Original Article

Asthma Phenotyping in Primary Care: Applying the International Severe Asthma Registry Eosinophil Phenotype Algorithm Across All Asthma Severities

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What is already known about this topic? Asthma remains poorly controlled and characterized in primary care. Many patients are given the diagnosis of asthma and receive regular asthma treatment, in accordance with a one-treatment-fits-all, step-up/step-down, guideline-directed approach, but with little clinical benefit.

What does this article add to our knowledge? Eosinophilic asthma predominates in UK primary care and is associated with a greater likelihood of having asthma attacks, reduced lung function despite a significantly greater steroid burden, and greater health care resource use.

How does this study impact current management guidelines? The eosinophil phenotype gradient algorithm will enable primary care physicians to identify and categorize asthma patients into those with and without eosinophilic asthma, and when appropriate, refer patients for phenotype-targeted treatment.

BACKGROUND: We developed an eosinophil phenotype gradient algorithm and applied it to a large severe asthma cohort (International Severe Asthma Registry).

OBJECTIVE: We sought to reapply this algorithm in a UK primary care asthma cohort, quantify the eosinophilic phenotype, and assess the relationship between the likelihood of

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Conflicts of interest: M. Kerkhof, L. Bulathsinhala, I. Chaudhry, and N. Eleangovan were employees of OPRI at the time of the study, which conducted this study in collaboration with OPC and AstraZeneca. V.A. Carter and C.A. Price are employees of OPC Global Ltd, which conducted this study in collaboration with OPRI and AstraZeneca. T.N. Tran is an employee of AstraZeneca, which is the funder of this study. R. Al-Lehebi has given lectures at meetings supported by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Sanofi and participated in advisory board fees from GlaxoSmithKline and Sanofi. G.W. Canonica has received research grants as well as lecture or advisory board fees from A. Menarini, Alk-Albello, Allergy Therapeutics, Anallergo, AstraZeneca, MedImmune, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia, Danone, Faes, Genentech, Guidotti Malesci, GlaxoSmithKline, Hal Allergy, Merck, MSD, Mundipharma, Novartis, Orion, Sanofi Aventis, Sanofi, Genzyme/Regeneron, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Thermo Fisher, and Valeas. L.G. Heaney has received grant funding, participated in advisory boards, and given lectures at meetings supported by MedImmune, Novartis, Genentech/Hoffman Roche, GlaxoSmithKline, Evelo Biosciences, Sanofi AstraZeneca, Teva, Theravance, and Circassia; has taken part in asthma clinical trials sponsored by Boehringer Ingelheim, Hoffmann la Roche, and GlaxoSmithKline, for which his institution received remuneration; and is the academic lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma, which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Medimmune, Genentech/Hoffman LaRoche, GlaxoSmithKline, Circassia, Vitalograph, and Boehringer Ingelheim. M. Hew declares grants and other advisory board fees (made to his institutional employer) from AstraZeneca, GlaxoSmithKline, Novartis, and Seqirus, for unrelated projects. L. Perez de Llano declares nonfinancial support, personal fees, and grants from Teva; nonfinancial support and personal fees from Boehringer Ingelheim, Esteve, GlaxoSmithKline, Mundipharma, and Novartis; personal fees and grants from AstraZeneca and Chiesi; and personal fees from Sanofi; and nonfinancial support from Menairi outside the submitted work. M.E. Wechsler reports receiving consulting honoraria from AstraZeneca, Boehringer Ingelheim, Cohero Health, Equillium, Genentech,

Abbreviations used
BEC- Blood eosinophil count
CPRD- Clinical Practice Research Datalink
EMR- Electronic medical record
GINA- Global Initiative for Asthma
GP- General practitioner
HCRU- Health care resource use
HES- Hospital episode statistics
ICS- Inhaled corticosteroid
ISAR- International Severe Asthma Registry
OCS- Oral corticosteroid
OPCRD- Optimum Patient Care Research Database

an eosinophilic phenotype and asthma severity/health care resource use (HCRU).
METHODS: Patients age 13 years and older with active asthma and blood eosinophil count or 1 or greater, who were included from the Optimum Patient Care Research Database and the Clinical Practice Research Datalink, were categorized according to the likelihood of eosinophilic phenotype using the International Severe Asthma Registry gradient eosinophilic algorithm. Patient demographic, clinical and HCRU characteristics were described for each phenotype.
RESULTS: Of 241,006 patients, 50.3%, 22.2%, and 21.9% most likely (grade 3), likely (grade 2), and least likely (grade 1), respectively, had an eosinophilic phenotype, and 5.6% had a noneosinophilic phenotype (grade 0). Compared with patients with noneosinophilic asthma, those most likely to have an eosinophilic phenotype tended to have more comorbidities (percentage with Charlson comorbidity index of ≥2: 28.2% vs 6.9%) and experienced more asthma attacks (percentage with one or more attack: 24.8% vs 15.3%). These patients were also more likely to have asthma that was difficult to treat (31.1% vs 18.3%), to receive more intensive treatment (percentage on Global Initiative for Asthma 2020 step 4 or 5: 44.2% vs 27.5%), and greater HCRU (eg, 10.8 vs 7.9 general practitioner all-cause consultations per year).
CONCLUSIONS: The eosinophilic asthma phenotype predominates in primary care and is associated with greater asthma severity and HCRU. These patients may benefit from earlier and targeted asthma therapy. © **2021 The Authors.**

Key words: *Asthma; Eosinophilic; Health care resource use; ISAR; Phenotypes; Primary care; Severity; United Kingdom*

INTRODUCTION

Primary care providers are the front line of asthma management and have a crucial role in the early identification and management of uncontrolled disease. However, asthma remains poorly controlled and characterized. Many patients are provided with the umbrella diagnosis of asthma and receive regular asthma treatment, in accordance with a one-treatment-fits-all, step-up/step-down, guideline-directed approach, but with little clinical benefit.[1] That is now changing with increased knowledge of the underlying mechanisms of asthma, identification of numerous biomarkers of airway inflammation, availability of biologics that target specific inflammatory pathways, and the switch in focus to treatable traits. According to the *Lancet* Asthma Commission, what is needed is a "third era of asthma management"[1] that considers the heterogeneity of asthma and delivers precision disease management based on disease characteristics.

Eosinophilic airway inflammation is one such treatable trait, with several reliable biomarkers (eg, FeNO, blood eosinophil count [BEC]) that provide information about the risk for asthma attacks and likely response to inhaled corticosteroids (ICS).[2-5] These biomarkers are easy to measure, which makes them particularly suited for use in primary care. They have been shown to stratify risk and to facilitate the targeting and economic use of asthma therapy.[2,6,7] Conversely, asthma, which is truly noneosinophilic (ie, no eosinophilic airway inflammation without ICS), tends to be mild in nature and low in risk.[8-10] Asthma phenotyping is specifically recommended at the specialist level.[11] Devising a simple way to categorize the primary care asthma population into those with and without eosinophilic asthma is an important first step in deconstructing this disease into its components and could introduce phenotype-directed precision treatment earlier in the patient's journey.

Work has commenced on this deconstruction in primary care.[12-15] Haldar and colleagues[15] identified three different

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phenotypes in a UK primary care population: early-onset eosinophilic, obese noneosinophilic, and benign asthma. The eosinophilic phenotype cluster was defined according to the presence of airway dysfunction, symptoms, and elevated FeNO and sputum eosinophil count. However, use of phenotype-defining variables not routinely measured (eg, sputum eosinophil count, reversibility) or burdensome to the patient (eg, peak flow variability) may limit the usefulness of these categorizations in primary care. A Swedish study employed an alternative approach and used only self-reported asthma characteristics from 1291 asthma patients.[12] They also found three distinct phenotype clusters: early-onset predominantly female, adult-onset predominantly female, and adult-onset predominantly male, the first of which had the highest disease burden.[12] However, what that study gained in accessibility of variables (ie, most parameters would be available from patients' electronic medical records [EMRs]), it lost in terms of a lack of characterization of the underlying inflammatory pathway.

A combination of phenotypic characteristics and biomarkers may be a better way to characterize asthma types. This was recently done to disentangle eosinophil phenotypes in a global, real-life, adult, severe asthma cohort (ie, International Severe Asthma Registry [ISAR]).[16] The ISAR multicomponent, eosinophil phenotype classification algorithm used variables accessible at specialist asthma centers as well as primary care and considered variability in BEC (using the highest recorded value) and the impact of oral corticosteroids (OCS), both of which can confound phenotype classification.[17]

The aims of our study were to (1) reapply the ISAR eosinophilic gradient algorithm in a broader and more heterogeneous primary care asthma cohort to quantify and characterize the eosinophilic phenotypes in this cohort; and (2) assess the relationship between the likelihood of eosinophilic phenotype asthma severity and health care resource use (HCRU).

METHODS

Hypothesis

Our hypotheses were that (1) the recently developed ISAR eosinophil classification algorithm[16] would have utility beyond the severe asthma population and may be applied to a broad primary care asthma cohort, (2) the prevalence of the asthma eosinophil phenotype in primary care would be higher than previously thought, and (3) this eosinophilic phenotype would be associated with greater disease severity and HCRU.

