allergic, eosinophilic and type 2 inflammatory subtypes in moderate-to-severe asthma

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Abstract

Background: Current biologic therapies target allergic, eosinophilic or type 2 inflammation phenotypic asthma. However, frequency and degree of overlap among these subtypes is unclear.

Objective: To characterize overlap among allergic, eosinophilic and type 2 asthma phenotypes.

Methods: Post hoc analyses of baseline data were performed in two adult populations: (a) not selected for any asthma subtype (N = 935) and (b) selected for allergic asthma (N = 1049). Degree of overlap was examined using commonly accepted phenotypic definitions to guide treatment for allergic asthma (skin prick-positive and/or positive serum-specific immunoglobulin E > 0.35 kU/L) and eosinophilic asthma (blood eosinophil high count \geq 300 cells/ μ L; low cut-off \geq 150 cells/ μ L). Consistent with previous studies, fractional exhaled nitric oxide high level of \geq 35 ppb and low cut-off of \geq 25 ppb were selected as local markers of type 2 inflammation and to prevent overlap with the systemic eosinophilic asthma definition.

Results: In the non-subtype-selected population, 78.0% had allergic asthma; of these, 39.5% had eosinophilic asthma and 29.5% had type 2 asthma. Within patients with eosinophilic asthma (40.6% of total), 75.8% had allergic asthma and 41.3% had type 2 asthma. Within patients with type 2 asthma (28.3% of total), 81.1% had allergic asthma and 59.2% had eosinophilic asthma. In the allergic asthma-selected population, 38.3% had eosinophilic asthma and 29.2% had type 2 asthma. Within patients with eosinophilic asthma, 46.3% had type 2 asthma. Within patients with type 2 asthma, 60.8% had eosinophilic asthma. Overlaps among subtypes increased at low cut-off values.

Conclusions and clinical relevance: In this post hoc analysis in adults with moderate-to-severe asthma, allergic asthma was the most prevalent phenotype, followed by eosinophilic and type 2 asthma. Despite observed overlaps, a considerable proportion of patients had only a predominantly allergic subtype. Understanding the degree of overlap across phenotypes will help patient management and guide treatment options.

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1 | INTRODUCTION

Asthma is a complex, chronic disease with marked heterogeneity in clinical symptoms, severity and treatment response.^{1,2} Several phenotypes of asthma have been defined based on various underlying clinical, inflammatory or molecular mechanisms, which may be used to classify asthma and personalize approaches to treatment.³⁻⁷

Allergic asthma affects approximately two-thirds of all patients with asthma and > 50% of patients with severe asthma.^{8,9} The allergic subtype is characterized by eosinophilic airway inflammation in response to allergens, bronchial hyperresponsiveness and elevated immunoglobulin E (IgE) levels.^{10,11} Eosinophilic asthma is a frequent, severe subtype of adult-onset asthma and is associated with tissue and sputum eosinophilia, thickening of the basement membrane zone and corticosteroid refractoriness. While positive allergy testing and blood eosinophil levels are often used as indicators of systemic atopic and type 2 inflammation, a high fractional exhaled nitric oxide (FeNO) level has been shown to be a reliable local marker for type 2 airway inflammation.¹²⁻¹⁴ Further, decreased levels of FeNO have been demonstrated to correlate with asthma control.^{12,13,15}

Current guidelines recommend high-dose inhaled corticosteroids (ICS) and long-acting β_2 -agonists in patients with poorly controlled asthma.¹⁶ However, a significant proportion of patients fail to achieve adequate asthma control despite high-dose ICS therapy.¹⁷ Until recently, therapeutic options for asthma, including oral corticosteroids, ICS or long-acting β_2 -agonists, have been broadly employed in patients irrespective of phenotype. More recently, the emergence of biologic agents directed towards specific subtypes of allergic asthma,¹⁴ eosinophilic asthma¹⁸ or type 2 asthma¹⁹ has allowed clinicians to provide more targeted therapy for patients based on differing asthma phenotypes. Biomarker cut-off levels may be used to guide patient and treatment selection for targeted therapy.^{20,21} However, these subtypes are not mutually exclusive, and understanding the degree of overlap among these subtypes would be useful in guiding asthma phenotype interpretation, treatment decisions, treatment optimization and overall care. Our study aimed to characterize the degree of overlap among allergic asthma, eosinophilic asthma and type 2 asthma, defined on the basis of high FeNO levels, to better understand the relationship among these asthma subtypes in two adult populations with moderate-to-severe asthma: those not selected for any of these subtypes (non-subtype-selected population) and, as a means of confirmation, those selected for perennial allergic asthma (allergic asthma-selected population).

2 | METHODS

Post hoc analyses were conducted with baseline data from adult patients with moderate-to-severe asthma aged 18-75 years from multi-centre studies in populations not selected for any subtype and those selected for allergic asthma. The non-subtype-selected population was from lebrikizumab phase 2b studies (LUTE [NCT01545440]²² and VERSE [NCT01545453])²² and phase 3 studies (LAVOLTA I

[NCT01867125]²³ and LAVOLTA II [NCT01868061]).²³ The allergic asthma-selected population was from an omalizumab phase 3b study (EXTRA [NCT00314574])²⁴ and real-world study with limited inclusion criteria (PROSPERO [NCT01922037]).²⁵ Patients with non-missing data necessary to define allergic, eosinophilic and type 2 asthma were included in the analyses. Data for the non-subtype-selected and allergic asthma-selected populations were pooled separately.

