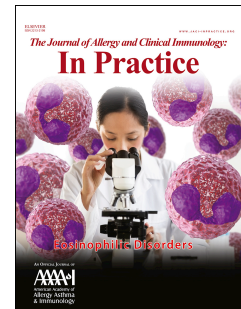


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Asthma phenotyping in primary care: applying the International Severe Asthma Registry eosinophil phenotype algorithm across all asthma severities.

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Asthma phenotyping in primary care: applying the International Severe Asthma Registry eosinophil phenotype algorithm across all asthma severities.

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Conflict of interest statement

Marjan Kerkhof, Lakmini Bulathsinhala, Isha Chaudhry, Neva Eleangovan were employees of Observational and Pragmatic Research Institute at the time of the study, which conducted this study in collaboration with OPC and AstraZeneca.

Victoria A. Carter and Chris A. Price are employees of Optimum Patient Care Global Ltd, which conducted this study in collaboration with OPRI and AstraZeneca.

Trung N. Tran is an employee of AstraZeneca, which is the funder of this study.

Riyad 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. Walter 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.

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David B. Price has board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva

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Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care
Ltd (Australia and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore);
5% shareholding in Timestamp which develops adherence monitoring technology; is peer reviewer for
grant committees of the Efficacy and Mechanism Evaluation programme, and Health Technology
Assessment; and was an expert witness for GlaxoSmithKline.

87 Highlight box

88 *What is already known about this topic?*

89 Asthma remains poorly controlled and characterized in primary care. Many patients are diagnosed
90 with 'asthma', receive regular asthma treatment, in accordance with a 'one treatment fits all', step-
91 up/step-down, guideline-directed approach, but with little clinical benefit.

92 *What does this article add to our knowledge?*

93 Eosinophilic asthma predominates in UK primary care and is associated with a greater likelihood of
94 having asthma attacks, reduced lung function despite a significantly greater steroid burden, and
95 greater healthcare resource utilization.

96 *How does this study impact current management guidelines?*

97 The eosinophil phenotype gradient algorithm will enable primary care physicians to identify and
98 categorize asthma patients into those with and without eosinophilic asthma, and refer, when
99 appropriate, for phenotype-targeted treatment.

100

101 Word count

102 Abstract: 246

103 Text: 4653

Abstract

Background: An eosinophil phenotype gradient algorithm has been developed and applied to a large severe asthma cohort (International Severe Asthma Registry; ISAR).

Objective: We sought to re-apply this algorithm in a UK primary care asthma cohort, quantify the eosinophilic phenotype and, assess the relationship between likelihood of eosinophilic phenotype and asthma severity/healthcare resource utilization (HCRU).

Methods: Patients (≥ 13 years old) with active asthma and ≥ 1 blood eosinophil count 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 ISAR 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) had an eosinophilic phenotype respectively, and 5.6% had a non-eosinophilic phenotype (Grade 0). Compared to patients with non-eosinophilic asthma, those “most likely” to have an eosinophilic phenotype tended to have more co-morbidities (% with Charlson co-morbidity index ≥ 2 : 28.2% vs 6.9%) and experienced more asthma attacks (% with ≥ 1 attack: 24.8% vs 15.3%). These patients were also more likely to have difficult-to-treat asthma (31.1% vs 18.3%), receive more intensive treatment (% on GINA (2020) Step 4 or 5: 44.2% vs 27.5%), and greater HCRU (e.g. 10.8 vs 7.9 GP all-cause consultations/year).

Conclusion: 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.

Keywords: asthma, eosinophilic, healthcare resource utilization, ISAR, phenotypes, primary care, severity, UK

Abbreviations:

129	A & E: accident & emergency
130	BEC: blood eosinophil count
131	CI: confidence interval
132	COPD: chronic obstructive pulmonary disease
133	CPRD: Clinical Practice Research Datalink
134	CRS: chronic rhinosinusitis
135	EMR: electronic medical record
136	FeNO: fractional exhaled nitric oxide
137	FEV ₁ : forced expiratory volume in one second
138	GINA: Global Initiative for Asthma
139	GP: general practitioner
140	HCRU: healthcare resource utilization
141	HES: hospital episode statistics
142	ICS: inhaled corticosteroid
143	IL: interleukin
144	IQR: inter-quartile range
145	ISAR: International Severe Asthma Registry
146	LABA: long-acting β_2 -agonist
147	LAMA: long-acting muscarinic antagonist
148	LTRA: leukotriene receptor antagonist
149	NP: nasal polyps
150	OCS: oral corticosteroid
151	OPC: Optimum Patient Care
152	OPCRD: Optimum Patient Care Research Database
153	OPRI: Observational Pragmatic Research Institute
154	PEF: peak expiratory flow rate
155	RCP: Royal College of Physicians
156	RR: relative risk
157	SABA: short-acting β_2 -agonist
158	SAMA: short-acting muscarinic antagonist
159	SD: standard deviation
160	SMD: standardized mean difference
161	
162	

Introduction

Primary care providers are at the front line of asthma management and play a crucial role in the early identification and management of uncontrolled disease. However, asthma remains poorly controlled and characterized, with many patients diagnosed under the umbrella term of 'asthma', who 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 our increased knowledge of the underlying mechanisms of asthma, identification of numerous biomarkers of airway inflammation, availability of biologics that target specific inflammatory pathways and a switch in focus to treatable traits. According to *The Lancet Asthma Commission*, what is needed is a '*third era of asthma management*', that takes into account the heterogeneity of asthma and that delivers precision disease management based on disease characteristics.

Eosinophilic airway inflammation is one such treatable trait, with several reliable biomarkers (e.g. fractional exhaled nitric oxide (FeNO), blood eosinophil count (BEC)) that provide information on risk of asthma attacks and likely response to inhaled corticosteroids (ICS).²⁻⁵ These biomarkers are easy to measure, making them particularly suited for use in primary care, and have been shown not only to stratify risk, but also to facilitate the targeting and economic use of asthma therapy.^{2,6,7} Conversely, asthma which is 'truly' non-eosinophilic (i.e. no eosinophilic airways inflammation off 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 component 'parts' and could introduce phenotype-directed precision treatment earlier in the 'patient journey'.

Work has already commenced on this deconstruction in primary care.¹²⁻¹⁵ Halder and colleagues¹⁵ identified 3 different phenotypes in a UK primary care population: early-onset eosinophilic, obese non-eosinophilic 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 (e.g. sputum eosinophil count, reversibility) or burdensome to the patient (e.g. peak flow variability) may limit the usefulness of these categorizations in primary care. A Swedish study took an alternative approach and used only self-reported asthma characteristics from 1,291 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 (i.e. most parameters would be available from patients' electronic medical records (EMRs)), it lost in terms of lack of characterization of the underlying inflammatory pathway.

A combination of phenotypic characteristics and biomarkers may be a better way to characterize asthma types, and this has recently been done to disentangle eosinophil phenotypes in a global, real-life, adult, severe asthma cohort (i.e. International Severe Asthma Registry (ISAR)).¹⁶ The ISAR multi-component, eosinophil phenotype classification algorithm used variables accessible not only at specialist asthma centres but also in primary care, and took variability in BEC (using the highest ever value) and impact of oral corticosteroids (OCS) into account, both of which can confound phenotype classification.¹⁷

The aims of our study were to (i) re-apply 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 (ii) assess the relationship between likelihood of eosinophilic phenotype asthma severity and healthcare resource utilization (HCRU).

Methods

Hypothesis

Our hypothesis was that (i) the recently developed ISAR eosinophil classification algorithm¹⁶ has utility beyond the severe asthma population and may be applied to a broad primary care asthma cohort, (ii) the prevalence of the asthma eosinophil phenotype in primary care is higher than previously thought and (iii) this eosinophilic phenotype is 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 GP practices in the UK. The current study protocol was approved by the Anonymized Data Ethics & Protocol Transparency committee (ADEPT 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 comprises medical records of more than 11 million patients from over 800 general practices across the UK (approximately 8% of the total UK population), and integrates with all UK clinical systems (EMIS, TPP SystmOne, InPS Vision, Microtest Evolution). It benefits from a long retrospective period (median time in the database is 19.8 (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 UK, with a median patient time in the database of 19.3 (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 ≥ 13 years old, with a diagnosis of active asthma and continuous EMRs for the 12 months prior to enrolment. Active asthma was defined as ≥ 1 prescription for an ICS or short-acting β_2 -agonist (SABA) containing inhaler in the last 12 months prior to enrolment. At least 1 BEC recording was also required after the date of first active asthma diagnosis without prescription for OCS or anti-interleukin (IL)5/5R therapy in the prior 4 weeks. For HCRU analysis, linkage with CPRD-HES was a

requirement. Those with uncertain information on 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 pre-defined gradient eosinophilic algorithm based on that 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 cut-offs included highest BEC ever, without recent (within 4 months) OCS prescription (>300 , ≥ 150 -300, <150 cells/ μ L), anti-IL-5/5R treatment, long-term OCS ever, diagnosis of nasal polyps ever, and late asthma onset (≥ 30 years old) (**Figure 1**). FeNO was omitted given 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 (non-eosinophilic). Patients most likely to have an eosinophilic phenotype (Grade 3) were those with highest BEC ever ≥ 300 cells/ μ L OR on anti-IL-5/5R therapy, OR with BEC ≥ 150 - 300 cells/ μ L on (i) long-term OCS or (ii) with both nasal polyps AND adult-onset. The non-eosinophilic phenotype (Grade 0) was defined by experts as highest BEC ever of <150 cells/ μ L in the absence of nasal polyps, adult onset, or maintenance OCS. See **Figure 1** for definitions of Grade 1 and 2 eosinophilic phenotypes.