Study design

This historical cohort study included a broad real-life population of patients with active asthma, registered at general practitioner (GP) practices in the United Kingdom. The current study protocol was approved by Anonymized Data Ethics and Protocol Transparency Committee 1919, performed in compliance with Good Clinical Practice and Good Pharmacoepidemiology Practice and registered with the European Union Electronic Register of Post-Authorization studies (EUPAS31500) and the Independent Scientific Advisory Committee (ISAC_19_229).[18]

Data sources

Data were obtained from the Optimum Patient Care Research Database (OPCRD)[19] and the Clinical Practice Research Datalink (CPRD). The OPCRD dataset is composed of medical records of more than 11 million patients from over 800 general practices across the United Kingdom (approximately 8% of the total UK population) and integrates with all UK clinical systems (EMIS, TPP SystmOne, InPS Vision, and Microtest Evolution). It benefits from a long retrospective period (median time in the database, is 19.8 years [range, 12.8-25.7 years], going back to birth for summary diagnostic data in many cases), and contains linked patient-completed respiratory questionnaires for approximately 10% of asthma patients included.[20] The OPCRD is approved by the UK National Health Service for clinical research use (Research Ethics Committee reference 15/EM/0150). The CPRD GOLD database is an ongoing primary care database of anonymized medical records from GPs, with coverage of over 11 million patients from 700 practices in the United Kingdom, with a median patient time in the database of 19.3 years (range, 9.9-25.2 years).[21] Only patients whose data could be linked to Hospital Episode Statistics (HES) were selected from the CPRD. Both the OPCRD and the CPRD are well-validated and used frequently for medical and health research.[22,23]

Patients

Patients included were aged 13 years and older, with a diagnosis of active asthma and continuous EMRs for the 12 months before enrolment. Active asthma was defined as one or more prescription for an ICS or short-acting $ß_2$-agonist containing inhaler in the past 12 months before enrolment. At least one BEC recording was also required after the date of first active asthma diagnosis without prescription for OCS or anti-IL-5/5R therapy in the prior 4 weeks. For HCRU analysis, linkage with CPRD-HES was a requirement. Those with uncertain information about the age of asthma onset or a diagnosis of chronic lower respiratory disease other than asthma were excluded.

Predefined eosinophil phenotypes

Patients were classified using a predefined gradient eosinophilic algorithm based on the one developed by the expert consensus of ISAR's steering committee.[14] This group of experts selected variables based on the evidence and feasibility of availability in real-life clinical practice. These variables and cutoffs included the highest recorded BEC, without recent (within 4 months) OCS prescription (>300, ≥150-300, or <150 cells/μL), anti−IL-5/5R treatment, history of or current long-term OCS, history of or current diagnosis of nasal polyps, and late asthma onset (age ≥30 years) (Figure 1). FeNO was omitted because of its limited availability in these two primary care datasets. Phenotypes were classified as grade 3 (most likely eosinophilic), grade 2 (likely eosinophilic), grade 1 (least likely eosinophilic), and grade 0 (noneosinophilic). Patients most likely to have an eosinophilic phenotype (grade 3) were those with the highest BEC recorded as 300 cells/μL or greater or to be receiving anti−IL-5/5R therapy, or with a BEC of 150 to 300 cells/μL or greater, (1) receiving long-term OCS or (2) with both nasal polyps and adult onset. The noneosinophilic phenotype (grade 0) was defined by experts as highest recorded BEC of less than 150 cells/μL in the absence of nasal polyps, adult onset, or maintenance OCS. Figure 1 provides definitions of grade 1 and 2 eosinophilic phenotypes.

Description of eosinophilic and noneosinophilic asthma phenotypes

Patient demographic, clinical, and HCRU characteristics were described and compared according to different likelihoods of

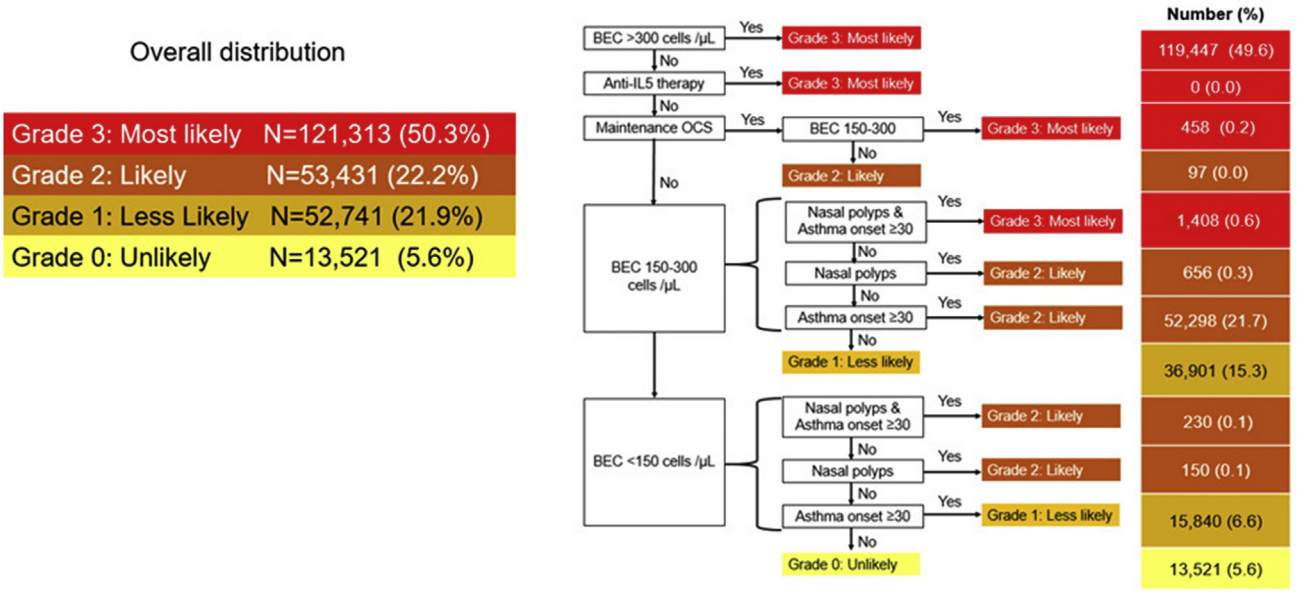

FIGURE 1. Algorithm flowchart showing prevalence of eosinophilic phenotypes within a UK primary care active asthma cohort (Optimum Patient Care Research Database plus Clinical Practice Research Datalink) (n = 241,006). For blood eosinophil count (BEC), the highest recorded value was used, without a recent (ie, within 4 months) oral corticosteroid (OCS) prescription.

eosinophilic phenotypes over 12 months of EMR data before a predefined date. For OPCRD, this predefined date was the most recent EMR data extraction from general practice. Because linkage to HES data was available up to March 1, 2019, the predefined date for the CPRD was either the date of the most recent EMR extraction (if extraction was before March 1, 2019) or a randomly chosen date in the 12 months before March 1, 2019 (if extraction was after March 1, 2019) (see the full list of variables collected in this article's Online Repository at www.jaci-inpractice.org).

Analysis

We used Stata software (version 14.1, College Station, Texas) to conduct all statistical analyses. The prevalence of predefined eosinophilic phenotypes was determined for the total population (OPCRD plus CPRD), for OPCRD and CPRD populations separately (in subpopulations with information about symptoms obtained during the annual review), and for patients with asthma that was difficult to treat (severe). Those with severe asthma were defined as having uncontrolled asthma at Global Initiative for Asthma (GINA) step 4 or GINA step 5, using the 2020 GINA definitions of step 4/5 asthma treatment.[11] We also performed a sensitivity analysis to determine eosinophil phenotype distribution in patients who had a recent assessment of asthma control (ie, within 15 months). Asthma control was assessed using the three Royal College of Physicians questions,[24] which is a quality of asthma care indicator within the UK Quality an Outcomes Framework, a voluntary annual reward and incentive program for all GP surgeries in the United Kingdom.

Demographics, diagnosed comorbidities, and clinical characteristics such as asthma therapy and control were described overall and for the predefined phenotypes, the total population (OPCRD plus CPRD), those with a recent asthma assessment, and those with asthma that was difficult to treat (severe). Asthma burden and HCRU variables were described overall and for the predefined phenotypes for the CPRD population. Demographic, clinical, and HCRU variables are described as numbers and prevalence rates per category for dichotomous and categorical variables. Means (SDs) and medians (interquartile ranges) as well as categorical distributions are described for counts and continuous variables. In addition, age-standardized means and prevalence rates with 95% confidence intervals are reported for predefined phenotypes, using the total population as the standard to account for artificial differences in age distribution among phenotype groups, caused by selection of the presence of late-onset asthma.