Full details of the studies have been published previously.²²⁻²⁵ Briefly, LUTE, VERSE and LAVOLTA I and II were randomized, double-blind studies conducted in patients aged 18-75 years with uncontrolled asthma despite treatment with medium- to high-dose ICS (500-2000 μg of fluticasone or equivalent daily) and one or more second controller medications.^{22,23} Further, for inclusion in all studies, patients were required to have uncontrolled moderate-to-severe asthma for ≥ 1 year and a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) between 40% and 80% of predicted.

EXTRA was a prospective, multi-centre, randomized, parallel-group, double-blind, placebo-controlled study in patients aged 12-75 years with a ≥ 1 -year history of severe persistent allergic asthma.²⁴ PROSPERO was a US-based, multi-centre, single-arm, prospective, 48-week, observational study.²⁵ Patients aged ≥ 12 years with allergic asthma initiating omalizumab based on physician-assessed need, and as per the drug label, were eligible for the study. Only patients aged ≥ 18 years from EXTRA and PROSPERO were included in our analysis because biomarker levels and subtypes may be different in the adolescent population.

All studies were approved by the institutional review boards and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from each participant.

2.1 | Subtype definitions

Allergic asthma was defined by allergic skin prick test positivity and/or allergen-specific IgE positivity (> 0.35 kU/L). Serum allergen-specific IgE levels were measured to the following perennial allergens: dog dander, American cockroach allergens (LAVOLTA I/II), *Alternaria tenuis*, *Aspergillus fumigatus* (EXTRA/PROSPERO/LUTE/VERSE), cat dander, *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* (all studies).

Blood eosinophil count is used as a marker of systemic inflammation; counts of ≥ 300 cells/ μL and ≥ 150 cells/ μL are common cut-off levels used to guide treatment with currently approved biologic agents for eosinophilic asthma. We therefore used both of these definitions for eosinophilic asthma and defined them as high or low, respectively. Blood eosinophils were quantified as part of complete blood counts, which were measured at central laboratories for all studies except PROSPERO, where this was undertaken in local laboratories. In all trials except PROSPERO, baseline eosinophil values were collected using similar criteria for inclusion as approved biologic agents for eosinophilic asthma; patients were required to be receiving a stable regimen of background medicines

(eg ICS + long-acting β_2 -agonist \pm other asthma controller medicines) and not have had an asthma exacerbation (requiring treatment with systemic corticosteroids or increase in systemic corticosteroid dose) within 30 days before screening.

Type 2 asthma was defined using FeNO, a marker of local type 2 inflammation.¹²⁻¹⁴ FeNO was measured using a NIOX[®] hand-held device (Aerocrine, Solna, Sweden) in all studies. A FeNO cut-off level of ≥ 35 ppb was selected based on a 2016 Cochrane review of commonly used FeNO cut-off levels in the clinical treatment of asthma in adult patients and referred to as the high level.¹³ A secondary, low FeNO cut-off level of ≥ 25 ppb was also selected based on the same Cochrane review.¹³ This cut-off level was used to define intermediate/high FeNO levels according to American Thoracic Society recommendations.¹⁴

2.2 | Statistical analysis

Descriptive statistics were used to summarize baseline characteristics for the non-subtype-selected and allergic asthma-selected populations. Baseline characteristics were presented by subtype group for both high and low cut-off values. Means (SD) or medians (interquartile range) were calculated for continuous variables, and frequency counts and percentages were calculated for categorical variables.

The percentage of patients with allergic, eosinophilic and type 2 asthma and the percentage of overlap/non-overlap was determined using the above-mentioned definitions. Due to the descriptive nature of the analysis, formal statistical comparisons were not made.

3 | RESULTS

3.1 | Baseline patient characteristics

A total of 935 patients were included in the non-subtype-selected population, and 1003 patients were included in the allergic asthma-selected population. Baseline patient demographics and clinical characteristics were generally similar among patients with allergic, eosinophilic and type 2 asthma within the non-subtype-selected or allergic asthma-selected populations (Tables 1 and 2). However, a higher proportion of patients in the allergic asthma-selected population with type 2 asthma identified by FeNO levels ≥ 35 ppb had three or more exacerbations in the past year (51.0%) compared with allergic asthma (39.8%), eosinophilic asthma (eosinophils ≥ 150 cells/ μ L [39.6%]; eosinophils ≥ 300 cells/ μ L [40.9%]) and type 2 asthma defined by FeNO levels ≥ 35 ppb (45.8%). Furthermore, percent predicted FEV₁ (range: 60.7%-62.2% vs. 69.0%-71.4%) and the percentage of patients experiencing three or more exacerbations (range: 10.2%-15.1% vs. 39.6%-51.0%) were consistently lower in the non-subtype-selected population than in the allergic asthma-selected population. Total IgE was similar among all asthma subpopulations and subtypes (Figure 1). In both the non-subtype-selected and allergic asthma-selected populations, blood eosinophil counts were highest in those with eosinophilic asthma defined by the high cut-off of ≥ 300 cells/ μ L. Similarly, FeNO levels were predictably higher in patients with type 2 asthma who had been identified as a result of their high FeNO levels (Figure 1).