Description of eosinophilic and non-eosinophilic asthma phenotypes

Patient demographic, clinical and HCRU characteristics were described and compared according to different likelihood of eosinophilic phenotype over a period of 12 months of EMR data prior to a pre-defined date. For OPCRd this predefined date was the date of most recent EMR data extraction from general practice. As linkage to HES data was available up to the 1st March 2019, the predefined date for the CPRD was either the date of most recent EMR extraction (if extraction was pre-1st March 2019) or a randomly chosen date in the 12 months prior to March 1st 2019 (if extraction was post 1st March 2019). A full list of variables collected is provided in the online repository.

Analysis

Stata version 14.1 (College Station, TX, US) was used to conduct all statistical analyses. The prevalence of pre-defined eosinophilic phenotypes was determined for the total population (OPCRd + CPRD), for OPCRd and CPRD populations separately (in sub-population with information on symptoms obtained during annual review), and for patients with difficult-to-treat (severe) asthma. Those with severe asthma were defined as those with uncontrolled asthma at Global Initiative for Asthma (GINA) step 4

or those at GINA step 5, using the 2020 GINA definitions of step 4/5 asthma treatment.¹¹ A sensitivity analysis was also performed to determine eosinophil phenotype distribution in patients who had a recent assessment of asthma control (i.e. within 15 months). Asthma control was assessed using the three Royal College of Physicians (RCP) questions,²⁴ which is a quality of asthma care indicator within the UK Quality and Outcomes Framework, a voluntary annual reward and incentive programme for all GP surgeries in the UK.

Demographics, diagnosed comorbidities, clinical characteristics, such as asthma therapy and control were described overall and for the pre-defined phenotypes, for the total population (OPCRD + CPRD), for those with a recent asthma assessment and for those with difficult-to-treat (severe) asthma. Asthma burden and HCRU variables were described overall and for the pre-defined phenotypes for the CPRD population. Demographic, clinical and HCRU variables were described as numbers and prevalence rates per category for dichotomous and categorical variables. Mean (Standard Deviation (SD)) and median (Interquartile range (IQR)) as well as categorical distributions were described for count and continuous variables. In addition, age-standardised means and prevalence rates with 95% confidence intervals were reported for the pre-defined phenotypes, using the total population as the standard to account for artificial differences in age distribution between phenotype groups caused by selection on the presence of late-onset asthma.

Pearson's chi-square tests of independent categories for categorical variables and the non-parametric Kruskal-Wallis equality-of-populations rank test for variables on a continuous or ordinal scale were performed to examine statistical significance of differences in distribution of characteristics among the phenotypes. Relevant differences in crude distribution of characteristics between phenotype grade 3 and grades 0, 1 and 2 were reported as the Standardised Mean Difference (SMD) with grade 3 as the reference. This measure is not affected by the number of observations and provides information on the magnitude of differences, and thus a better way to judge relevant differences than 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**. We considered an SMD >10% to indicate a relevant difference. Rate ratios with 95% confidence intervals comparing HCRU events for patients with grades 2/3 vs 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 was adequately powered to detect any difference due to 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, BMI, smoking status, eczema, chronic sinusitis, diabetes, osteoporosis,

hypertension, cardiovascular diseases, anxiety/depression, chronic kidney disease, apnea, pneumonia and CCI-score.

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 (% 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 one-by-one, sorted by their bias potential in a descending order and the bias was measured against the previous model. In case the bias was $\geq 2\%$ the candidate was retained in the model and the next candidate confounder was tested. Age, BMI and CCI-score were included in the model as confounders for all outcomes. Additional identified confounders are reported below table 2 for the different outcomes

Role of the funding source

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

Results

Patients

We attempted to maximise study power by drawing our final sample size from a large potential pool of over 20 million people in primary care, approximately 1/3 of the UK population. From a total of 1,135,808 patients with asthma diagnosis, ≥ 1 BEC and aged ≥ 13 years old in the OPCR and CPRD, 241,006 patients were eligible for inclusion: 127,588 patients from the OPCR and 113,148 patients from the CPRD (**Figure E1**). This final sample size chosen for analysis included those patients with sufficient longitudinal data (i.e. >12 months), those with active asthma (i.e. at least 1 inhaler prescription in the last year), with sufficient information to categorize phenotype according to the eosinophil gradient algorithm (ie. at least 1 BEC 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 pre 1st March 2019 for CPRD data extracted after 1st March 2019) from general practices ranged from 2008 to 2019, with almost half of the data being uploaded in 2019 and 79% in the last 5 years (**Figure E2**). The mean age was 53.7 (SD:18.8) years, 63.1% of patients were female, 15.7% were current smokers and 69.6% were either overweight or obese (**Table 2**). First asthma diagnosis was recorded at a median age of 35 years (**Figure E3**).

Blood eosinophil count distribution

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

Eosinophil phenotype characterization

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 >300 cells/ μ L at any time during follow up (**Figure 1; Table 1**). 22.2% of patients were “likely” (Grade 2), and 21.9% were “least likely” (Grade 1) to have an eosinophilic phenotype (**Figure 1; Table 1**). Almost all patients classified as “likely” eosinophilic had late onset asthma and a highest BEC in the range 150-300 cells/ μ L, without nasal polyps. The majority of patients classified as “least likely” eosinophilic had a highest BEC of 150-300 cells/ μ L without any other feature of eosinophilic disease. The remaining patients had late-onset disease with a low BEC (<150 cells/ μ L). 5.6% of patients had non-eosinophilic asthma (Grade 0). These phenotype classifications were validated by cross-examining their defining characteristics, showing an increase of BEC, age of onset, incidence of nasal polyps long-term ICS from Grade 0 (non-eosinophilic) to Grade 3 (most-likely eosinophilic) phenotypes (**Table E2**).

A similar pattern of “most likely” eosinophil phenotype predominance was noted in both the OPCR (52.6%), CPRD populations (47.8%), those with a recent asthma assessment (51.6%), and those with severe asthma (56.3%), with treatment step defined according to GINA 2020 (**Table 1**). Patients who had a recent assessment of symptoms during annual review of their asthma were more frequently defined as “most likely” having an eosinophilic phenotype than those not recently reviewed (51.6% vs 48.6%) (**Figure 3A**). A greater proportion of severe asthma patients had an eosinophilic phenotype than those without severe disease (56.3% vs 49.8% using GINA 2020 treatment steps to define severity) (**Figure 3B**).

Demographic and clinical characteristics

Compared to patients with non-eosinophilic asthma, those who “most likely” had an eosinophilic phenotype were significantly (all $p < 0.0001$, non-parametric Kruskal Wallis) more likely to have a co-morbidity (e.g. % with Charlson co-morbidity index score ≥ 2 : 28.2% vs 6.9%) and experience more asthma attacks (e.g. % with ≥ 1 attack: 24.9% vs 15.3%). They were also significantly (all $p < 0.001$, non-parametric Kruskal Wallis) more likely to have difficult-to-treat asthma (31.1% vs 18.3%) and to receive more intensive treatment (e.g. on GINA (2020) Step 4 or 5 treatment: 44.2% vs 27.5%) (**Table 2, Figure 4**). Age standardized means and prevalence rates showed a gradient increase in asthma attack rates, asthma control score, symptoms, asthma severity, co-morbidities, and intensity of asthma treatment with an increasing likelihood of eosinophilic phenotype (**Figure 5A; Tables E3-E5**). Results were similar in those with a recent asthma assessment (**Table E6**) and for those with severe asthma, with treatment steps defined according to GINA 2020 (**Table E7**).

Healthcare resource utilization

Many HCRU variables assessed showed an increase of HRCU along the eosinophil phenotype gradient in the total population (**Table 3; Figure 5B; Table E8**). An increase in RR from Grade 0/1 to Grade 2/3 was particularly evident for GP consultations, out-patient visits, A&E attendances, respiratory hospital admissions and length of respiratory overnight stay, and was even more apparent in those with severe asthma (**Table 3**). For example, patients at Grade 2/3 of the eosinophilic spectrum had a 32% higher risk of a hospital admission with asthma as the primary diagnosis than those at Grade 0/1 (adjusted RR 1.32 (95% CI 1.10, 1.59), $p = 0.003$). The non-adjusted RR was slightly lower but still statistically significant (non-adjusted RR 1.21 (95% CI 1.02, 1.44), $p = 0.027$). Conversely, patients at Grade 2/3 had a 25% reduced risk of having a ≥ 1 overnight hospital stay that those at Grade 0/1 (adjusted RR 0.75 (95% CI 0.62, 0.91), $p = 0.004$), or a 10% reduced risk for the non-adjusted analysis (non-adjusted RR 0.90 (95% CI 0.75, 1.08), $p = 0.254$). All p-values around RR were calculated using negative binomial regression. Indeed, those at Grade 2 or 3 (with difficult to treat asthma) hospitalized for asthma had

399 a mean hospital stay of 6-7 days compared to 10 days for those at Grade 0 or 1 (**Table E9**), a pattern
400 which was also seen in the total HCRU population (**Table E3**).

401

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Discussion

Using a multi-component, eosinophil classification algorithm, modified for use in primary care, and a broad primary care asthma cohort, we classified patients into 4 groups along a gradient of eosinophilic phenotype likelihood (from “non-eosinophilic” 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 non-eosinophilic phenotype is rare. Notably, this eosinophilic phenotype was apparent not only in those with severe asthma (56.3% of patients) but in those with non-severe asthma as well (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 UK.