Pearson's chi-square tests of independent categories for categorical variables and nonparametric Kruskal-Wallis equality of populations rank test for variables on a continuous or ordinal scale were performed to examine the statistical significance of differences in distribution of characteristics among phenotypes. Relevant differences in the crude distribution of characteristics between phenotype grade 3 and grades 0, 1, and 2 are reported as the standardized mean difference (SMD) with grade 3 as the reference. This measure is not affected by the number of observations and provides information about the magnitude of differences; thus, it is a better way to judge relevant differences compared with a *P* value of a hypothesis test of difference. The SMD was calculated for both continuous and categorical variables using the formula shown in Table E1 (in this article's Online Repository at www.jaci-inpractice.org). We considered an SMD greater than 10% to indicate a relevant difference. Rate ratios with 95% confidence intervals comparing HCRU events for patients with grades 2/3 versus 0/1 were estimated using negative binomial regression in the total study population. Although prior sample size planning was not done, we assumed the study to be adequately powered to detect any difference resulting from the large sample size. Analyses were adjusted for variables included in the model that gave a change in coefficient of the association of at least 2%. These variables were age, sex, body mass index, smoking status, eczema, chronic sinusitis, diabetes, osteoporosis, hypertension,

TABLE I. Demographic and clinical characteristics according to eosinophilic and noneosinophilic phenotype in primary care UK cohort (Optimum Patient Care Research Database plus Clinical Practice Research Datalink) with active asthma

Variable	Grade 0 (n = 13,521)	Grade 1 (n = 52,741)	Grade 2 (n = 53,431)	Grade 3 (n = 121,313)	Total (n = 241,006)	*P*	SMD 0-3	SMD 1-3	SMD 2-3
Sex									
Female, n (%)	8533 (63.1)	33,688 (63.9)	36,194 (67.7)	73,709 (60.8)	152,129 (63.1)	<.0001	4.8	6.4	14.6
Age at last extraction date, y									
Mean (SD)	36.7 (14.1)	46.9 (17.4)	64.0 (13.0)	54.1 (19.4)	53.7 (18.8)	<.0001	102.3	39.2	60.1
13-17, n (%)	973 (7.2)	1757 (3.3)	16 (0.0)	4207 (3.5)	6953 (2.9)	<.0001	75.0	33.3	36.7
18-64, n (%)	12,008 (88.8)	41,900 (79.4)	27,309 (51.1)	76,588 (63.1)	157,805 (65.5)				
≥65, n (%)	540 (4.0)	9084 (17.2)	26,106 (48.9)	40,518 (33.4)	76,248 (31.6)				
Body mass index, kg/m^2									
n	11,808	48,178	51,182	113,475	224,643	<.0001	25.8	6.4	14.4
Underweight (<18.5), n (%)	476 (4.0)	1250 (2.6)	668 (1.3)	2956 (2.6)	5350 (2.4)				
Normal (≥18.5 to <25), n (%)	4454 (37.7)	14,922 (31.0)	11,862 (23.2)	31,748 (28.0)	62,986 (28.0)				
Overweight (≥25 to <30), n (%)	3752 (31.8)	15,763 (32.7)	17,651 (34.5)	37,594 (33.1)	74,760 (33.3)				
Obese (≥30), n (%)	3126 (26.5)	16,243 (33.7)	21,001 (41.0)	41,177 (36.3)	81,547 (36.3)				
Smoking status									
n	13,076	51,105	51,747	118,160	234,088	<.0001	28.7	9.2	12.9
Current smoker, n (%)	2179 (16.7)	9367 (18.3)	7508 (14.5)	17,716 (15.0)	36,770 (15.7)				
Ex-smoker, n (%)	4115 (31.5)	20,158 (39.4)	26,625 (51.5)	53,541 (45.3)	104,439 (44.6)				
Never smoker, n (%)	6782 (51.9)	21,580 (42.2)	17,614 (34.0)	46,903 (39.7)	92,879 (39.7)				
Age at asthma onset, y									
Mean (SD)	13.0 (8.4)	24.3 (19.5)	49.9 (13.9)	34.2 (22.2)	34.3 (21.9)	<.0001	125.5	47.5	84.7
Childhood onset (<18 y), n (%)	9630 (71.2)	25,455 (48.3)	534 (1.0)	37,808 (31.2)	73,427 (30.5)	<.0001	135.5	49.4	110.0
Adult onset (18-29 y), n (%)	3891 (28.8)	11,446 (21.7)	289 (0.5)	14,824 (12.2)	30,450 (12.6)				
Late onset (≥30 y), n (%)	0	15,840 (30.0)	52,608 (98.5)	68,681 (56.6)	137,129 (56.9)				
Comorbidity ever									
Eczema, n (%)	3812 (28.2)	14,694 (27.9)	13,128 (24.6)	38,806 (32.0)	70,440 (29.2)	<.0001	8.3	9.0	16.5
Allergic rhinitis, n (%)	4738 (35.0)	18,165 (34.4)	14,751 (27.6)	45,986 (37.9)	83,640 (34.7)	<.0001	6.0	7.2	22.1
Chronic rhinosinusitis without nasal polyps, n (%)	1013 (7.5)	4716 (8.9)	5576 (10.4)	12,738 (10.5)	24,043 (10.0)	<.0001	23.7	19.2	11.6
Chronic rhinosinusitis with nasal polyps, n (%)	<5	<5	286 (0.5)	3339 (2.8)	3625 (1.5)	<.0001			
Charlson comorbidity index						<.0001	57.7	32.3	11.5
0-1, n (%)	12,583 (93.1)	44,621 (84.6)	35,139 (65.8)	87,151 (71.8)	179,494 (74.5)				
2-3, n (%)	812 (6.0)	6479 (12.3)	13,204 (24.7)	24,262 (20.0)	44,757 (18.6)				

(continued)

TABLE I. *(Continued)*

Variable	Grade 0 (n = 13,521)	Grade 1 (n = 52,741)	Grade 2 (n = 53,431)	Grade 3 (n = 121,313)	Total (n = 241,006)	*P*	SMD 0-3	SMD 1-3	SMD 2-3
≥4, n (%)	126 (0.9)	1641 (3.1)	5088 (9.5)	9900 (8.2)	16,755 (7.0)				
Asthma control									
Asthma attacks (electronic medical record data) (mean [SD])	0.2 (0.8)	0.3 (1.0)	0.5 (1.3)	0.5 (1.5)	0.5 (1.3)	<.0001	26.3	19.1	5.9
0, n (%)	11,452 (84.7)	43,219 (81.9)	40,879 (76.5)	91,168 (75.2)	186,718 (77.5)	<.0001	28.4	20.6	5.3
1, n (%)	1488 (11.0)	6521 (12.4)	7671 (14.4)	17,292 (14.3)	32,972 (13.7)				
2, n (%)	347 (2.6)	1641 (3.1)	2334 (4.4)	5687 (4.7)	10,009 (4.2)				
3, n (%)	114 (0.8)	603 (1.1)	1018 (1.9)	2572 (2.1)	4307 (1.8)				
≥4, n (%)	120 (0.9)	757 (1.4)	1529 (2.9)	4594 (3.8)	7000 (2.9)				
Royal College of Physicians 3 questions score, n	6878	28,560	31,295	71,236	137,969	.0002	3.3	2.4	0.2
0, n (%)	1986 (28.9)	8228 (28.8)	8818 (28.2)	20,299 (28.5)	39,331 (28.5)				
1, n (%)	2810 (40.9)	11,555 (40.5)	12,581 (40.2)	28,307 (39.7)	55,253 (40.0)				
2, n (%)	1508 (21.9)	6307 (22.1)	7024 (22.4)	15,827 (22.2)	30,666 (22.2)				
3, n (%)	574 (8.3)	2470 (8.6)	2872 (9.2)	6803 (9.5)	12,719 (9.2)				
n	6878	28,560	31,295	71,236	137,969	.0002	3.7	2.6	1.3
Poor symptom control, n (%)	1886 (27.4)	7978 (27.9)	8927 (28.5)	20,735 (29.1)	39,526 (28.6)				
n	6878	28,560	31,295	71,236	137,969	<.0001	30.0‖	18.1‖	2.6
Difficult to treat (GINA 2020), n (%)	1259 (18.3)	6596 (23.1)	9350 (29.9)	22,152 (31.1)	39,357 (28.5)				
Lung function									
n	1468	8783	16,251	27,419	53,921	<.0001	25.7‖	16.3‖	5.9
FEV_1 % predicted (mean [SD])	86.9 (20.8)	85.0 (22.4)	82.7 (23.1)	81.3 (22.7)	82.5 (22.7)				
n	9758	40,232	44,043	96,778	190,811	<.0001	24.0‖	13.6‖	1.8
Peak expiratory flow % predicted (mean [SD])	86.6 (17.9)	84.7 (19.3)	82.4 (21.3)	82.0 (20.5)	82.9 (20.3)				
Asthma therapy									
GINA 1 (2020), n (%)	2728 (20.2)	7991 (15.2)	4654 (8.7)	11,803 (9.7)	27,176 (11.3)	<.0001	43.8‖	24.5‖	0.4
GINA 2 (2020), n (%)	4890 (36.2)	17,261 (32.7)	15,668 (29.3)	34,324 (28.3)	72,143 (29.9)				
GINA 3 (2020), n (%)	2182 (16.1)	9207 (17.5)	9913 (18.6)	21,567 (17.8)	42,869 (17.8)				
GINA 4 (2020), n (%)	2499 (18.5)	11,708 (22.2)	13,399 (25.1)	30,434 (25.1)	58,040 (24.1)				
GINA 5 (2020), n (%)	1222 (9.0)	6574 (12.5)	9797 (18.3)	23,185 (19.1)	40,778 (16.9)				
Inhaled corticosteroid daily dose,* μg (mean [SD])	170.6 (261.9)	222.0 (297.3)	293.8 (332.0)	274.6 (327.5)	261.5 (320.5)	<.0001	35.1‖	16.8‖	5.8
0, n (%)	2769 (20.5)	8242 (15.6)	5099 (9.5)	12,531 (10.3)	28,641 (11.9)	<.0001	45.9‖	22.0‖	8.5
>0 to <100, n (%)	4796 (35.5)	15,206 (28.8)	11,208 (21.0)	29,804 (24.6)	61,014 (25.3)				
100-200, n (%)	2284 (16.9)	10,116 (19.2)	10,903 (20.4)	24,170 (19.9)	47, 473 (19.7)				