TABLE 1 Baseline demographic and clinical characteristics of the non-subtype-selected population (N = 935)

Characteristic	Allergic asthma (n = 729)	EOS ≥ 150 cells/ μ L (n = 740)	EOS ≥ 300 cells/ μ L (n = 380)	FeNO ≥ 25 ppb (n = 424)	FeNO ≥ 35 ppb (n = 265)
Age (y), mean (SD)	47.0 (13.2)	47.7 (13.4)	46.3 (13.9)	47.4 (14.0)	45.4 (14.5)
Age at diagnosis (y), mean (SD)	16.2 (16.3)	18.1 (17.6)	18.7 (17.6)	19.5 (18.0)	19.1 (18.0)
Female, n (%)	422 (57.9)	449 (60.7)	233 (61.3)	255 (60.1)	154 (58.1)
Race, n (%)					
White	544 (74.6)	558 (75.4)	290 (76.3)	298 (70.3)	183 (69.1)
Black	145 (19.9)	136 (18.4)	59 (15.5)	95 (22.4)	58 (21.9)
Other	40 (5.5)	46 (6.2)	31 (8.2)	31 (7.3)	24 (9.1)
Current smoker, n (%)	3 (0.4)	3 (0.4)	1 (0.3)	2 (0.5)	2 (0.8)
BMI ≥ 30 kg/m ² , median (IQR)	30.3 (8.2)	29.9 (8.3)	29.6 (8.1)	29.4 (7.6)	28.9 (7.3)
Baseline OCS use, n (%)	NA	NA	NA	NA	NA
Asthma exacerbations in past year, n (%)					
0	400 (55.0)	389 (52.7)	194 (51.3)	221 (52.2)	126 (47.7)
1-2	253 (34.8)	263 (35.6)	127 (33.6)	149 (35.2)	101 (38.3)
≥ 3	74 (10.2)	86 (11.7)	57 (15.1)	53 (12.5)	37 (14.0)
ACQ5 score, mean (SD)	3.0 (0.8)	3.0 (0.9)	3.1 (0.9)	3.0 (0.9)	3.0 (0.9)
ppFEV ₁ , mean (SD)	62.2 (10.5)	61.8 (10.4)	60.7 (10.1)	61.6 (10.7)	61.2 (10.8)

Abbreviations: ACQ5, Asthma Control Questionnaire 5; BMI, body mass index; EOS, eosinophils; FeNO, fractional exhaled nitric oxide; IQR, interquartile range; NA, not available; OCS, oral corticosteroids; ppFEV₁, percent predicted forced expiratory volume in 1 s.

TABLE 2 Baseline demographic and clinical characteristics of the allergic asthma–selected population (N = 1003)

Characteristic	Allergic asthma (n = 1003)	EOS ≥ 150 cells/μL (n = 722)	EOS ≥ 300 cells/μL (n = 384)	FeNO ≥ 25 ppb (n = 419)	FeNO ≥ 35 ppb (n = 290)
Age (y), mean (SD)	48.6 (14.3)	47.9 (14.3)	48.0 (13.9)	48.1 (14.4)	47.5 (14.5)
Age at asthma diagnosis (y), mean (SD)	24.8 (19.9)	24.4 (20.0)	25.6 (20.6)	26.5 (19.9)	27.0 (19.7)
Female, n (%)	667 (66.5)	473 (65.5)	257 (66.9)	259 (61.8)	179 (61.7)
Race, n (%)					
White	736 (73.4)	523 (72.4)	276 (71.9)	291 (69.5)	194 (66.9)
Black	157 (15.7)	113 (15.7)	61 (15.9)	76 (18.1)	54 (18.6)
Other	110 (11.0)	86 (11.9)	47 (12.2)	52 (12.5)	42 (14.5)
Current smoker, n (%)	46 (4.6)	35 (4.8)	12 (3.1)	8 (1.9)	5 (1.7)
BMI ≥ 30 kg/m ² , median (IQR)	30.6 (9.8)	30.7 (9.3)	30.7 (9.8)	29.7 (8.2)	29.3 (8.0)
Baseline OCS use, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Asthma exacerbations in past year, n (%)					
0	163 (16.3)	109 (15.1)	59 (15.4)	58 (13.8)	33 (11.4)
1-2	441 (44.0)	327 (45.3)	168 (43.8)	169 (40.3)	109 (37.6)
≥ 3	399 (39.8)	286 (39.6)	157 (40.9)	192 (45.8)	148 (51.0)
ppFEV ₁ , mean (SD)	71.4 (18.9)	70.4 (18.1)	69.0 (17.6)	70.0 (18.3)	69.9 (18.3)

Abbreviations: BMI, body mass index; EOS, eosinophils; FeNO, fractional exhaled nitric oxide; IQR, interquartile range; OCS, oral corticosteroids; ppFEV₁, percent predicted forced expiratory volume in 1 s.

3.2 | Degree of overlap among allergic, eosinophilic and type 2 asthma subtypes

3.2.1 | Non-subtype–selected population

Applying commonly used subtype definitions to the 935 patients in the non-subtype–selected population, 78.0% (n = 729) had allergic asthma, 40.6% (n = 380) had eosinophilic asthma and 28.3% (n = 265) had type 2 asthma (Figure 2). Of the 729 patients in the allergic asthma population, 39.5% (n = 288) had eosinophilic asthma and 29.5% (n = 215) had type 2 asthma (Figure 2). Of the 380 patients in the eosinophilic asthma population, 75.8% (n = 288) had allergic asthma and 41.3% (n = 157) had type 2 asthma (Figure 2). Of the 265 patients in the type 2 asthma population, 81.1% (n = 215) had allergic asthma and 59.2% (n = 157) had eosinophilic asthma (Figure 2).