After decades of modest advancements in our understanding of asthma, we are now in the midst of a ‘new era’ of asthma management; an era which has provided a greater understanding of the underlying pathophysiology of asthma, re-categorized and re-classified 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 the need to provide a clear and pragmatic way forward to guide physicians in primary care, where most asthma cases are diagnosed and managed. Identification of those with an eosinophilic phenotype is important as these patients have a relatively high risk of asthma attacks (even those with ‘mild’ asthma) and an increased risk of re-admission to hospital.^{4,25,26} Additionally, although eosinophilic asthma does, in general, respond to corticosteroids, there is a sub-group of primary care patients with insufficient response to standard inhaler treatment regimens (failing GINA 4) who frequently exacerbate and experience rapid lung function decline. These patients should be identified and categorized in primary care, require careful follow up and may benefit from appropriate referral and early intervention with a targeted therapy. Currently, international asthma management guidelines provide little guidance on phenotyping patients with asthma in primary care, seeing it as the purview of specialists.¹¹

The multi-component, 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, based on a combination of clinical characteristics and biomarkers may be a better way to characterize asthma types. GINA also recommends using different combinations of

factors to identify Type 2 inflammatory phenotypes, including BEC, FeNO, sputum eosinophils, need for maintenance OCS and presence of multiple co-morbidities.²⁷ Such a combination approach arguably affords a more practical means of determining eosinophilic asthma status than reliance on protracted, sequential BEC.²⁸ Our algorithm was based on extensive literature review and expert consensus, uses variables readily accessible in primary care, and importantly takes variability in BEC (using the highest ever value) and impact of OCS into account, 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 as this is not routinely measured, and late onset asthma (>30 yrs) was used instead of adult onset (>18 yrs), as age of onset is used as a predictor of response to anti-IL5. It is worth mentioning that these modifications to the ISAR algorithm is unlikely to have altered our findings as removal of FeNO and adult onset from the algorithm did not alter the findings in the ISAR cohort.¹⁶ Application of this algorithm to a UK primary care population found that approximately 50% of these patients 'most likely' have an eosinophilic asthma phenotype, a finding which was confirmed in both the OPCR (52.6%) and CPR (47.8%). The slightly lower eosinophil phenotype prevalence in the CPR was most likely driven by lower recorded numbers of counts and shorter duration of follow up compared to OPCR 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. Indeed, a recent study found that there are large numbers of asthma patients in the UK with potential severe asthma (8%) who are effectively hidden in primary care.³⁰ In either case a structured assessment by primary care physicians is warranted, with referral to specialist care if 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 which merits further study. As expected, the prevalence of the eosinophilic asthma phenotype was lower than that recently estimated in a severe asthma cohort (83.8%),¹⁶ due to our broader and more heterogeneous asthma population, including those with severe and non-severe disease. However, in the current study sensitivity of the algorithm was shown by the greater likelihood of eosinophilic phenotype in those with severe asthma. We also found a very low prevalence of non-eosinophilic asthma in UK primary care (5.6%), a finding which appears to be independent of disease severity, being also very low in ISAR (1.6%)¹⁶ and other severe asthma cohorts,³¹ and is most likely a reflection of OCS over-treatment.

Compared to those with non-eosinophilic asthma, those who were “most likely eosinophilic” had a very different phenotype; they were more obese, and were more likely to have a co-morbidity, in agreement with findings in the severe asthma ISAR cohort.¹⁶ Although it is unlikely that eczema, allergic rhinitis or chronic rhinosinusitis (with/without nasal polyps) were iatrogenic, other co-morbidities may have been (e.g. GERD, osteoporosis, hypertension, anxiety/depression; Table E3).

Just as for 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, had a worse lung function, and a 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%); an important finding when considering that greater systemic corticosteroid dose has been correlated with a greater cumulative incidence of adverse events and greater HCRU, and also points to the increasing likelihood of significant over-treatment as one moves up the eosinophilic phenotype gradient.³² The finding that over a quarter (27.5%) of patients with non-eosinophilic asthma were treated at GINA Step 4 and above indicates that many of them are likely over-treated an issue well recognized by others including RASP UK. Interestingly biomarker alone-based corticosteroid adjustment does not appear to reduce corticosteroid load, a finding likely confounded by patient choice to not follow treatment advice.³³ At the other end of the eosinophil phenotype spectrum the smoking history of those “most likely” and “likely” to have an eosinophilic phenotype (i.e. >60% current or previous smokers) may suggest that some of them had chronic obstructive pulmonary disease (COPD) or asthma COPD overlap, although almost half of those with non-eosinophilic 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, due to the tightly defined severe asthma population in the latter. Using the OPCR/CRPD primary care cohort has, thus, allowed us to apply the ISAR algorithm in a broader patient population and to more clearly disentangle phenotypic characteristics across the gradient, enabling us to more clearly ‘see’ phenotype-associated treatable traits.

We also sought to disentangle eosinophilic phenotypes, based not only on clinical characteristics, but according to HCRU too, and found an increase in HCRU with increasing likelihood of eosinophilic phenotype, particularly for out-patient visits and hospital admissions. Compared to those with non-eosinophilic asthma or least likely to have an eosinophilic phenotype (i.e. Grade 0 or 1), those most likely or likely to have an eosinophilic phenotype (Grade 2 or 3) had 33% more respiratory-related out-

patient visits/year, 18% more respiratory A&E attendances and 32% more hospital admissions with asthma as the primary diagnosis. This increase in HCRU mirrors the increase in disease severity, treatment and co-morbidity burdens across the eosinophil phenotype gradient. We have previously found that HCRU and costs are four times greater for patients with severe uncontrolled eosinophilic asthma than for non-severe patients with asthma.²⁵ Conversely, we found a decrease in duration of hospital stay (with asthma as a primary diagnosis) moving from left (non-eosinophilic) to right (most likely eosinophilic) across the gradient, perhaps due to the rapid steroid responsiveness of most patients with eosinophilic asthma.

Limitations of the study include reliance on BEC rather than sputum eosinophilic count, the use of data from the UK only, and the fact that within OPCRCD prescription data is used to assess treatment burden with the assumptions that medications were (i) prescribed correctly in line with GINA 2020 recommendations and (ii) taken as directed. Additionally, 43% of patients ever diagnosed with asthma in the OPCRCD had no BEC available, which may have biased the results. To counterbalance these limitations it should be noted that BEC have been consistently linked to increased risk of asthma attacks across a range of asthma severities.^{4,8,34} Furthermore, due to its combined size, the OPCRCD/CPRD enabled us to identify and study a large cohort of asthma patients, with large numbers in each phenotype group providing 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 power calculations were not performed, confidence intervals of rate ratios (Table 3) show that even small increases in variable prevalence were found to be highly statistically significant, illustrating that these analyses had sufficient statistical power to find relevant associations. Finally, our study included a broad heterogeneous patient population removing the issue of selection bias which may have occurred in the ISAR cohort. Data contained within the OPCRCD and CPRD comes from EMRs and has been used frequently for observational research.³⁵⁻³⁷ These data provide a snapshot of patients with asthma managed in real-life in practices all over the UK.

In conclusion, 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, with both disease burden and HCRU increasing with increasing likelihood of eosinophilic phenotype. The eosinophil phenotype gradient algorithm presented here is an important first step in deconstructing asthma into its component 'parts', enabling us to more clearly 'see' phenotype-associated treatable traits, and the opportunity to precisely treat those traits. 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 investigation of the impact of early intervention with targeted therapies (e.g. biologics that target the eosinophilic phenotype) on disease outcomes and trajectory and testing the implementation of this algorithm as part of quality improvement in primary care.

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Table 1: characterization of eosinophilic and non-eosinophilic phenotypes and the proportion of asthma patients with these phenotypes in a UK primary care cohort with active asthma

Highest BEC (cells/ μ L) ^a	Treatment or clinical characteristic	Eosinophilic phenotype	Total study population (n=241,006)		OPCRD (n=127,858)		CPRD (n=113,148)		Recent assessment ^b (n=137,969)		Severe asthma ^d GINA 2020 (n=39,357)	
			N (%)	(%)	N (%)	%	N (%)	%	N (%)	%	N (%)	%
≥ 300	BEC >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 (0.0)		0 (0.0)		0 (0.0)		0 (0.0)	
≥ 150 to <300	Long-term OCS	Grade 3: most likely	458 (0.2)	22.0	277 (0.2)	21.8	181 (0.2)	22.2	246 (0.2)	22.5	246 (0.6)	23.5
	Presence of nasal polyps and adult onset ^e (no long-term OCS)	Grade 3: most likely	1,408 (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 ^e (no long-term OCS)	Grade 2: likely	52,298 (21.7)		27,604 (21.6)		24,694 (21.8)		30,643 (22.2)		9,138 (23.2)	
	No nasal polyps, adult onset ^e 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	4,162 (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 ^e 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 ^e (no long-term OCS)	Grade 1: least likely	15,840 (6.6)	6.6	7,694 (6.0)	6.0	8,146 (7.2)	7.2	8,957 (6.5)	6.5	2,434 (6.2)	6.2

	No nasal polyps, adult onset ^e or long-term OCS	Grade 0: non-eosinophilic	13,521 (5.6)	5.6	6,666 (5.2)	5.2	6,855 (6.1)	6.1	6,878 (5.0)	5.0	1,259 (3.2)	3.2
Anti-IL-5/5R: anti-interleukin 5/5-receptor; BEC: blood eosinophil count; CPRD: Clinical Practice Research Datalink; GINA: Global Initiative for Asthma; OCS: oral corticosteroids; OPCR: Optimum Patient Care Research Database. ^a independent criteria specified in each row; pre-anti-IL-5/5R or long-term OCS was used wherever possible; ^b within the last 15 months; ^c Severe asthma defined as those at GINA 2020 treatment step 5 or those with uncontrolled asthma at GINA 2020 step 4; ^d Severe asthma defined as those at GINA 2019 treatment step 5 or with uncontrolled asthma at GINA 2019 step 4; ^e onset of asthma: ≥30 years old												