>200-500, n (%)	2612 (19.3)	13,115 (24.9)	17,183 (32.2)	36,093 (29.8)	69,003 (28.6)				
>500, n (%)	1060 (7.8)	6062 (11.5)	9038 (16.9)	18,715 (15.4)	34,875 (14.5)				
Inhaled corticosteroid inhalers,† n (mean [SD])	5.3 (6.1)	6.4 (6.5)	8.0 (6.8)	7.3 (6.5)	7.1 (6.6)	<.0001	32.0‖	13.5‖	10.9‖
Short-acting β_2-agonist daily dose, μg‡ (mean [SD])	196.3 (302.2)	235.3 (355.4)	253.2 (403.3)	282.9 (450.0)	261.0 (414.0)	<.0001	22.6‖	11.8‖	7.0
Oral corticosteroid daily dose, mg (mean [SD])	0.2 (0.9)	0.2 (1.2)	0.3 (1.4)	0.4 (1.7)	0.3 (1.5)	<.0001	19.8‖	14.1‖	6.2
Short-acting muscarinic antagonist,§ n (%)	95 (0.7)	657 (1.2)	1159 (2.2)	2118 (1.7)	4029 (1.7)	<.0001	9.5	4.1	3.1
Long-acting muscarinic antagonist,§ n (%)	242 (1.8)	1973 (3.7)	4536 (8.5)	8225 (6.8)	14,976 (6.2)	<.0001	24.8‖	13.6‖	6.4
Long-acting β_2-agonist,§ n (%)	350 (2.6)	1557 (3.0)	1949 (3.6)	3931 (3.2)	7787 (3.2)	<.0001	3.9	1.7	2.2
Theophylline,§ n (%)	76 (0.6)	374 (0.7)	617 (1.2)	1840 (1.5)	2907 (1.2)	<.0001	9.4	7.7	3.2
Leukotriene receptor antagonist,§ n (%)	878 (6.5)	3543 (6.7)	3915 (7.3)	10,745 (8.9)	19,081 (7.9)	<.0001	8.9	8.0	5.6

GINA, Global Initiative for Asthma; *SMD*, standardized mean difference.

Grade 0 indicates noneosinophilic; grade 1, least likely eosinophilic; grade 2, likely eosinophilic; and grade 3, most likely eosinophilic (see Figure 1 for a definition of eosinophil phenotype grades). For categorical variables, *P* values were calculated using Pearson's chi-square tests of independent categories.

For continuous or ordinal variables, *P* values were calculated using nonparametric Kruskal-Wallis equality of populations rank test.

*Fluticasone propionate equivalent (μg).

†For 30 d dispensed in baseline year.

‡Salbutamol equivalent (μg).

§One or more prescription in the past 12 mo (see Table E1 for how to calculate).

‖An SMD is considered to be >10% to indicate a relevant difference.

TABLE II. Characterization of eosinophilic and noneosinophilic phenotypes and proportion of asthma patients with these phenotypes in UK primary care cohort with active asthma

Highest blood eosinophil count, cells/μL*	Treatment or clinical characteristic	Eosinophilic phenotype	Total study population (n = 241,006)		Optimum Patient Care Research Database (n = 127,858)		Clinical Practice Research Datalink (n = 113,148)		Recent assessment† (n = 137,969)		Severe asthma‡ (GINA 2020) (n = 39,357)	
			n (%)	(%)	n (%)	%	n (%)	%	n (%)	%	n (%)	%
≥300	Blood eosinophil count > 300	Grade 3: most likely	119,477 (49.6)	50.3	66,230 (51.8)	52.6	53,217 (47.0)	47.8	70,077 (50.8)	51.6	21,649 (55.0)	56.3
	Anti−IL-5/5R	Grade 3: most likely	0		0		0		0		0	
≥150 to <300	Long-term OCS	Grade 3: most likely	458 (0.2)		277 (0.2)		181 (0.2)		246 (0.2)		246 (0.6)	
	Presence of nasal polyps and adult onset (no long-term OCS)	Grade 3: most likely	1408 (0.6)		702 (0.6)		706 (0.6)		913 (0.6)		257 (0.7)	
	And nasal polyps (no long-term OCS)	Grade 2: likely	656 (0.3)	22.0	286 (0.2)	21.8	370 (0.3)	22.2	384 (0.3)	22.5	112 (0.3)	23.5
	And adult onset (no long-term OCS)	Grade 2: likely	52,298 (21.7)		27,604 (21.6)		24,694 (21.8)		30,643 (22.2)		9138 (23.2)	
	No nasal polyps, adult onset, or long-term OCS	Grade 1: least likely	36,901 (15.3)	15.3	18,181 (14.2)	14.2	18,720 (16.5)	16.5	19,603 (14.2)	14.2	4162 (10.6)	10.6
<150	Long-term OCS	Grade 2: likely	97 (0.0)	0.2	51 (0.0)	0.2	46 (0.0)	0.2	40 (0.0)	0.2	40 (0.1)	0.3
	Adult onset and nasal polyps (no long-term OCS)	Grade 2: likely	230 (0.1)		100 (0.1)		130 (0.1)		134 (0.1)		37 (0.1)	
	Nasal polyps (no long-term OCS)	Grade 2: likely	150 (0.1)		67 (0.1)		83 (0.1)		94 (0.1)		23 (0.1)	
	And adult onset (no long-term OCS)	Grade 1: least likely	15,840 (6.6)	6.6	7694 (6.0)	6.0	8146 (7.2)	7.2	8957 (6.5)	6.5	2434 (6.2)	6.2
	No nasal polyps, adult onset, or long-term OCS	Grade 0: noneosinophilic	13,521 (5.6)	5.6	6666 (5.2)	5.2	6855 (6.1)	6.1	6878 (5.0)	5.0	1259 (3.2)	3.2

Anti−IL-5/5R, anti−interleukin 5/5 receptor; *GINA*, Global Initiative for Asthma; *OCS*, oral corticosteroids.

*Independent criteria are specified in each row. Pre−anti−IL-5/5R or long-term OCS was used whenever possible.

†Within the past 15 mo.

‡Severe asthma was defined as patients at GINA 2020 treatment step 5 or those with uncontrolled asthma at GINA 2020 step 4.

cardiovascular diseases, anxiety or depression, chronic kidney disease, apnea, pneumonia and Charlson comorbidity index score.

The best fitting model was determined as follows. For each association, starting with the crude negative binomial regression model with the outcome under study and grades as variables, the biased caused (percent change in the coefficient of grades) when the candidate confounder was added to the model was assessed for each candidate separately. After that, the candidate confounders were added sequentially, sorted by their bias potential in descending order, and the bias was measured against the previous model. If the bias was 2% or greater, the candidate was retained in the model and the next candidate confounder was tested. Age, body mass index, and Charlson comorbidity index score were included in the model as confounders for all outcomes. Additional identified confounders are reported in Table I for the different outcomes.

The OPCRD is established and maintained by Optimum Patient Care Ltd. This study was funded by AstraZeneca and conducted by the Observational and Pragmatic Research Institute Pte Ltd. The Observational and Pragmatic Research Institute Pte Ltd, Optimum Patient Care, and AZ members of the ISAR Steering Committee had input into the study design, data analysis and interpretation, and manuscript writing, and are authors of this article in line with International Committee of Medical Journal Editors author criteria.

RESULTS

Patients

We attempted to maximize study power by drawing the final sample size from a large potential pool of over 20 million people in primary care, approximately one-third of the UK population. From a total of 1,135,808 patients with asthma diagnosis, a BEC of 1 or greater, and age13 years or older in the OPCRD and CPRD, 241,006 patients were eligible for inclusion: 127,588 from the OPCRD and 113,148 from the CPRD (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). The final sample size chosen for analysis included patients with sufficient longitudinal data (ie, >12 months), with active asthma (ie, at least one inhaler prescription in the past year), with sufficient information to categorize the phenotype according to the eosinophil gradient algorithm (ie, a BEC of at least 1 without OCS and age of asthma onset), and with no other chronic lower respiratory conditions (which may have confounded results). Dates of last data collection (or random date before March 1, 2019 for CPRD data extracted after March 1, 2019) from general practices ranged from 2008 to 2019; almost half of the data were uploaded in 2019 and 79% were in the last 5 years (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Mean age was 53.7 years (SD, 18.8 years); 63.1% of patients were female, 15.7% were current smokers, and 69.6% were either overweight or obese (Table I). First asthma diagnosis was recorded at a median age of 35 years (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org).

Blood eosinophil count distribution

Almost half of patients (49.6%) had the highest BEC recorded of greater than 300 cells/μL, 38.1% had an intermediate BEC (≥150-300 cells/μL), and 12.4% had a low BEC (<150 cells/μL) (Figure 2, *A*). The presence of nasal polyps was associated with a higher BEC for all age groups (Figure 2, *B*).

Eosinophil phenotype characterization

A total of 50.3% of patients were identified as most likely (grade 3) to have an eosinophilic phenotype, almost all based on the presence of a BEC greater than 300 cells/μL at any time during follow-up (Figure 1 and Table II). Moreover, 22.2% of patients were likely (grade 2) and 21.9% were least likely (grade 1) to have an eosinophilic phenotype (Figure 1 and Table II). Almost all patients classified as likely eosinophilic had late-onset asthma and a highest BEC in the range of 150 to 300 cells/μL, without nasal polyps. Most patients classified as least likely eosinophilic had a highest BEC of 150 to 300 cells/μL with no other feature of eosinophilic disease. The remaining patients had late-onset disease with a low BEC (<150 cells/μL). In addition, 5.6% of patients had noneosinophilic asthma (grade 0). These phenotype classifications were validated by cross-examining their defining characteristics, which showed an increase in BEC, age at onset, incidence of nasal polyps, and long-term use of ICS, from grade 0 (noneosinophilic) to grade 3 (most-likely eosinophilic) phenotypes (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

A similar pattern of most likely eosinophil phenotype predominance was noted in the OPCRD (52.6%) and CPRD populations (47.8%), those with a recent asthma assessment (51.6%) and those with severe asthma (56.3%), with the treatment step defined according to GINA 2020 (Table II). Patients who had a recent assessment of symptoms during annual review of asthma were more frequently defined as most likely to have an eosinophilic phenotype compared with those who were not recently reviewed (51.6% vs 48.6%) (Figure 3, *A*). A greater proportion of severe asthma patients had an eosinophilic phenotype compared with those without severe disease (56.3% vs 49.8% using GINA 2020 treatment steps to define severity) (Figure 3, *B*).