Applying the low cut-off values for eosinophils (≥ 150 cells/μL) or FeNO (≥ 25 ppb) to the 935 patients in the non-subtype–selected population, 79.1% (n = 740) had eosinophilic asthma and 45.3% (n = 424) had type 2 asthma (Table 3). Within the allergic asthma population, the proportion of patients who also had eosinophilic asthma or type 2 asthma increased to 80.5% (n = 587) and 46.5% (n = 339) of patients, respectively. Of the 740 patients in the eosinophilic asthma population, 79.3% (n = 587) had allergic asthma and 49.9% (n = 369) had type 2 asthma. Of the 424 patients in the type 2 asthma population, 80.0% (n = 339) had allergic asthma and 87.0% (n = 369) had eosinophilic asthma.

In the non-subtype–selected population, a small proportion of patients did not classify as having allergic, eosinophilic or type 2 asthma using high or low cut-off values. For the high eosinophil and

FeNO cut-offs, this percentage was 11.0% (n = 103/935); for the low cut-offs, only 4.2% (n = 39/935) did not have evidence of any of the three subtypes.

3.2.2 | Allergic asthma–selected population

Applying commonly used subtype definitions to the 1003 patients in the allergic asthma–selected population, predictably, 100.0% (n = 1003) had allergic asthma, 38.3% (n = 384) had eosinophilic asthma and 28.9% (n = 290) had type 2 asthma (Figure 3). Of the 384 patients in the eosinophilic asthma population, 45.3% (n = 174) had type 2 asthma (Figure 3). Of the 290 patients in the type 2 asthma population, 60.0% (n = 174) had eosinophilic asthma (Figure 3).

3.2.3 | Lower cut-off values

As with the non-subtype–selected population, the proportion of patients with eosinophilic and type 2 asthma and the overlap among all subtypes increased when low cut-off values were used. Applying the low cut-off values for eosinophils (≥ 150 cells/μL) or FeNO (≥ 25 ppb) to the 1003 patients in the allergic asthma–selected population, 72.0% (n = 722) had eosinophilic asthma and 41.8% (n = 419) had type 2 asthma (Table 3). Of the 722 patients in the eosinophilic asthma population, 48.3% (n = 363) had concomitant type 2 asthma. Of the 419 patients in the type 2 asthma population, 81.6% (n = 363) had concomitant eosinophilic asthma.