Table 2: Demographic and clinical characteristics according to eosinophilic and non-eosinophilic phenotype in a primary care UK cohort (OPCRD + CPRD) 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 to 3	SMD 1 to 3	SMD 2 to 3
Gender									
Female, n (%)	8,533 (63.1)	33,688 (63.9)	36,194 (67.7)	73,709 (60.8)	152,129 (63.1)	<0.0001	4.8	6.4	14.6
Age (at last extraction date)									
Mean (SD)	36.7 (14.1)	46.9 (17.4)	64.0 (13.0)	54.1 (19.4)	53.7 (18.8)	<0.0001	102.3	39.2	60.1
13-17, n (%)	973 (7.2)	1,757 (3.3)	16 (0.0)	4,207 (3.5)	6,953 (2.9)	<0.0001	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)	9,084 (17.2)	26,106 (48.9)	40,518 (33.4)	76,248 (31.6)				
Body Mass Index (kg/m²)									
N	11,808	48,178	51,182	113,475	224,643	<0.0001	25.8	6.4	14.4
Under weight (<18.5), n (%)	476 (4.0)	1,250 (2.6)	668 (1.3)	2,956 (2.6)	5,350 (2.4)				
Normal (≥18.5 <25), n (%)	4,454 (37.7)	14,922 (31.0)	11,862 (23.2)	31,748 (28.0)	62,986 (28.0)				
Overweight (≥25 <30), n (%)	3,752 (31.8)	15,763 (32.7)	17,651 (34.5)	37,594 (33.1)	74,760 (33.3)				
Obese (≥30), n (%)	3,126 (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	<0.0001	28.7	9.2	12.9
Current smoker, n (%)	2,179 (16.7)	9,367 (18.3)	7,508 (14.5)	17,716 (15.0)	36,770 (15.7)				
Ex-smoker, n (%)	4,115 (31.5)	20,158 (39.4)	26,625 (51.5)	53,541 (45.3)	104,439 (44.6)				
Never smoker, n (%)	6,782 (51.9)	21,580 (42.2)	17,614 (34.0)	46,903 (39.7)	92,879 (39.7)				
Age of asthma onset									
Mean (SD)	13.0 (8.4)	24.3 (19.5)	49.9 (13.9)	34.2 (22.2)	34.3 (21.9)	<0.0001	125.5	47.5	84.7
Childhood-onset (<18 yrs), n (%)	9,630 (71.2)	25,455 (48.3)	534 (1.0)	37,808 (31.2)	73,427 (30.5)				

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 to 3	SMD 1 to 3	SMD 2 to 3
Adult-onset (18-29 yrs), n (%)	3,891 (28.8)	11,446 (21.7)	289 (0.5)	14,824 (12.2)	30,450 (12.6)	<0.0001	135.5	49.4	110.0
Late-onset (≥30 yrs), n (%)	0 (0.0)	15,840 (30.0)	52,608 (98.5)	68,681 (56.6)	137,129 (56.9)				
Co-morbidity ever									
Eczema, n (%)	3,812 (28.2)	14,694 (27.9)	13,128 (24.6)	38,806 (32.0)	70,440 (29.2)	<0.0001	8.3	9.0	16.5
Allergic rhinitis, n (%)	4,738 (35.0)	18,165 (34.4)	14,751 (27.6)	45,986 (37.9)	83,640 (34.7)	<0.0001	6.0	7.2	22.1
CRS, without nasal polyps, n (%)	1,013 (7.5)	4,716 (8.9)	5,576 (10.4)	12,738 (10.5)	24,043 (10.0)	<0.0001	23.7	19.2	11.6
CRS, with nasal polyps, n (%)	<5	<5	286 (0.5)	3,339 (2.8)	3,625 (1.5)	<0.0001			
Charlson co-morbidity index									
0-1, n (%)	12,583 (93.1)	44,621(84.6)	35,139 (65.8)	87,151 (71.8)	179,494 (74.5)	<0.0001	57.7	32.3	11.5
2-3, n (%)	812 (6.0)	6,479 (12.3)	13,204 (24.7)	24,262 (20.0)	44,757 (18.6)				
≥4, n (%)	126 (0.9)	1,641 (3.1)	5,088 (9.5)	9,900 (8.2)	16,755 (7.0)				
Asthma control									
Asthma attacks (EMR data), Mean (SD)	0.2 (0.8)	0.3 (1.0)	0.5 (1.3)	0.5 (1.5)	0.5 (1.3)	<0.0001	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)	<0.0001	28.4	20.6	5.3
1, n (%)	1,488 (11.0)	6,521 (12.4)	7,671 (14.4)	17,292 (14.3)	32,972 (13.7)				
2, n (%)	347 (2.6)	1,641 (3.1)	2,334 (4.4)	5,687 (4.7)	10,009 (4.2)				
3, n (%)	114 (0.8)	603 (1.1)	1,018 (1.9)	2,572 (2.1)	4,307 (1.8)				
≥4, n (%)	120 (0.9)	757 (1.4)	1,529 (2.9)	4,594 (3.8)	7,000 (2.9)				
RCP (3) score, N	6,878	28,560	31,295	71,236	137,969	0.0002	3.3	2.4	0.2
0, n (%)	1,986 (28.9)	8,228 (28.8)	8,818 (28.2)	20,299 (28.5)	39,331 (28.5)				
1, n (%)	2,810 (40.9)	11,555 (40.5)	12,581 (40.2)	28,307 (39.7)	55,253 (40.0)				
2, n (%)	1,508 (21.9)	6,307 (22.1)	7,024 (22.4)	15,827 (22.2)	30,666 (22.2)				

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 to 3	SMD 1 to 3	SMD 2 to 3
3, n (%)	574 (8.3)	2,470 (8.6)	2,872 (9.2)	6,803 (9.5)	12,719 (9.2)				
N	6,878	28,560	31,295	71,236	137,969	0.0002	3.7	2.6	1.3
Poor symptom control, n (%)	1,886 (27.4)	7,978 (27.9)	8,927 (28.5)	20,735 (29.1)	39,526 (28.6)				
N	6,878	28,560	31,295	71,236	137,969	<0.0001	30.0 ^d	18.1 ^d	2.6
Difficult to treat (GINA 2020), n (%)	1,259 (18.3)	6,596 (23.1)	9,350 (29.9)	22,152 (31.1)	39,357 (28.5)				
Lung function									
N	1,468	8,783	16,251	27,419	53,921	<0.0001			
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)		25.7 ^d	16.3 ^d	5.9
N	9,758	40,232	44,043	96,778	190,811	<0.0001			
PEF % predicted, Mean (SD)	86.6 (17.9)	84.7 (19.3)	82.4 (21.3)	82.0 (20.5)	82.9 (20.3)		24.0 ^d	13.6 ^d	1.8
Asthma therapy									
GINA 1 (2020), n (%)	2,728 (20.2)	7,991 (15.2)	4,654 (8.7)	11,803 (9.7)	27,176 (11.3)	<0.0001			
GINA 2 (2020), n (%)	4,890 (36.2)	17,261 (32.7)	15,668 (29.3)	34,324 (28.3)	72,143 (29.9)		43.8 ^d	24.5 ^d	0.4
GINA 3 (2020), n (%)	2,182 (16.1)	9,207 (17.5)	9,913 (18.6)	21,567 (17.8)	42,869 (17.8)				
GINA 4 (2020), n (%)	2,499 (18.5)	11,708 (22.2)	13,399 (25.1)	30,434 (25.1)	58,040 (24.1)				
GINA 5 (2020), n (%)	1,222 (9.0)	6,574 (12.5)	9,797 (18.3)	23,185 (19.1)	40,778 (16.9)				
ICS daily dose ^a (mcg), Mean (SD)	170.6 (261.9)	222.0 (297.3)	293.8 (332.0)	274.6 (327.5)	261.5 (320.5)	<0.0001	35.1 ^d	16.8 ^d	5.8
0, n (%)	2,769 (20.5)	8,242 (15.6)	5,099 (9.5)	12,531 (10.3)	28,641 (11.9)				
>0 <100, n (%)	4,796 (35.5)	15,206 (28.8)	11,208 (21.0)	29,804 (24.6)	61,014 (25.3)				
100-200, n (%)	2,284 (16.9)	10,116 (19.2)	10,903 (20.4)	24,170 (19.9)	47,473 (19.7)	<0.0001	45.9 ^d	22.0 ^d	8.5
>200-500, n (%)	2,612 (19.3)	13,115 (24.9)	17,183 (32.2)	36,093 (29.8)	69,003 (28.6)				
>500, n (%)	1,060 (7.8)	6,062 (11.5)	9,038 (16.9)	18,715 (15.4)	34,875 (14.5)				
Number ICS inhalers ^b Mean (SD)	5.3 (6.1)	6.4 (6.5)	8.0 (6.8)	7.3 (6.5)	7.1 (6.6)	<0.0001	32.0 ^d	13.5 ^d	10.9 ^d
SABA daily dose (mcg), ^c Mean (SD)	196.3 (302.2)	235.3 (355.4)	253.2 (403.3)	282.9 (450.0)	261.0 (414.0)	<0.0001	22.6 ^d	11.8 ^d	7.0
OCS 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)	<0.0001	19.8 ^d	14.1 ^d	6.2
SAMA\$, n (%)	95 (0.7)	657 (1.2)	1,159 (2.2)	2,118 (1.7)	4,029 (1.7)	<0.0001	9.5	4.1	3.1