Demographic and clinical characteristics

Compared with patients with noneosinophilic asthma, those who most likely had an eosinophilic phenotype were significantly (all $P < .0001$, nonparametric Kruskal-Wallis) more likely to have a comorbidity (eg, the percentage with a Charlson comorbidity index score of ≥2: 28.2% vs 6.9%) and to experience more asthma attacks (eg, the percentage with one or more attacks: 24.9% vs 15.3%). They were also significantly (all $P < .001$, nonparametric Kruskal-Wallis) more likely to have asthma that was difficult to treat (31.1% vs 18.3%) and to receive more intensive treatment (eg, with GINA 2020 step 4 or 5 treatment: 44.2% vs 27.5%) (Table I and Figure 4). Age-standardized means and prevalence rates showed a gradient increase in asthma attack rates, asthma control score, symptoms, asthma severity, comorbidities, and intensity of asthma treatment with an increasing likelihood of eosinophilic phenotype (Figure 5, *A* and Tables E3-E5, in this article's Online Repository at www.jaci-inpractice.org). Results were similar in those with a recent asthma assessment (see Table E6 in this article's Online Repository at www.jaci-inpractice.org) and for those with severe asthma, with treatment steps defined

according to GINA 2020 (see Table E7 in this article's Online Repository at www.jaci-inpractice.org).

Health care resource use

Many HCRU variables assessed showed an increase in HRCU along the eosinophil phenotype gradient in the total population (Table III and Figure 5, *B*; see Table E8 in this article's Online Repository at www.jaci-inpractice.org). An increase in relative risk (RR) from grade 0/1 to grade 2/3 was particularly evident for GP consultations, outpatient visits, accident and emergency attendances, respiratory hospital admissions, and length of respiratory overnight stay, and was even more apparent in those with severe asthma (Table III). For example, patients at grade 2/3 of the eosinophilic spectrum had a 32% higher risk for a hospital admission with asthma as the primary diagnosis compared with those at grade 0/1 (adjusted RR = 1.32 (95% confidence interval [CI], 1.10-1.59; $P = .003$). The unadjusted RR was slightly lower but still statistically significant (unadjusted RR = 1.21 (95% CI, 1.02-1.44; $P = .027$). Conversely, patients at grade 2/3 had a 25% reduced risk for having one or more overnight hospital stay compared with those at grade 0/1 (adjusted RR = 0.75 (95% CI, 0.62-0.91; $P = .004$) or a 10% reduced risk for the unadjusted analysis (unadjusted RR = 0.90; 95% CI, 0.75-1.08; $P = .254$). All P values for RR were calculated using negative binomial regression. Patients at grade 2 or 3 (with difficult-to-treat asthma) hospitalized for asthma had a mean hospital stay of 6 to 7 days, compared with 10 days for those at grade 0 or 1 (see Table E9 in this article's Online Repository at www.jaci-inpractice.org), a pattern also seen in the total HCRU population (Table E3).

DISCUSSION

Using a multicomponent eosinophil classification algorithm modified for use in primary care and a broad primary care asthma cohort, we classified patients into four groups along a gradient of eosinophilic phenotype likelihood, from noneosinophilic to most likely. We showed an associated greater likelihood of having asthma attacks, reduced lung function (despite a significantly greater treatment burden, particularly ICS and OCS burden), and greater HCRU along this gradient. We demonstrated that the eosinophilic asthma phenotype is prevalent in UK primary care, and the noneosinophilic phenotype is rare. Notably, this eosinophilic phenotype was apparent in those with severe asthma (56.3% of patients) as well as in those with nonsevere asthma (49.8%). Finally, we described each of these phenotypes using variables readily available in primary care (using both inflammatory indices and disease characteristics), applying the algorithm for use in populations beyond severe asthma, and confirmed its robustness in a sufficiently large population generalizable to the primary care asthma population in the United Kingdom.

After decades of modest advancements in the understanding of asthma, we are now in the midst of the era of asthma management, which has provided a greater understanding of the underlying pathophysiology of asthma, recategorized and reclassified asthma into different types, and concomitantly delivered new ways to test and treat these different types. This ongoing revolution in how asthma is defined and treated necessitates a clear and pragmatic way forward to guide physicians in primary care, where most asthma patients are provided with a diagnosis and managed. Identification of those with an eosinophilic phenotype is important because these patients have a relatively high risk for asthma attacks (even those with mild asthma) and an increased risk for readmission to hospital.[4,25,26] In addition, although eosinophilic asthma generally responds to corticosteroids, a subgroup of primary care patients with insufficient response to standard inhaler treatment regimens (failing GINA step 4) frequently experiences exacerbations and rapid lung function decline. These patients should be identified and categorized in primary care; they require careful follow-up and may benefit from appropriate referral and early intervention with targeted therapy. Currently, international asthma management guidelines provide little guidance regarding phenotyping patients with asthma in primary care. It is seen as the purview of specialists.[11]

The multicomponent eosinophil phenotype classification algorithm described in the current study was based on that used to describe eosinophilic phenotypes in ISAR, a global, real-life severe asthma cohort.[16] This algorithm, which is based on a combination of clinical characteristics and biomarkers, may be a better way to characterize asthma types. Global Initiative for Asthma also recommends using different combinations of factors to identify type 2 inflammatory phenotypes, including BEC, FeNO, sputum eosinophils, the need for maintenance OCS, and the presence of multiple comorbidities.[27] Such a combination approach arguably affords a more practical means to determine eosinophilic asthma status compared with reliance on protracted, sequential BEC.[28] Our algorithm was based on an extensive literature review and expert consensus; it uses variables readily accessible in primary care, and considers variability in BEC (using the highest recorded value) and impact of OCS, both of which can confound phenotype classification.[16,17,29] However, some modifications were made to apply it to a primary care cohort. For example, elevated FeNO was not included because this is not routinely measured, and late-onset asthma (>30 years) was used instead of adult onset (>18 years), because age at onset is used as a predictor of response to anti-IL-5. These modifications to the ISAR algorithm are unlikely to have altered our findings, because the removal of FeNO and adult onset from the algorithm did not alter findings in the ISAR cohort.[16] When this algorithm was applied to a UK primary care population, approximately 50% of patients were most likely have an eosinophilic asthma phenotype, a finding confirmed in both the OPCRD (52.6%) and CPRD (47.8%). The slightly lower eosinophil phenotype prevalence in the CPRD was most likely driven by lower recorded numbers of counts and shorter duration of follow-up compared with OPCRD counts.

The eosinophilic phenotype existed across the spectrum of asthma severity (severe: 56.3%; not severe: 49.8%), indicating that eosinophilic asthma may be present even in mild to moderate disease, and/or that severity may be inappropriately classified in primary care. A recent study found that large numbers of asthma patients in the United Kingdom with potential severe asthma (8%) are effectively hidden in primary care.[30] In either case, a structured assessment by primary care physicians is warranted, with referral to specialist care when appropriate. The utility of our eosinophil gradient algorithm lies in identifying these patients (using clinical characteristics and biomarker concentrations routinely recorded in primary care), who may benefit most. Whether these patients have a better prognosis is the next logical clinical question, and one that merits further study. As expected, the prevalence of the eosinophilic asthma phenotype was lower than that recently estimated in a severe asthma cohort