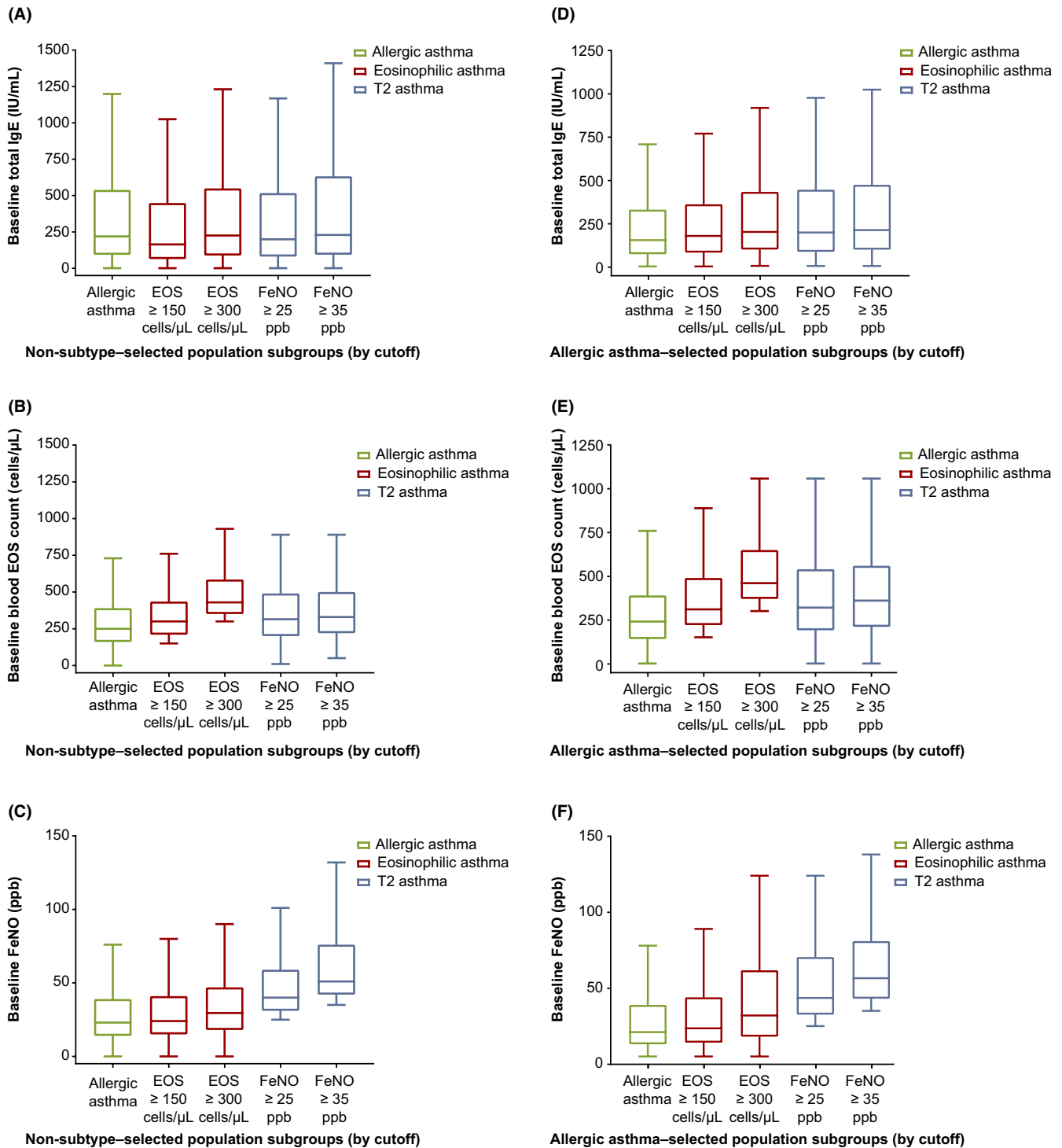


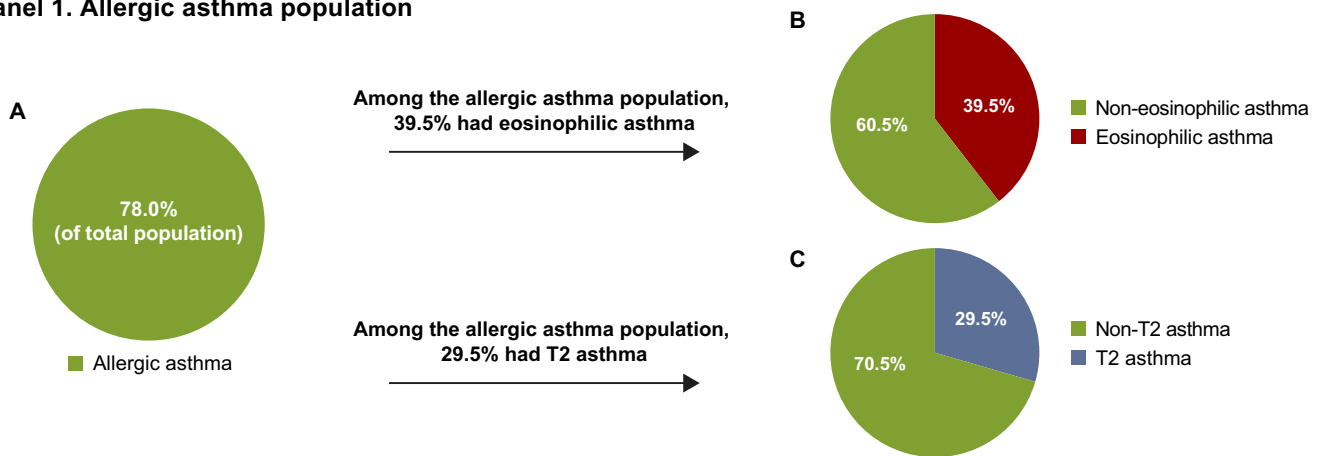
FIGURE 1 (A-C) Baseline total IgE, EOS counts and FeNO levels in the non-subtype-selected and (D-F) allergic asthma-selected populations. For each box plot, the top and bottom box edges correspond to the third and first quartiles. The line inside the box represents the median. The top and bottom whisker lines represent maximum and minimum values that are within the 1.5× the interquartile range distance from the third and first quartiles, respectively. Outliers are not shown for visualization purposes. EOS, eosinophils; FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; T2, type 2

4 | DISCUSSION

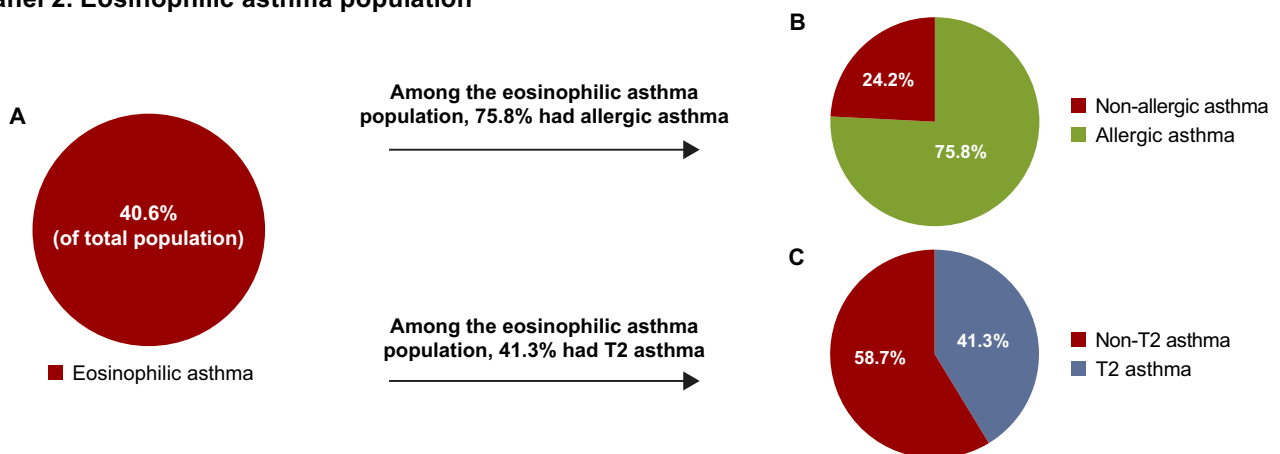
In this large post hoc analysis conducted in both a non-subtype-selected population and an allergic asthma-selected population, most

patients had allergic asthma, followed by eosinophilic asthma and type 2 asthma, based on high subtype definitions used (eosinophils ≥ 300 cells/ μ L; FeNO ≥ 35 ppb).²⁶⁻²⁸ Based on these definitions, a minority of patients with allergic asthma had concomitant