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 to 3	SMD 1 to 3	SMD 2 to 3
LAMA\$, n (%)	242 (1.8)	1,973 (3.7)	4,536 (8.5)	8,225 (6.8)	14,976 (6.2)	<0.0001	24.8 ^d	13.6 ^d	6.4
LABA\$, n (%)	350 (2.6)	1,557 (3.0)	1,949 (3.6)	3,931 (3.2)	7,787 (3.2)	<0.0001	3.9	1.7	2.2
Theophylline\$, n (%)	76 (0.6)	374 (0.7)	617 (1.2)	1,840 (1.5)	2,907 (1.2)	<0.0001	9.4	7.7	3.2
LTRA\$, n (%)	878 (6.5)	3,543 (6.7)	3,915 (7.3)	10,745 (8.9)	19,081 (7.9)	<0.0001	8.9	8.0	5.6
Grade 0: non-eosinophilic; Grade 1: least likely eosinophilic; Grade 2: likely eosinophilic; Grade 3 most likely eosinophilic (see Figure 1 for definition of eosinophil phenotype grades). ^a fluticasone propionate equivalent (mcg); ^b of 30 days dispensed in baseline year; ^c salbutamol equivalent (mcg); ^d ≥ 1 prescription in the last 12 months. CPRD: Clinical Practice Research Datalink; CRS: chronic rhinosinusitis; EMR: Electronic Medical Record; FEV₁: forced expiratory volume in one second; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; OPCR: Optimum Patient Care Research Database; PEF: peak expiratory flow; RCP(3): Royal College of Physicians 3 questions; SABA: short-acting β_2-agonist; SAMA: short-acting muscarinic antagonist; SD: standard deviation; SMD: Standardized Mean Difference (see Table E1 for how to calculate). ^dWe consider an SMD >10% to indicate a relevant difference Categorical variables: p-values were calculated using Pearson's chi-square tests of independent categories. Continuous or ordinal variables: p-values were calculated using the non-parametric Kruskal-Wallis equality of populations rank test.									

Table 3. Distribution of healthcare resource utilization in the total population of asthma patients from CPRD with HES available

Variable		Grade 0 (N= 6,855) Mean (SD)	Grade 1 (N= 26,866) Mean (SD)	Grade 2 (N= 25,323) Mean (SD)	Grade 3 (N= 54,104) Mean (SD)	P*	Relative of Grades 2/3 to 0/1 RR (95% CI) adjusted	Relative of Grades 2/3 to 0/1 RR (95% CI) Non-adjusted
All-cause GP consultations		7.92 (7.13)	9.21 (8.24)	11.37 (9.54)	10.75 (9.58)	<0.0001		
	0, n (%)	231 (3.4)	710 (2.6)	405 (1.6)	1,073 (2.0)	<0.0001	1.07 (1.06, 1.08) P<0.0001	1.22 (1.21, 1.24) P=0.000
	1-4, n (%)	2,324 (33.9)	7,765 (28.9)	5,062 (20.0)	12,668 (23.4)			
	5-8, n (%)	1,914 (27.9)	7,338 (27.3)	6,447 (25.5)	14,167 (26.2)			
	9-11, n (%)	918 (13.4)	3,607 (13.4)	3,920 (15.5)	7,761 (14.3)			
	12-24, n(%)	1,239 (18.1)	6,068 (22.6)	7,439 (29.4)	14,331 (26.5)			
	≥25, n (%)	229 (3.3)	1,378 (5.1)	2,050 (8.1)	4,104 (7.6)			
Respiratory- related GP consultations		3.78 (4.65)	4.17 (4.73)	4.88 (4.94)	4.53 (4.87)	<0.0001		
	0, n (%)	2,272 (33.1)	8,227 (30.6)	6,313 (24.9)	15,195 (28.1)	<0.0001	1.03 (1.02, 1.05) P<0.0001	1.14 (1.12, 1.15) P=0.000
	1-4, n (%)	2,082 (30.4)	7,810 (29.1)	7,113 (28.1)	15,201 (28.1)			
	5-8, n (%)	1,627 (23.7)	6,745 (25.1)	6,989 (27.6)	14,385 (26.6)			
	9-11, n (%)	450 (6.6)	2,126 (7.9)	2,505 (9.9)	4,750 (8.8)			
	12-24, n (%)	403 (5.9)	1,846 (6.9)	2,282 (9.0)	4,342 (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)	<0.0001		
	0, n (%)	3,839 (56.0)	13,436 (50.0)	10,134 (40.0)	23,215 (42.9)	<0.0001	1.10 (1.08, 1.13) P<0.0001	1.33 (1.30, 1.36) P=0.000
	1, n (%)	758 (11.1)	3,071 (11.4)	3,003 (11.9)	6,135 (11.3)			
	2, n (%)	546 (8.0)	2,263 (8.4)	2,394 (9.5)	4,875 (9.0)			
	3, n (%)	380 (5.5)	1,664 (6.2)	1,888 (7.5)	3,747 (6.9)			
	≥4, n (%)	1,332 (19.4)	6,432 (23.9)	7,904 (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)	<0.0001		
	0, n (%)	6,716 (98.0)	26,116 (97.2)	24,295 (95.9)	51,881 (95.9)	<0.0001	1.33 (1.20, 1.47) P<0.0001	1.62 (1.47, 1.78) P=0.000
	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)			

Variable		Grade 0 (N= 6,855) Mean (SD)	Grade 1 (N= 26,866) Mean (SD)	Grade 2 (N= 25,323) Mean (SD)	Grade 3 (N= 54,104) Mean (SD)	p*	Relative of Grades 2/3 to 0/1 RR (95% CI) adjusted	Relative of Grades 2/3 to 0/1 RR (95% CI) Non-adjusted
	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 A&E attendances		0.46 (1.28)	0.43 (1.34)	0.42 (1.35)	0.47 (1.27)	<0.0001		
	0, n (%)	5,049 (73.7)	20,124 (74.9)	19,089 (75.4)	39,546 (73.1)	<0.0001	1.05 (1.02, 1.08) P=0.002	1.03 (1.00, 1.06) P=0.039
	1, n (%)	1,181 (17.2)	4,484 (16.7)	4,086 (16.1)	9,401 (17.4)			
	2, n (%)	348 (5.1)	1,297 (4.8)	1,258 (5.0)	2,946 (5.4)			
	3, n (%)	149 (2.2)	506 (1.9)	450 (1.8)	1,104 (2.0)			
	≥4, n (%)	128 (1.9)	455 (1.7)	440 (1.7)	1,107 (2.0)			
Respiratory A&E attendances		0.04 (0.46)	0.03 (0.30)	0.04 (0.26)	0.05 (0.32)	<0.0001		
	0, n (%)	6,694 (97.7)	26,235 (97.7)	24,522 (96.8)	52,219 (96.5)	<0.0001	1.18 (1.08, 1.30) ^a P<0.0001	1.40 (1.29, 1.53) P=0.000
	1, n (%)	137 (2.0)	533 (2.0)	648 (2.6)	1,515 (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 (%)	6,805 (99.3)	26,691 (99.3)	25,159 (99.4)	53,554 (99.0)	<0.0001	1.32 (1.10, 1.59) ^b P=0.003	1.21 (1.02, 1.44) P=0.027
	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		0.02 (0.28)	0.03 (0.27)	0.04 (0.32)	0.05 (0.36)	<0.0001		
	0, n (%)	6,744 (98.4)	26,359 (98.1)	24,567 (97.0)	52,246 (96.6)	<0.0001	1.35 (1.22, 1.49) P<0.0001	1.74 (1.58, 1.91) P=0.000
	1, n (%)	91 (1.3)	397 (1.5)	601 (2.4)	1,489 (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)			

Variable		Grade 0 (N= 6,855) Mean (SD)	Grade 1 (N= 26,866) Mean (SD)	Grade 2 (N= 25,323) Mean (SD)	Grade 3 (N= 54,104) Mean (SD)	p*	Relative of Grades 2/3 to 0/1 RR (95% CI) adjusted	Relative of Grades 2/3 to 0/1 RR (95% CI) Non-adjusted
primary diagnosis								
Length of stay, ≥1 overnight asthma primary	N	36	132	125	414	0.5111		
		7.33 (11.31)	6.70 (10.19)	6.47 (10.22)	6.04 (10.08)			
	1, n (%)	10 (27.8)	32 (24.2)	30 (24.0)	108 (26.1)	0.0059	0.75 (0.62, 0.91) ^c P=0.004	0.90 (0.75, 1.08) P=0.254
	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, ≥1 overnight respiratory condition as primary diagnosis	N	75	361	602	1,395	0.0003		
		5.81 (10.10)	7.29 (10.32)	9.27 (13.37)	8.69 (14.11)			
	1, n (%)	25 (33.3)	86 (23.8)	126 (20.9)	321 (23.0)	0.0918	0.91 (0.80, 1.03) P=0.133	1.26 (1.12, 1.42) P=0.000
	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: non-eosinophilic; Grade 1: least likely eosinophilic; Grade 2: likely eosinophilic; Grade 3 most likely eosinophilic (see Figure 1 for definition of eosinophil phenotype grades). CPRD: Clinical Practice Research Datalink; HES: Hospital Episode Statistics; SD: standard deviation

^aadditionally adjusted for COPD diagnosis; ^bAdditionally adjusted for osteoporosis and diabetes ever; ^cAdditionally adjusted for pneumonia, GERD, and anxiety/depression diagnosis ever

*Categorical variables: p-values were calculated using Pearson's chi-square tests of independent categories.

*Continuous or ordinal variables: p-values were calculated using the non-parametric 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, BMI, smoking status, eczema, chronic sinusitis, diabetes, osteoporosis, hypertension, cardiovascular diseases, anxiety/depression, chronic kidney disease, apnea, pneumonia and CCI-score.

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Legend to figures

Figure 1: algorithm flowchart showing prevalence of eosinophilic phenotypes within a UK primary care active asthma cohort (OPCRD + CPRD; n=241,006). BEC: blood eosinophil count; anti-IL-5: anti-interleukin-5; CPRD: Clinical Practice Research Datalink; OCS: oral corticosteroid; OPCRD: Optimum Patient Care Research Database. For BEC the highest ever value was used, without recent (i.e. within 4 months) OCS prescription.