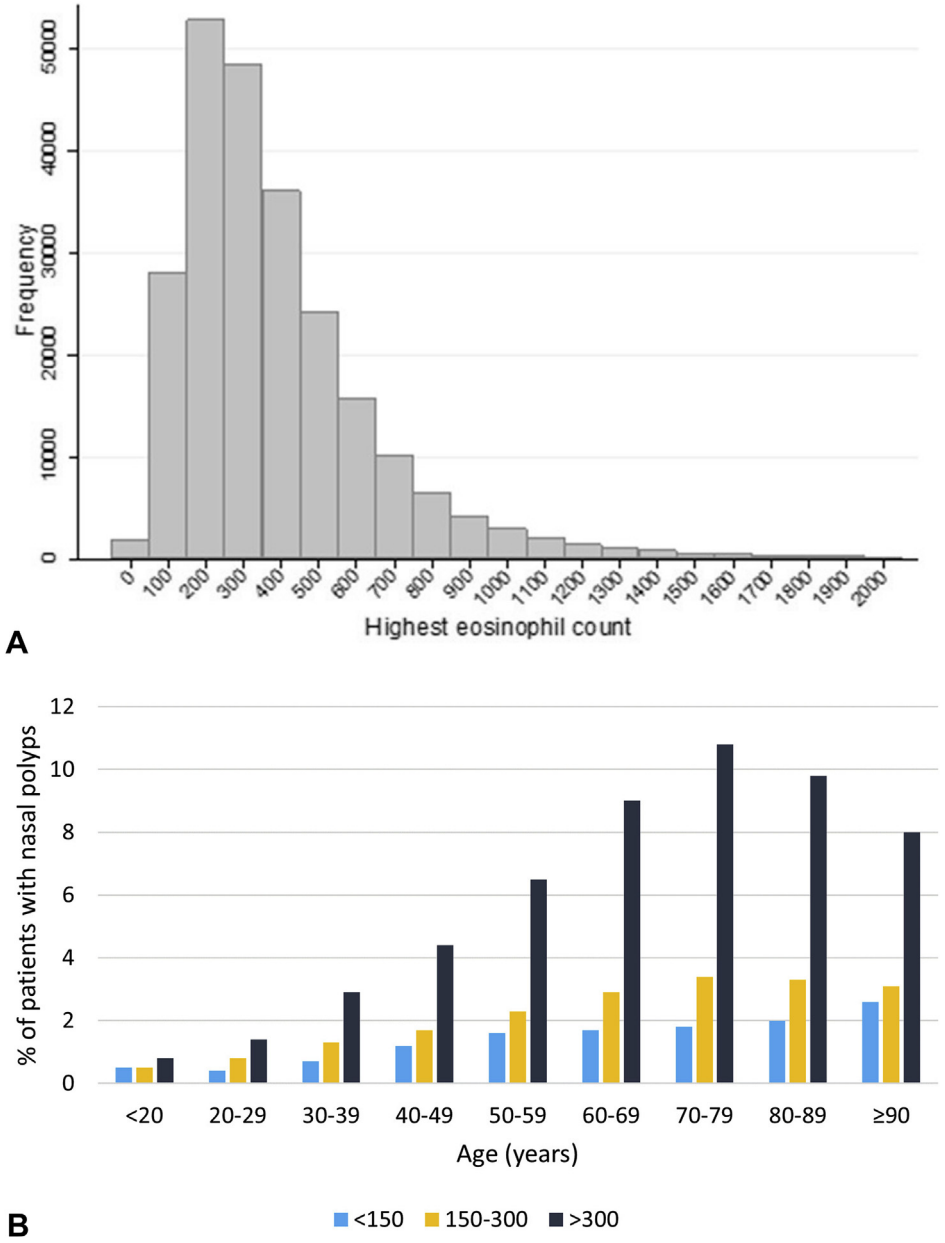

FIGURE 2. (**A**) Highest blood eosinophil count (BEC) ever distribution and (**B**) BEC distribution in those with nasal polyps stratified by age, in a UK primary care cohort of patients with active asthma (Optimum Patient Care Research Database plus Clinical Practice Research Datalink) (n = 241,006). Blood eosinophil count is expressed as cells per microliter; the highest BEC recorded was used, without recent (ie, within 4 months) oral corticosteroid prescription.

(83.8%),[16] owing to our broader and more heterogeneous asthma population, including those with severe and nonsevere disease. However, in the current study, the sensitivity of the algorithm was shown by the greater likelihood of eosinophilic phenotype in patients with severe asthma. We also found a low prevalence of noneosinophilic asthma in UK primary care (5.6%), a finding that appears to be independent of disease severity. It was also low in ISAR (1.6%)[16] and other severe asthma cohorts[31] and likely reflects OCS overtreatment.

Compared with patients with noneosinophilic asthma, those who were most likely eosinophilic had a different phenotype; they were more obese and were more likely to have a comorbidity, which is in agreement with findings in the severe asthma ISAR cohort.[16] Although it is unlikely that eczema, allergic rhinitis, and chronic rhinosinusitis (with or without nasal polyps) were iatrogenic, other comorbidities may have been (eg, gastroesophageal reflux disease, osteoporosis, hypertension, anxiety or depression) (Table E3).

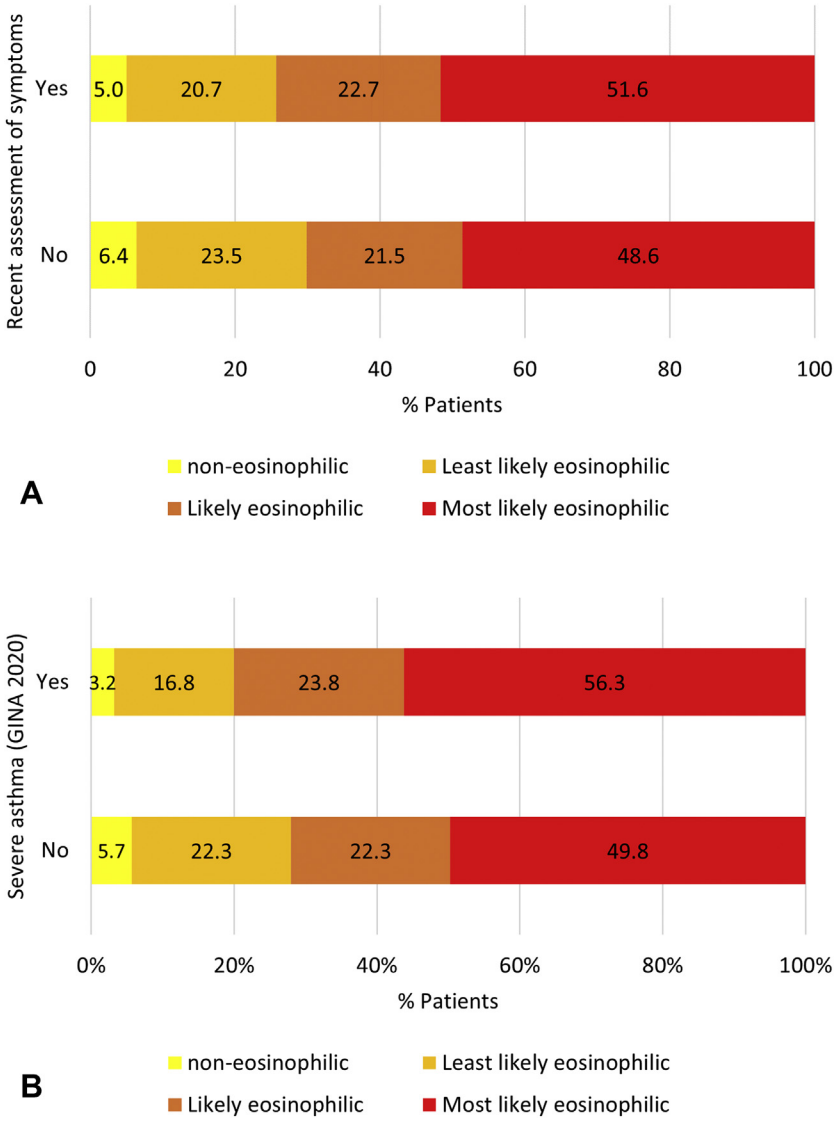

FIGURE 3. Distribution of grades of eosinophilic asthma in a UK primary care cohort (Optimum Patient Care Research Database plus Clinical Practice Research Datalink) **(A)** with (n = 137,969) and without (n = 103,037) a recent assessment of symptoms, and **(B)** in a subgroup of patients with (n = 39,357) and without (n = 201,649) severe asthma. Severe asthma was defined as patients at Global Initiative for Asthma (GINA) step 5 treatment or with uncontrolled asthma at GINA step 4, in which steps 4 and 5 were defined according GINA 2020 guidelines.[11]

Similar to the ISAR cohort, those with the most likely eosinophilic phenotype had the most severe disease; they experienced on average more than twice the asthma attacks per year and had worse lung function and markedly higher treatment burden. Notably, the mean daily ICS dose was about 60% higher in the most likely eosinophilic phenotype group (vs non-eosinophilic), the daily OCS dose was doubled, and the proportion of patients at GINA step 4 treatment and above was higher (44.2% vs 27.5%). This is an important finding considering that a greater systemic corticosteroid dose has been correlated with a greater cumulative incidence of adverse events and greater HCRU. It also points to the increasing likelihood of significant overtreatment as one moves up the eosinophilic phenotype gradient.[32] That over a quarter of patients with noneosinophilic asthma were treated at GINA step 4 and above (27.5%) indicates that many were likely overtreated; this is an issue well-recognized by others, including Refractory Asthma Stratification Project UK. Interestingly, biomarker alone—based corticosteroid adjustment does not appear to reduce corticosteroid load, a finding likely confounded by patient choice not to follow treatment advice.[33] At the other end of the eosinophil phenotype spectrum, the smoking history for those most likely and likely to have an eosinophilic phenotype (ie, >60% current or previous smokers) suggests that some had chronic obstructive pulmonary disease or asthma chronic obstructive pulmonary disease overlap, although almost half of those with

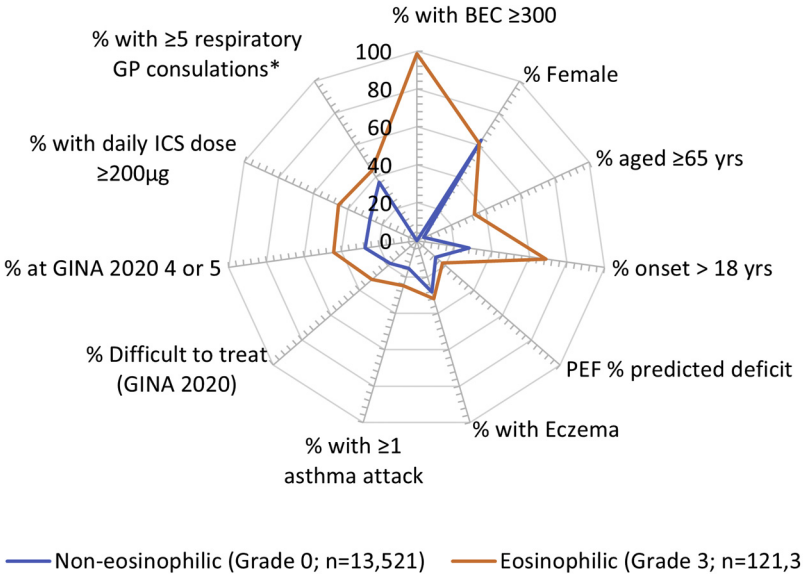

FIGURE 4. Spider plot showing phenotype and endotype variable distribution pattern for eosinophilic (grade 3; n = 80,397) and non-eosinophilic (grade 0; n = 8067) phenotype in a UK primary care cohort (Optimum Patient Care Research Database plus Clinical Practice Research Datalink). For blood eosinophil count (BEC), the highest recorded value was used, without recent (ie, within 4 months) oral corticosteroid prescription. *Clinical Practice Research Datalink database only, grade 0: n = 6855; grade 3: n = 54,104. *GINA*, Global Initiative for Asthma 2020; *GP*, general practitioner; *ICS*, inhaled corticosteroid; *PEF*, peak expiratory flow rate.

noneosinophilic asthma were also current or ex-smokers. An age-adjusted gradient in clinical characteristics was also noted along the eosinophil phenotype gradient, which was not always visible in the ISAR cohort, owing to the tightly defined severe asthma population in the latter. Use of the OPCRD/CRPD primary care cohort thus allowed us to apply the ISAR algorithm to a broader patient population and to disentangle phenotypic characteristics across the gradient, enabling us to see phenotype-associated treatable traits more clearly.