Panel 1. Allergic asthma population



Panel 2. Eosinophilic asthma population



Panel 3. T2 asthma population

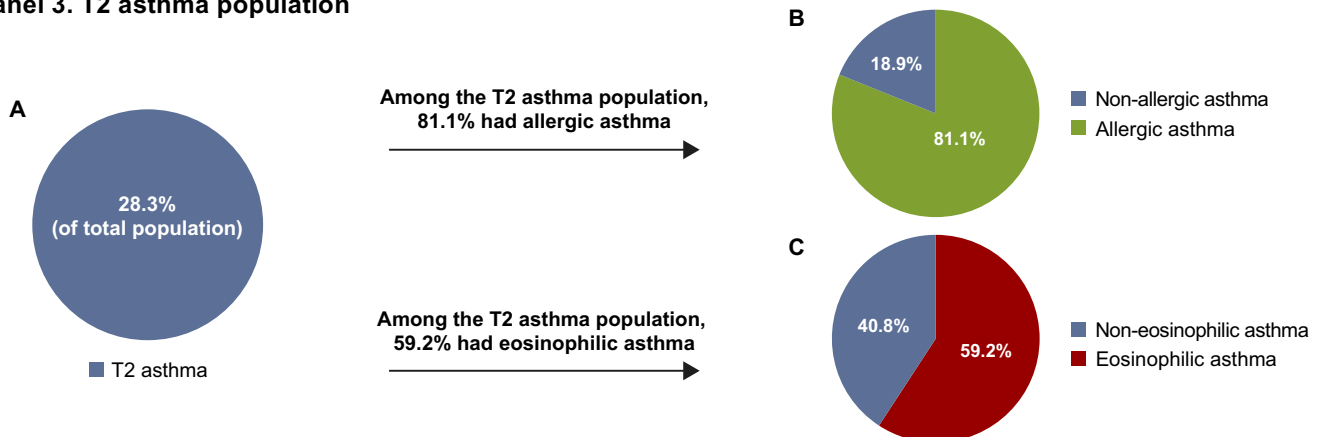


FIGURE 2 Overlap among (A) allergic, (B) eosinophilic and (C) T2 asthma subtypes in the non-subtype-selected population. Definitions: eosinophilic asthma, eosinophil count ≥ 300 cells/ μ L; T2 asthma, FeNO level ≥ 35 ppb. FeNO, fractional exhaled nitric oxide; T2, type 2

eosinophilic or type 2 asthma, suggesting there is a substantial proportion of patients with allergic asthma as the only dominant subtype. Most patients with eosinophilic or type 2 asthma had concurrent allergic asthma, suggesting overlap with allergic asthma is

common. A minority of eosinophilic patients did not have allergic asthma and a little less than half did not have type 2 inflammation. A small proportion of type 2 patients did not have allergic asthma, but did have eosinophilic inflammation. Only a small proportion of

TABLE 3 Overlap among allergic, eosinophilic and type 2 asthma subtypes in the non-subtype-selected and allergic asthma-selected populations using low cut-off values (eosinophil count ≥ 150 cells/ μ L)

	Non-subtype-selected population (N = 935)			Allergic asthma-selected population (N = 1003)		
	Allergic asthma (n = 729; 78.0% ^a)	Eosinophilic asthma (n = 740; 79.1% ^a)	Type 2 asthma (n = 424; 45.3% ^a)	Allergic asthma (n = 1003; 100% ^a)	Eosinophilic asthma (n = 722; 72.0% ^a)	Type 2 asthma (n = 419; 41.8% ^a)
Overlap within allergic asthma, % (n) ^b	-	79.3 (587)	80.0 (339)	-	100 (722)	100 (419)
Overlap within eosinophilic asthma, % (n) ^b	80.5 (587)	-	87.0 (369)	72.0 (722)	-	82.6 (346)
Overlap within type 2 asthma, % (n) ^b	46.5 (339)	49.9 (369)	-	41.8 (419)	47.9 (346)	-

^aBased on the total sample size for the non-subtype-selected (N = 935) and allergic asthma-selected (N = 1003) populations, respectively.

^bBased on the column total for each asthma subtype, respectively.

the non-subtype-selected population had no evidence of allergic, eosinophilic or type 2 asthma.

Two cut-off values for both eosinophilic asthma and high-FeNO asthma were chosen in our analyses based on common levels used to guide treatment options. Use of the lower cut-off values for eosinophilic asthma (eosinophils ≥ 150 cells/ μ L) or type 2 asthma (FeNO ≥ 25 ppb) increased the proportion of patients classified as having eosinophilic or type 2 asthma and the overlap among subtypes. Thus, the degree of overlap among subtypes was dependent on the cut-off level definitions used.