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 (OPCRD + CPRD; n=241,006). CPRD: Clinical Practice Research Datalink; OPCRD: Optimum Patient Care Research Database; BEC expressed as cells/ μ L, and the highest BEC ever was used, without recent (i.e. within 4 months) OCS prescription.

Figure 3: Distribution of grades of eosinophilic asthma in a UK primary care cohort (OPCRD + CPRD) **(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 those at GINA Step 5 treatment or with uncontrolled asthma at GINA Step 4, with Step 4 and 5 defined according GINA 2020 guidelines.¹¹ CPRD: Clinical Practice Research Datalink; GINA: Global Initiative for Asthma; OPCRD: Optimum Patient Care Research Database

Figure 4: Spider plot showing the phenotype and endotype variable distribution pattern for eosinophilic (Grade 3; n=80,397) and non-eosinophilic (Grade 0; n=8,067) phenotype in a UK primary care cohort (OPCRD + CPRD). BEC: blood eosinophil count; CPRD: Clinical Practice Research Datalink; GINA: Global Initiative for Asthma 2020; GP: general practitioner; ICS: inhaled corticosteroid; OPCRD: Optimum Patient Care Research Database; PEF: peak expiratory flow rate. For BEC the highest ever value was used, without recent (i.e. within 4 months) OCS prescription. *CPRD database only, Grade 0: n=6,855; Grade 3: n=54,104

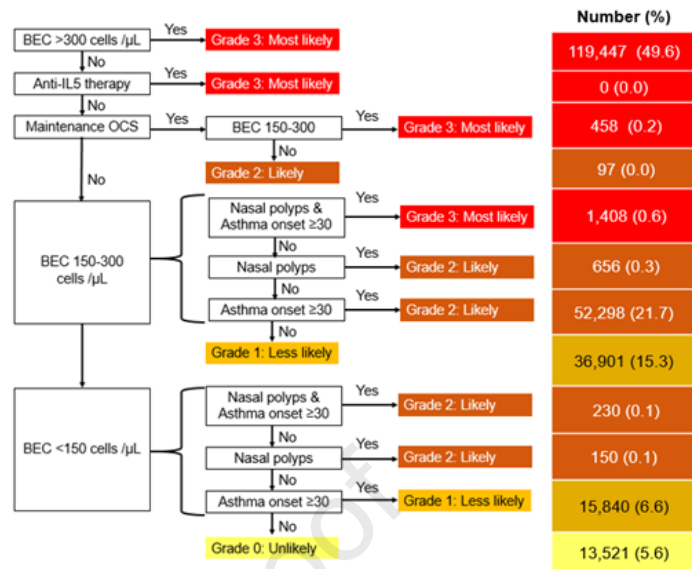
Figure 5: **(A)** Prevalence rates of key asthma variables along the eosinophil phenotype gradient (data from Optimum Patient Care Research Database (OPCRD) and Clinical Practice Research Datalink (CPRD)). Grade 0 (non-eosinophil; n=13,521), Grade 1 (least likely eosinophilic; n=52,741), Grade 2 (Likely eosinophilic; n=53,431), Grade 3 (most likely eosinophilic; n=121,313). CCI: Charlson Comorbidity Index; GINA 5; Global Initiative for Asthma Step 5 treatment (2020); RCP: Royal College of Physicians assessment of asthma control questionnaire. Results are presented as mean (95% confidence intervals). **(B)** Relative Risk (RR; 95% CI) to Grade 0 for health care resource utilization variables along the eosinophil phenotype gradient (data from CPRD). Grade 1 (n=26,866); Grade 2 (n=25,323); Grade 3 (n=54,104). A&E: accident & emergency; CI: confidence variable; GP: general

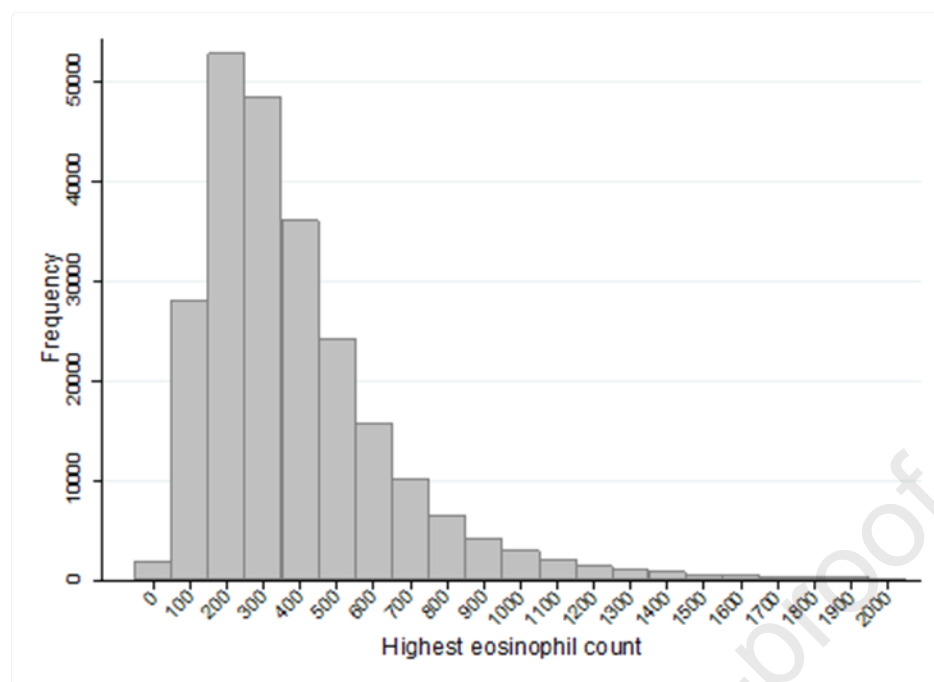
practitioner. Grade 0: non-eosinophilic; Grade 1: least likely eosinophilic; Grade 2: likely eosinophilic; Grade 3 most likely eosinophilic (see Figure 1 for definition of eosinophil phenotype grades). Rate ratios with 95% confidence intervals and p-values were estimated using negative binomial regression in the total study population. Analyses were adjusted for: age, sex, BMI, smoking status, eczema, chronic sinusitis, diabetes, osteoporosis, hypertension, cardiovascular diseases, anxiety/depression, chronic kidney disease, apnea, pneumonia and CCI-score. * $p=0.0399$ vs Grade 0; † $p=0.0044$ vs Grade 0; ‡ $p=0.0004$ vs Grade 0; § $p<0.00001$ vs Grade 0.

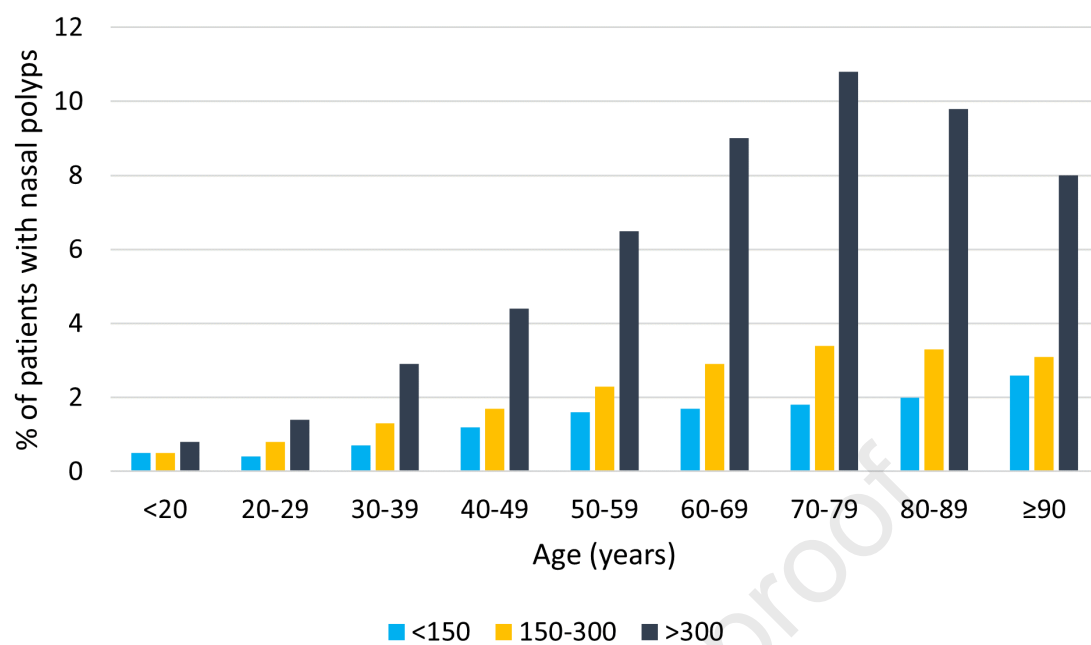
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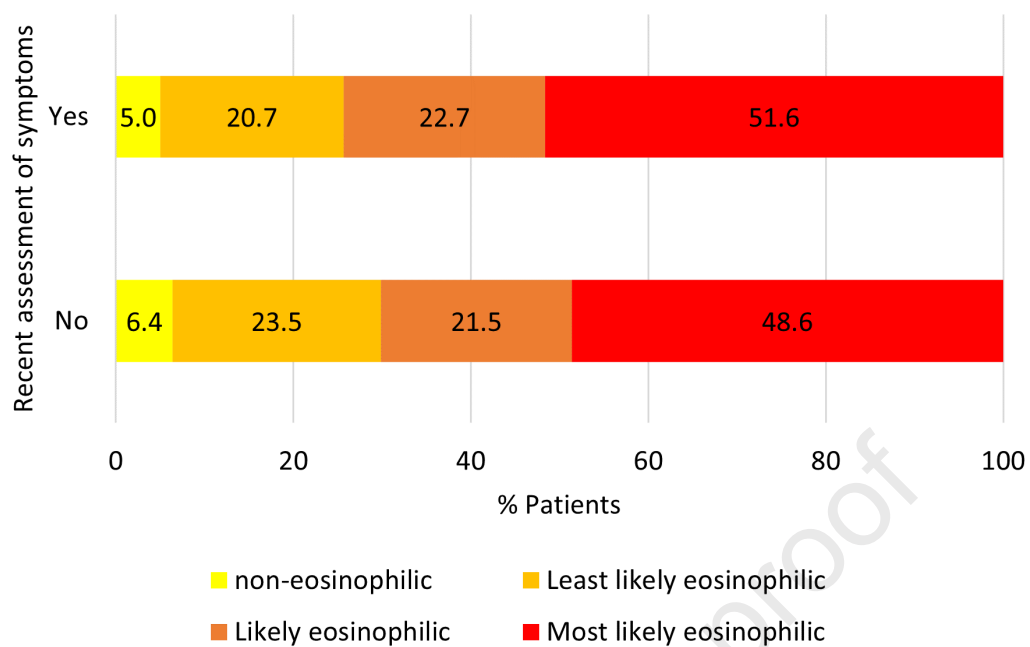
Overall distribution