We also sought to disentangle eosinophilic phenotypes based on clinical characteristics as well as HCRU, and found an increase in HCRU with increasing likelihood of eosinophilic phenotype, particularly for outpatient visits and hospital admissions. Compared with those with noneosinophilic asthma, or patients who were least likely to have an eosinophilic phenotype (ie, grade 0 or 1), those most likely or likely to have an eosinophilic phenotype (grade 2 or 3) had 33% more respiratory-related outpatient visits per year, 18% more respiratory accident and emergency attendances, and 32% more hospital admissions with asthma as the primary diagnosis. This increase in HCRU mirrors the increase in disease severity, treatment, and comorbidity burdens across the eosinophil phenotype gradient. We previously found that HCRU and costs were four times greater for patients with severe uncontrolled eosinophilic asthma compared with nonsevere patients with asthma.[25] Conversely, we found a decrease in the duration of hospital stay (with asthma as a primary diagnosis), moving from left (noneosinophilic) to right (most likely eosinophilic) across the gradient, perhaps owing to the rapid steroid responsiveness of most patients with eosinophilic asthma.

Limitations of this study include reliance on BEC rather than sputum eosinophilic count, the use of data from the United Kingdom only, and the fact that within OPCRD, prescription data are used to assess treatment burden with the assumptions that medications were (1) prescribed correctly in line with GINA 2020 recommendations and (2) taken as directed. In addition, 43% of patients ever diagnosed with asthma in the OPCRD had no BEC available, which may have biased the results. To counterbalance these limitations, it should be noted that BEC has been consistently linked to increased risk for asthma attacks across a range of asthma severities.[4,8,34] Furthermore, because of its combined size, the OPRCD/CPRD enabled us to identify and study a large cohort of asthma patients, in which large numbers in each phenotype group provided a balanced representation of demographic and clinical characteristics across groups. The large number of disease-specific variables collected by these databases facilitated comparison of cohorts using a comprehensive list of demographic and clinical characteristics. Although we did not perform power calculations, CIs of rate ratios (Table III) show that even small increases in variable prevalence were highly statistically significant, illustrating that these analyses had sufficient statistical power to find relevant associations. Finally, our study included a broad heterogeneous patient population, which removed the issue of selection bias that may have occurred in the ISAR cohort. Data contained within the OPCRD and CPRD came from EMRs and were frequently used for observational research.[35-37] These data provide a snapshot of patients with asthma managed in real life in practices all over the United Kingdom.

Asthma phenotype assessment should become part of routine asthma assessment in primary care. Half of asthma patients in UK primary care have an eosinophilic asthma phenotype, in which both disease burden and HCRU increase with an increasing likelihood of eosinophilic phenotype. The eosinophil

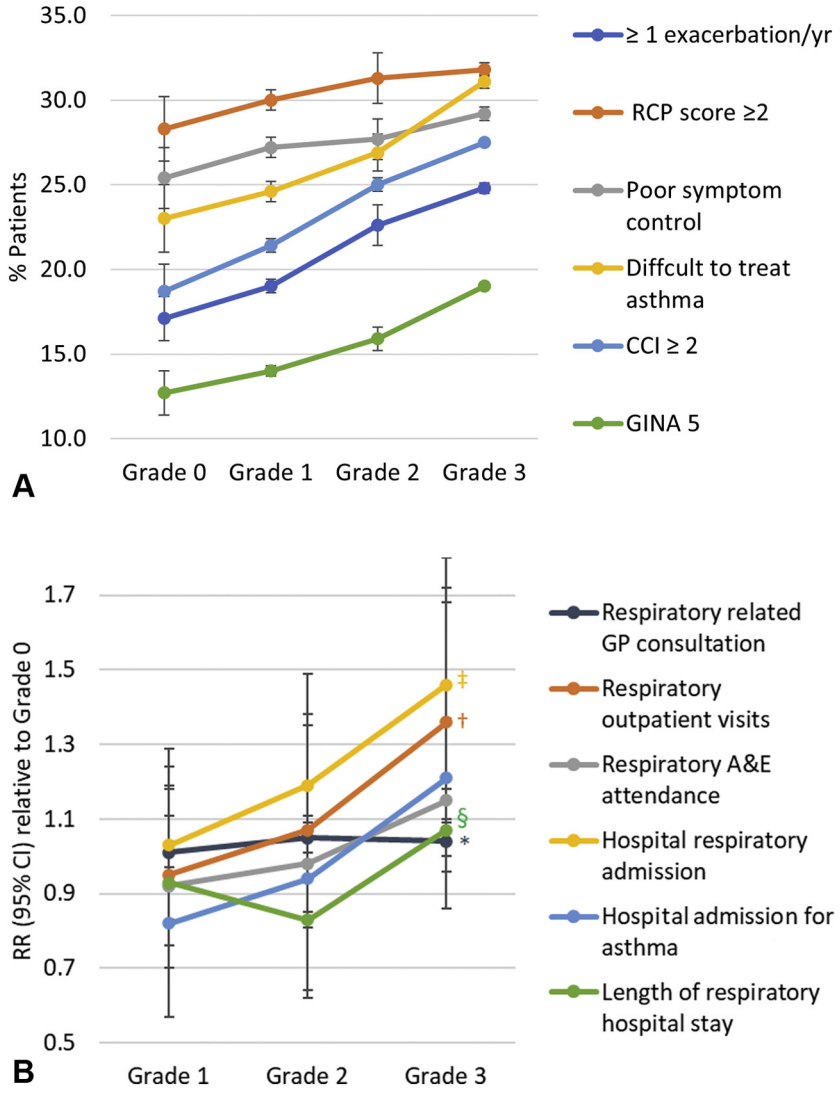

FIGURE 5. (**A**) Prevalence rates of key asthma variables along eosinophil phenotype gradient (data from Optimum Patient Care Research Database and Clinical Practice Research Datalink). Grade 0 indicates non-eosinophil (n = 13,521); grade 1, least likely eosinophilic (n = 52,741); grade 2, likely eosinophilic (n = 53,431; and grade 3, most likely eosinophilic (n = 121,313). Results are presented as means (95% confidence intervals (CI). (**B**) Relative risk (RR; 95% CI) to grade 0 for health care resource use variables along eosinophil phenotype gradient (data from Clinical Practice Research Datalink). For grade 1, n = 26,866; for grade 2, n = 25,323; and for grade 3, n = 54,104. Grade 0 indicates noneosinophilic; grade 1, least likely eosinophilic; grade 2, likely eosinophilic; and grade 3, most likely eosinophilic (see Figure 1 for a definition of eosinophil phenotype grades). Rate ratios with 95% CIs and *P* values were estimated using negative binomial regression in the total study population. Analyses were adjusted for age, sex, body mass index, smoking status, eczema, chronic sinusitis, diabetes, osteoporosis, hypertension, cardiovascular diseases, anxiety or depression, chronic kidney disease, apnea, pneumonia and Charlson comorbidity index score. *$P = .0399$ versus grade 0. †$P = .0044$ versus grade 0. ‡$P = .0004$ versus grade 0. §$P < .00001$ versus grade 0. *A&E*, accident and emergency; *GINA 5*, Global Initiative for Asthma Step 5 treatment (2020); *GP*, general practitioner; *RCP*, Royal College of Physicians assessment of asthma control questionnaire.

phenotype gradient algorithm presented here is an important first step in deconstructing asthma into its component parts, enabling us to see phenotype-associated treatable traits more clearly and the opportunity to treat those traits precisely. Routine asthma phenotyping in general practice may encourage earlier intervention with phenotype-directed treatments and discourage unnecessary or inappropriately high steroid doses. Avenues for future research include an investigation of the impact of early intervention with targeted therapies (eg, biologics that target the eosinophilic phenotype) on disease outcomes and trajectory, and a test of the implementation of this algorithm as part of quality improvement in primary care.