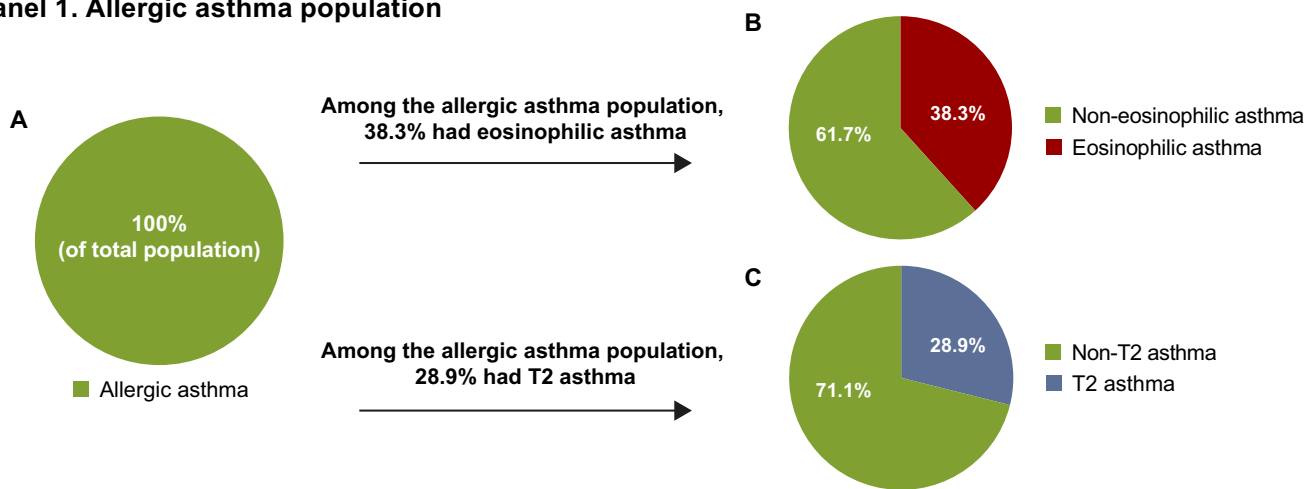
Our findings are consistent with the results of a previous analysis investigating the overlap among atopic, eosinophilic and type 2 asthma, although the definition of type 2 asthma was different (total IgE ≥ 100 IU/mL; blood eosinophils ≥ 140 cells/ μ L).¹⁵ In that study, Tran et al also observed that different eosinophil cut-off levels affected the degree of overlap among asthma subtypes.

In the current study, clinical baseline characteristics, including asthma symptoms and percent predicted FEV₁, were generally similar in the different subpopulations, with a few exceptions. In the allergic asthma-selected population, a higher proportion of patients with the type 2 subtype had three or more exacerbations in the previous year. Although not observed in the non-subtype-selected population, this difference may indicate a greater need for close patient management for this group. Indeed, several investigators have noted the benefits of tailoring asthma interventions based on FeNO levels, augmented or reduced pharmacotherapy and reduced asthma exacerbations.^{29,30}

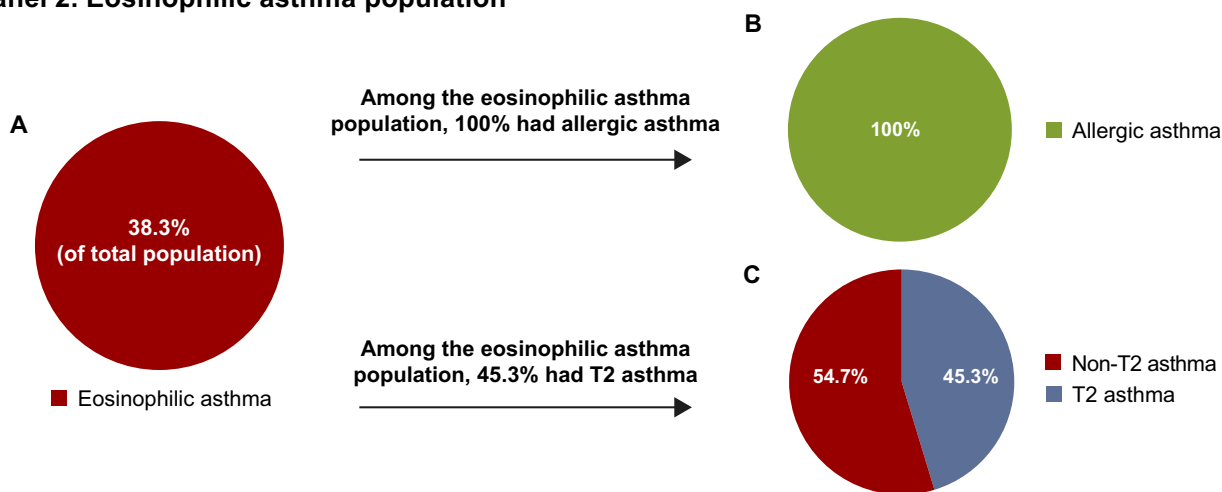
Interestingly, when comparing patients who have no evidence of any of the subtypes (based on the high cut-off definitions used) with patients who have evidence of all three subtypes, or all other patients, patients with no evidence of any subtype seem to be more frequently female, Black and have a later age of asthma onset. The data when comparing no subtype (based on high cut-offs), all three subtypes and all other patients were as follows: female, 77.7% vs. 61.0% vs. 58.7%; Black, 26.2% vs. 18.6% vs. 19.6%; age of diagnosis, mean (SD) 28.6 (18.6) vs. 17.7 (17.9) and 17.6 (17.1) years, respectively. Similar trends were observed for the low cut-off groups (data not shown). This patient population may benefit from additional assessment of underlying airway inflammation and corresponding revision of treatment plans.

There is an increasing awareness of the importance of asthma phenotypes during diagnosis and also in personalizing approaches to treatment.^{5-7,28} This has progressed to the extent that a single biomarker is often used to identify patients likely to respond to biologic therapies targeting IgE, interleukin-5, interleukin-5R and interleukin-4RA.^{24,28} For example, blood eosinophil levels and/or FeNO are used as markers of eosinophilic or type 2 inflammation, while a skin prick test and specific IgE are used to diagnose patients with atopic or allergic asthma.^{5,9,31} However, it should be noted that total IgE levels do not correspond to asthma subtypes or number of allergic sensitizations³² and do not correlate well with eosinophil or FeNO levels.³³ Total IgE, therefore, is not as useful for identification of asthma subtype or to guide selection