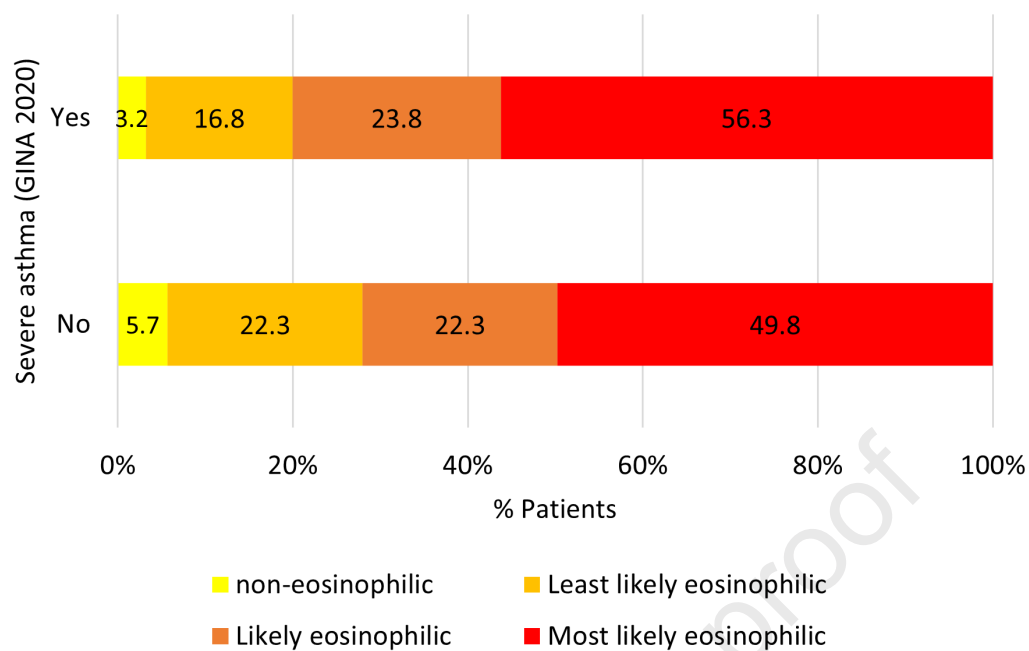
Grade 3: Most likely	N=121,313 (50.3%)
Grade 2: Likely	N=53,431 (22.2%)
Grade 1: Less Likely	N=52,741 (21.9%)
Grade 0: Unlikely	N=13,521 (5.6%)