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TABLE III. Distribution of health care resource use in total population of asthma patients from: Clinical Practice Research Datalink with hospital episode statistics available

Variable	Grade 0 (n = 6855) (mean [SD])	Grade 1 (n = 26,866) (mean [SD])	Grade 2 (n = 25,323) (mean [SD])	Grade 3 (n = 54,104) (mean [SD])	*P*	Grade 2/3 to 0/1 relative risk (95% confidence interval) adjusted	Grade 2/3 to 0/1 relative risk (95% confidence interval) not adjusted
All-cause general practitioner consultations	7.92 (7.13)	9.21 (8.24)	11.37 (9.54)	10.75 (9.58)	<.0001		
0, n (%)	231 (3.4)	710 (2.6)	405 (1.6)	1073 (2.0)	<.0001	1.07 (1.06-1.08) $P < .0001$	1.22 (1.21-1.24) $P < .0001$
1-4, n (%)	2324 (33.9)	7765 (28.9)	5062 (20.0)	12,668 (23.4)			
5-8, n (%)	1914 (27.9)	7338 (27.3)	6447 (25.5)	14,167 (26.2)			
9-11, n (%)	918 (13.4)	3607 (13.4)	3920 (15.5)	7761 (14.3)			
12-24, n(%)	1239 (18.1)	6068 (22.6)	7439 (29.4)	14,331 (26.5)			
≥25, n (%)	229 (3.3)	1378 (5.1)	2050 (8.1)	4104 (7.6)			
Respiratory-related general practitioner consultations	3.78 (4.65)	4.17 (4.73)	4.88 (4.94)	4.53 (4.87)	<.0001		
0, n (%)	2272 (33.1)	8227 (30.6)	6313 (24.9)	15,195 (28.1)	<.0001	1.03 (1.02-1.05) $P < .0001$	1.14 (1.12-1.15) $P < .0001$
1-4, n (%)	2082 (30.4)	7810 (29.1)	7113 (28.1)	15,201 (28.1)			
5-8, n (%)	1627 (23.7)	6745 (25.1)	6989 (27.6)	14,385 (26.6)			
9-11, n (%)	450 (6.6)	2126 (7.9)	2505 (9.9)	4750 (8.8)			
12-24, n (%)	403 (5.9)	1846 (6.9)	2282 (9.0)	4342 (8.0)			
≥25, n (%)	21 (0.3)	112 (0.4)	121 (0.5)	231 (0.4)			
All-cause outpatient visits	2.27 (5.53)	2.65 (5.42)	3.49 (6.23)	3.40 (6.39)	<.0001		
0, n (%)	3839 (56.0)	13,436 (50.0)	10,134 (40.0)	23,215 (42.9)	<.0001	1.10 (1.08-1.13) $P < .0001$	1.33 (1.30-1.36) $P < .0001$
1, n (%)	758 (11.1)	3071 (11.4)	3003 (11.9)	6135 (11.3)			
2, n (%)	546 (8.0)	2263 (8.4)	2394 (9.5)	4875 (9.0)			
3, n (%)	380 (5.5)	1664 (6.2)	1888 (7.5)	3747 (6.9)			
≥4, n (%)	1332 (19.4)	6432 (23.9)	7904 (31.2)	16,132 (29.8)			
Respiratory outpatient visits	0.06 (0.64)	0.07 (0.65)	0.11 (0.72)	0.12 (0.89)	<.0001		
0, n (%)	6716 (98.0)	26,116 (97.2)	24,295 (95.9)	51,881 (95.9)	<.0001	1.33 (1.20-1.47) $P < .0001$	1.62 (1.47-1.78) $P < .0001$
1, n (%)	61 (0.9)	296 (1.1)	409 (1.6)	856 (1.6)			
2, n (%)	30 (0.4)	188 (0.7)	259 (1.0)	498 (0.9)			
3, n (%)	17 (0.2)	109 (0.4)	131 (0.5)	346 (0.6)			
≥4, n (%)	31 (0.5)	157 (0.6)	229 (0.9)	523 (1.0)			
All-cause accident and emergency attendances	0.46 (1.28)	0.43 (1.34)	0.42 (1.35)	0.47 (1.27)	<.0001		
0, n (%)	5049 (73.7)	20,124 (74.9)	19,089 (75.4)	39,546 (73.1)	<.0001	1.05 (1.02-1.08) $P = .002$	1.03 (1.00-1.06) $P = .039$
1, n (%)	1181 (17.2)	4484 (16.7)	4086 (16.1)	9401 (17.4)			
2, n (%)	348 (5.1)	1297 (4.8)	1258 (5.0)	2946 (5.4)			

(continued)

TABLE III. *(Continued)*

Variable	Grade 0 (n = 6855) (mean [SD])	Grade 1 (n = 26,866) (mean [SD])	Grade 2 (n = 25,323) (mean [SD])	Grade 3 (n = 54,104) (mean [SD])	*P*	Grade 2/3 to 0/1 relative risk (95% confidence interval) adjusted	Grade 2/3 to 0/1 relative risk (95% confidence interval) not adjusted
3, n (%)	149 (2.2)	506 (1.9)	450 (1.8)	1104 (2.0)			
≥4, n (%)	128 (1.9)	455 (1.7)	440 (1.7)	1107 (2.0)			
Respiratory accident and emergency attendances	0.04 (0.46)	0.03 (0.30)	0.04 (0.26)	0.05 (0.32)	<.0001		
0, n (%)	6694 (97.7)	26,235 (97.7)	24,522 (96.8)	52,219 (96.5)	<.0001	1.18 (1.08-1.30)* $P < .0001$	1.40 (1.29-1.53) $P < .0001$
1, n (%)	137 (2.0)	533 (2.0)	648 (2.6)	1515 (2.8)			
2, n (%)	12 (0.2)	64 (0.2)	110 (0.4)	257 (0.5)			
3, n (%)	6 (0.1)	17 (0.1)	22 (0.1)	46 (0.1)			
≥4, n (%)	6 (0.1)	17 (0.1)	21 (0.1)	67 (0.1)			
Hospital admissions with asthma as primary diagnosis	0.01 (0.23)	0.01 (0.19)	0.01 (0.20)	0.01 (0.23)	<0.0001		
0, n (%)	6805 (99.3)	26,691 (99.3)	25,159 (99.4)	53,554 (99.0)	<.0001	1.32 (1.10-1.59)† $P = .003$	1.21 (1.02-1.44) $P = .027$
1, n (%)	37 (0.5)	138 (0.5)	143 (0.6)	451 (0.8)			
2, n (%)	8 (0.1)	20 (0.1)	11 (0.0)	62 (0.1)			
3, n (%)	<5	5 (0.0)	5 (0.0)	9 (0.0)			
≥4, n (%)	4 (0.1)	12 (0.0)	5 (0.0)	28 (0.1)			
Hospital admissions with respiratory condition as primary diagnosis	0.02 (0.28)	0.03 (0.27)	0.04 (0.32)	0.05 (0.36)	<.0001		
0, n (%)	6,744 (98.4)	26,359 (98.1)	24,567 (97.0)	52,246 (96.6)	<.0001	1.35 (1.22-1.49) $P < .0001$	1.74 (1.58-1.91) $P < .0001$
1, n (%)	91 (1.3)	397 (1.5)	601 (2.4)	1489 (2.8)			
2, n (%)	12 (0.2)	74 (0.3)	101 (0.4)	232 (0.4)			
3, n (%)	<5	15 (0.1)	26 (0.1)	63 (0.1)			
≥4, n (%)	5 (0.1)	21 (0.1)	28 (0.1)	74 (0.1)			
Length of stay, one or more overnight asthma primary							
N	36	132	125	414			
	7.33 (11.31)	6.70 (10.19)	6.47 (10.22)	6.04 (10.08)	.5111		
1, n (%)	10 (27.8)	32 (24.2)	30 (24.0)	108 (26.1)	.0059	0.75 (0.62-0.91)‡ $P = .004$	0.90 (0.75-1.08) $P = .254$
2-7, n (%)	18 (50.0)	73 (55.3)	62 (49.6)	228 (55.1)			
8-13, n (%)	<5	7 (5.3)	25 (20.0)	42 (10.1)			
≥14, n (%)	6 (16.7)	20 (15.2)	8 (6.4)	36 (8.7)			

Length of stay, one or more overnight respiratory condition as primary diagnosis						
N	75	361	602	1,395		
	5.81 (10.10)	7.29 (10.32)	9.27 (13.37)	8.69 (14.11)	.0003	
1, n (%)	25 (33.3)	86 (23.8)	126 (20.9)	321 (23.0)	.0918	0.91 (0.80-1.03) $P = .133$	1.26 (1.12-1.42) $P < .0001$
2-7, n (%)	38 (50.7)	171 (47.4)	266 (44.2)	638 (45.7)		
8-13, n (%)	<5	48 (13.3)	96 (15.9)	205 (14.7)		
≥14, n (%)	8 (10.7)	56 (15.5)	114 (18.9)	231 (16.6)		

Grade 0 indicates noneosinophilic; grade 1, least likely eosinophilic; grade 2, likely eosinophilic; and grade 3, most likely eosinophilic (see Figure 1 for a definition of eosinophil phenotype grades). For categorical variables, *P* values were calculated using Pearson's chi-square tests of independent categories. For continuous or ordinal variables, *P* values were calculated using nonparametric Kruskal-Wallis equality of populations rank test. Rate ratios with 95% confidence intervals and *P* values were estimated using negative binomial regression in the total study population. Analyses were adjusted for age, sex, body mass index, smoking status, eczema, chronic sinusitis, diabetes, osteoporosis, hypertension, cardiovascular diseases, anxiety or depression, chronic kidney disease, apnea, pneumonia, and Charlson comorbidity index score.

*Also adjusted for chronic obstructive pulmonary disease diagnosis.

†Also adjusted for osteoporosis and diabetes ever.

‡Also adjusted for pneumonia, gastroesophageal reflux disease, and anxiety or depression diagnosis ever.

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