Panel 1. Allergic asthma population



Panel 2. Eosinophilic asthma population



Panel 3. T2 asthma population

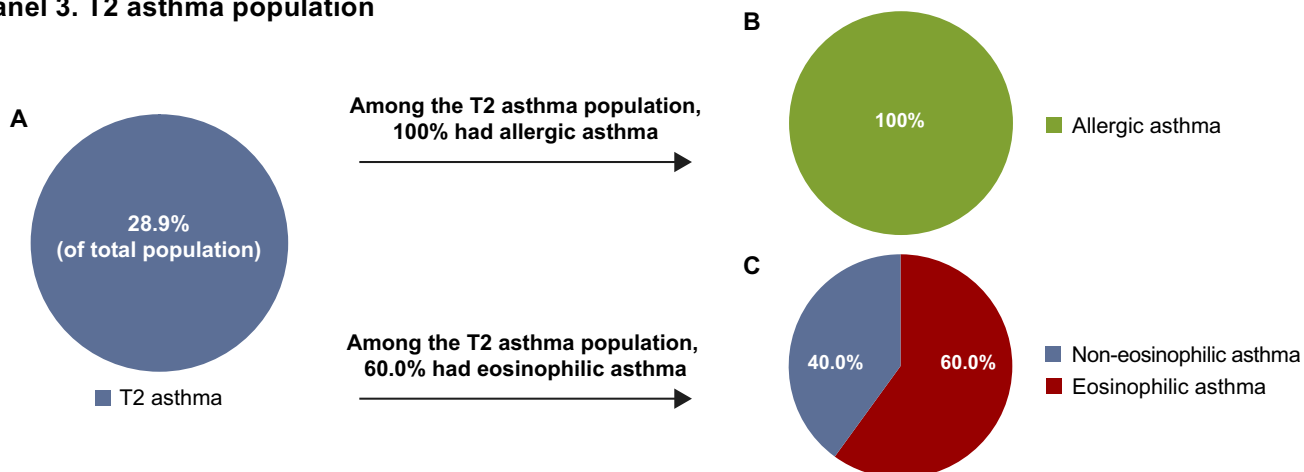


FIGURE 3 Overlap among allergic, eosinophilic and T2 asthma subtypes in the allergic asthma–selected population. Definitions: eosinophilic asthma, eosinophil count ≥ 300 cells/ μ L; T2 asthma, FeNO level ≥ 35 ppb. FeNO, fractional exhaled nitric oxide; T2, type 2

of treatment modality. Total IgE was used in this study only for determining omalizumab dosing as described in the omalizumab prescribing information.³⁴

As we and others have shown,¹⁵ it is important to recognize that substantial overlap may exist among subtypes and that these subtypes are not mutually exclusive. In addition, the biologic treatments currently approved for asthma target different aspects of similar pathways.^{18,19,28} Therefore, when selecting the right treatment from those currently available, testing for one biomarker may be insufficient to establish which asthma subtype(s) are involved. Further, as the development of treatments for asthma that target similar and distinct molecular pathways continues, it will become increasingly important for asthma phenotypes to be thoroughly investigated using both biologic and clinical variables to ensure optimal patient management.

Limitations of this analysis include those inherent to post hoc analyses, including the integration of data from studies that may possess important differences in patient populations. For instance, the allergens used to define the allergic phenotype differed between the studies. Further, because type 2 asthma is not well defined, an arbitrary definition was used, according to FeNO levels. Additional biomarkers, such as blood eosinophils,³⁵ were not used to define type 2 asthma because this would have overlapped with the definition used for eosinophilic asthma. In addition, levels of all biomarkers may be influenced by several factors leading to patients being included in a subtype at this snapshot in time, but could be classified differently at a different point in time. Because this was a post hoc analysis, methodological details regarding skin prick testing and allergen-specific IgE positivity were unavailable since patients were often enrolled into studies based on a historical positive finding. Each of the studies had missing data for markers used in the diagnosis of asthma subtypes in this study, which may have introduced bias. Because this study included only adults with moderate-to-severe asthma, these data may not be extrapolated to those with milder disease or to children and adolescents. Nevertheless, a large number of patients across the subgroups was studied. The consistency of findings across populations analysed provides robustness to the observations reported.

In conclusion, in this large post hoc analysis, there was overlap among allergic, eosinophilic and type 2 asthma subtypes. In a substantial proportion of patients, allergic asthma was the only dominant subtype. In contrast, for patients with eosinophilic asthma or type 2 asthma, a majority had concurrent allergic asthma, suggesting overlap with allergic asthma is common. A very small proportion of patients had no evidence of any of the three subtypes. The degree of overlap among subtypes was dependent on the definitions used and increased with less-stringent subtype definitions. The consistency of findings across populations analysed provided robustness to the overlaps identified.

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CONFLICT OF INTEREST

M. Chen has received fellowship grant support from Genentech, Inc., and is an employee of Southwest Asthma and Allergy Associates. K. Shepard II has no conflicts of interest to disclose. M. Yang, P. Raut, H. Pazwash and C. T. J. Holweg are employees of Genentech, Inc., and stockholders in Roche. E. Choo has acted as a paid consultant to GlaxoSmithKline and a speaker to AstraZeneca and Teva Pharmaceutical Industries Ltd.

AUTHOR CONTRIBUTIONS

M. Chen, M. Yang and C. T. J. Holweg conceived and designed the study. M. Yang and P. Raut analysed data. All authors critically reviewed the data, drafted the manuscript and approved the final version of the manuscript submitted.

DATA AVAILABILITY STATEMENT

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (<https://vivli.org/>). Further details on Roche's criteria for eligible studies are available here (<https://vivli.org/members/ourmembers/>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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