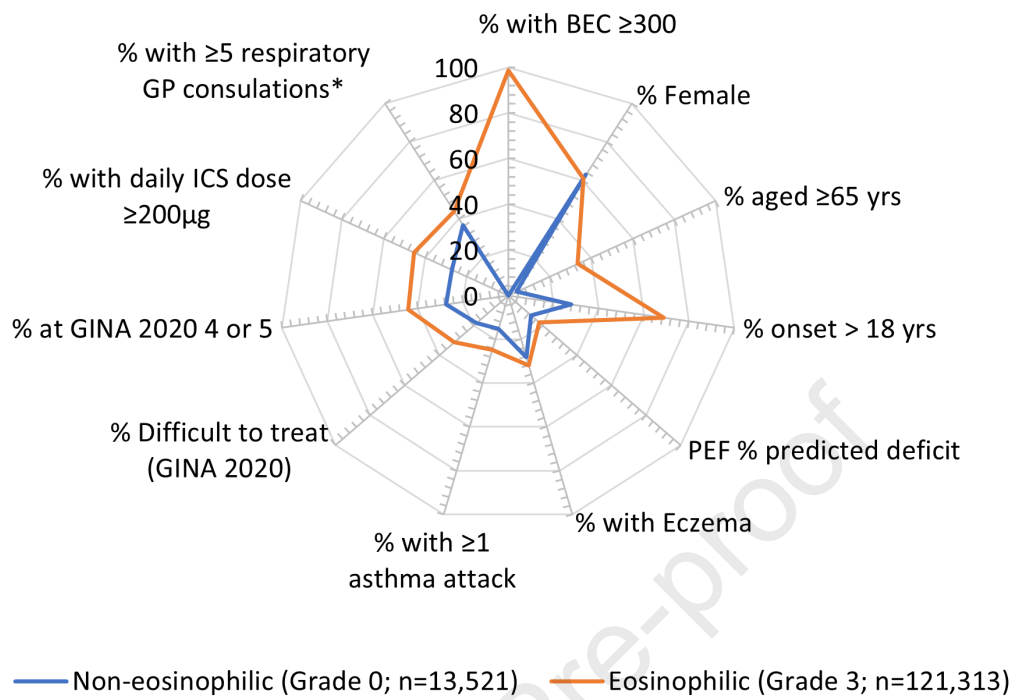


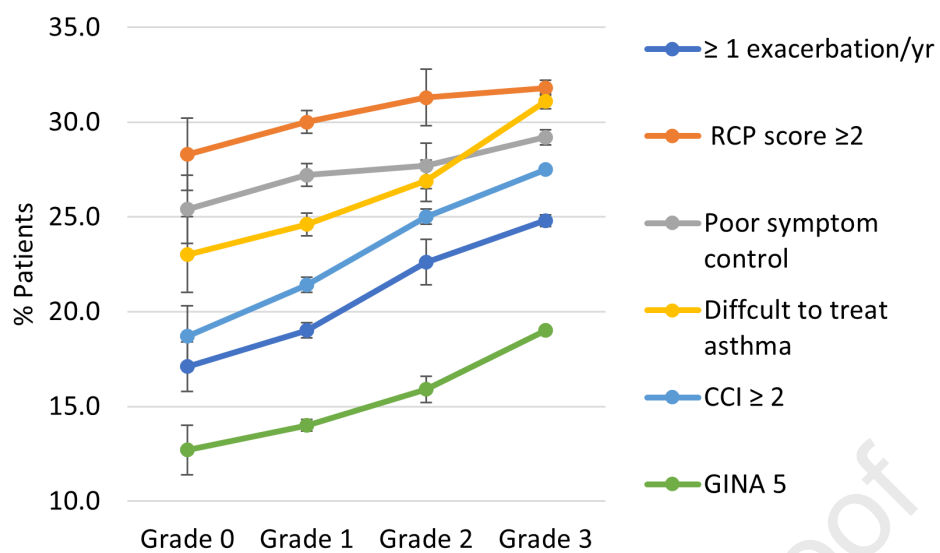


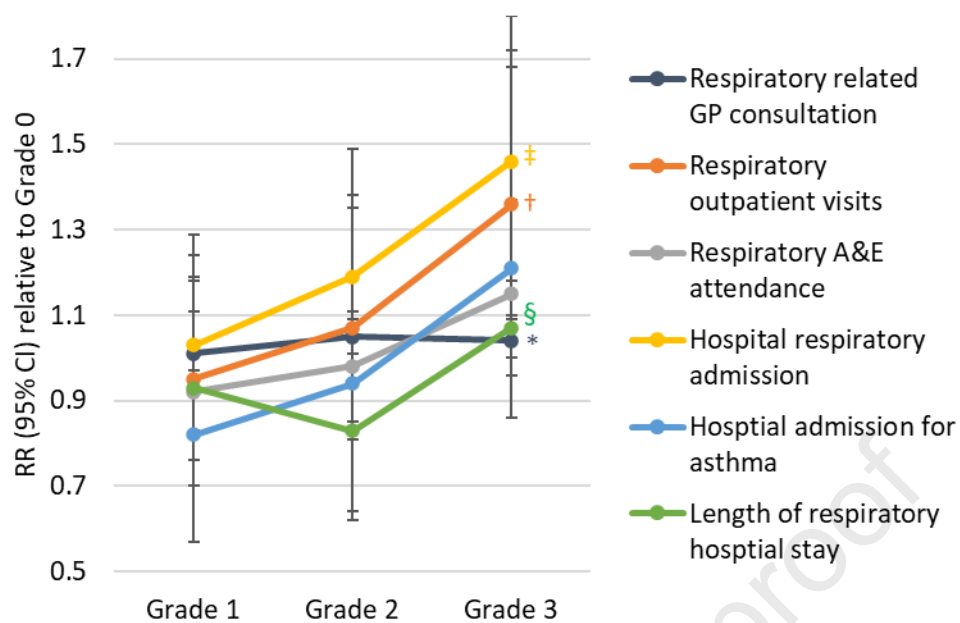












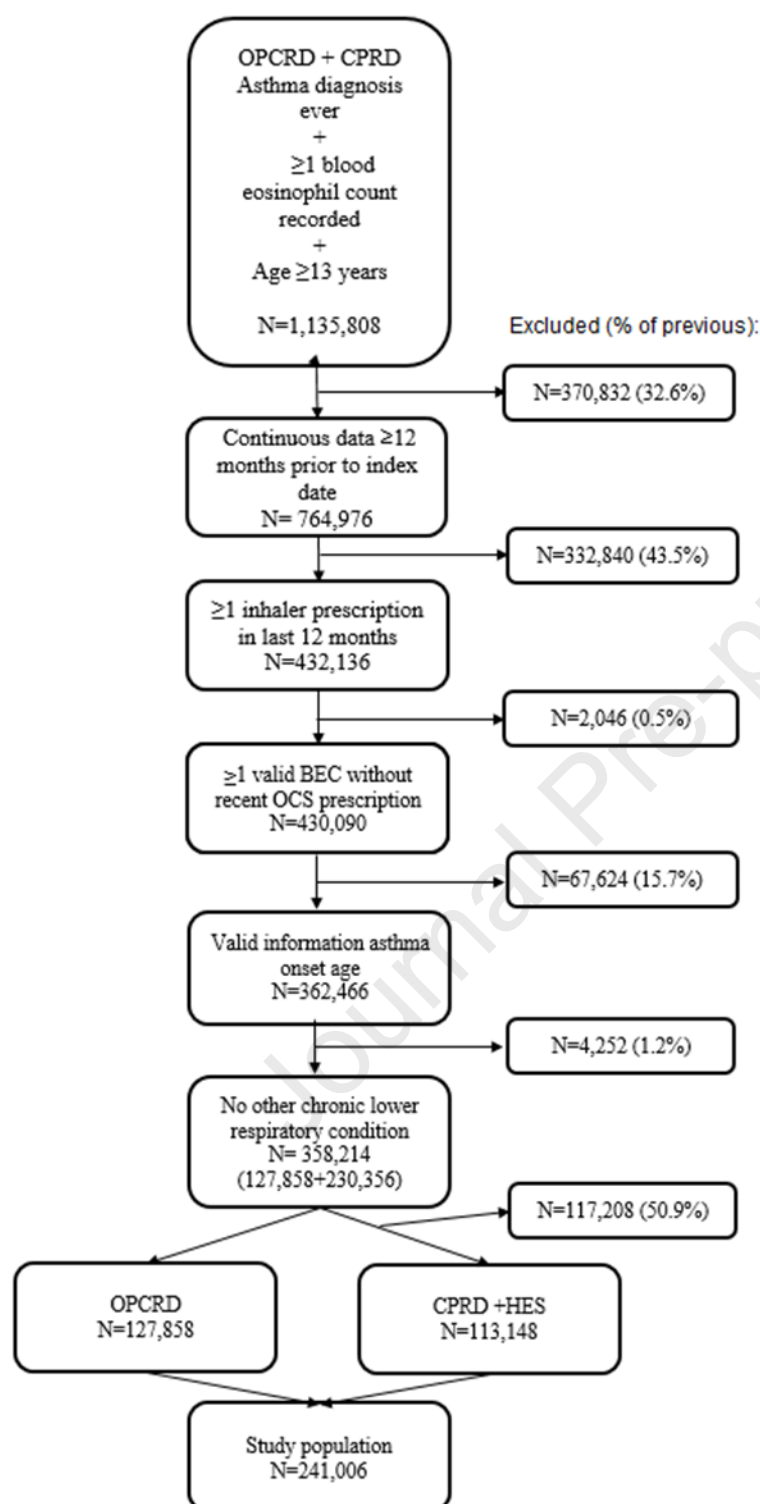
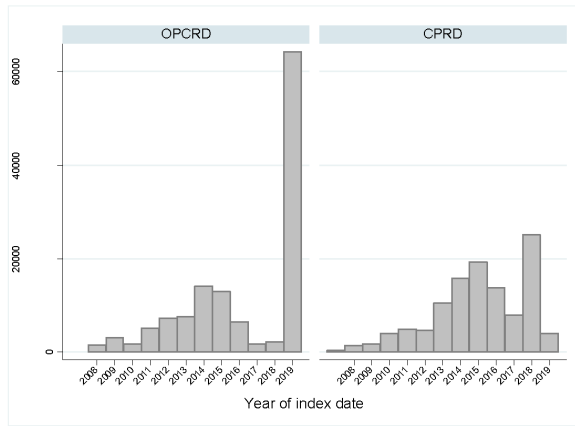
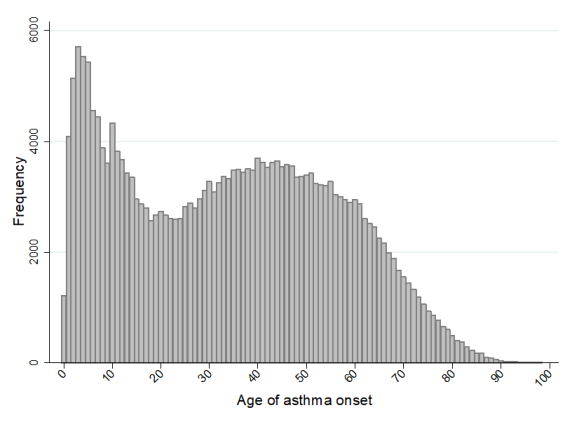


Figure E2: Number of patients included by year and data source (n=241006)



OPCRD: Optimum Patient Care Research Database; CPRD: Clinical Practice Research Datalink

Figure E3 Frequency distribution of age of onset of the study population (OPCRD + CPRD
n=241,006)



OPCRD: Optimum Patient Care Research Database; CPRD: Clinical Practice Research Datalink

Online Repository Text

Eosinophilic asthma phenotypes and associated clinical outcomes in a primary care cohort from the UK

The following demographic and clinical variables were described:

Demographics

1. Age at ID, years, mean (standard deviation (SD)), median (interquartile range (IQR)) and categorized as:
 - a. 13– 17
 - b. 18 – 64
 - c. ≥65, n (%)
2. Sex, male n (%)
3. Smoking Status, closest prior to and including ID within 5 years, n (%)
 - a. Current smokers
 - b. Former smokers
 - c. Never smokers
4. Body Mass Index (BMI), kg/m², closest prior to and including ID within 5 years, mean (SD) and mean (IQR), and categorized as:
 - a. Underweight, <18.5
 - b. Normal Weight, ≥18.5 and <25
 - c. Overweight, ≥25 and <30
 - d. Obese, ≥30

Comorbidities

At least one diagnostic read code prior to and including ID, n (%) for:

1. Eczema
 - a. Never
 - b. Active^a
 - c. Ever, not active
2. Rhinitis
 - a. Never
 - b. Active^a
 - c. Ever, not active
3. Urticaria (ever/never)
4. Food allergy (ever/never)
5. Anaphylaxis
6. Aspirin sensitivity
7. Chronic sinusitis
 - a. No
 - b. Yes, without nasal polyps
 - c. Yes, with nasal polyps
8. Chronic Obstructive Pulmonary Disease (COPD) (ever/never)

^a 'Active' refers to those for which a diagnosis or active treatment was recorded in the baseline year. 'Ever' refers to diagnostic Read code at any time before or during the baseline period

9. Gastroesophageal reflux disease (GERD) (ever/never)
10. Diabetes Mellitus (ever/never)
11. Osteoporosis (ever/never)
12. Hypertension (ever/never)
13. Cardiovascular disease (ever/never):
 - a. Any
 - b. Ischaemic heart disease
 - c. Heart failure
 - d. Myocardial infarction
14. Chronic kidney disease (ever/never), stage 3-5
15. Depression/anxiety (ever/never)
16. Obstructive Sleep apnoea (ever/never)
17. Pneumonia (ever/never)
18. Charlson co-morbidity index ^{E1,E2}: based on diagnoses (ever/never), categorized as:
 - a. ≤ 1
 - b. 2-3
 - c. ≥ 4

Clinical characteristics of asthma

Asthma therapy

The following variables will be described over the last year of EMR data (objectives 1-3) or the last year prior to the last BEC recording (objective 4), unless otherwise specified:

1. GINA steps of asthma management. Results will be presented for both the 2018 definition applied in ISAR³ and the latest definition (2019),⁴ based on the most recent treatment prescribed.
 - The 2018 definition:^{E3}
 - Step 1:
 - Step 2:
 - Step 3:
 - Step 4
 - Step 5
 - The 2019 definition:^{E4}
 - Step 1: As-needed low-dose inhaled corticosteroids (ICS)-formoterol (only 1 inhaler prescribed over baseline year with “as-needed” dosing instructions^b) OR short-acting bronchodilators prescribed only
 - Step 2: Maintenance low-dose ICS monotherapy OR “as needed” low dose ICS-formoterol (≥ 2 inhalers in baseline year with “as-needed” dosing instructions^b) OR Leukotriene receptor antagonist (LTRA) monotherapy
 - Step 3: Maintenance low-dose ICS/Long-acting $\beta 2$ -agonist (LABA) OR maintenance medium-dose ICS monotherapy OR low-dose ICS+LTRA
 - Step 4: Maintenance medium-dose ICS/LABA OR high-dose ICS monotherapy OR low-dose ICS/LABA+(Long-acting muscarinic antagonist (LAMA) and/or LTRA and/or theophylline)
 - Step 5: Maintenance high-dose ICS/LABA OR medium-dose ICS+(LAMA or LTRA or theophylline) OR maintenance OCS OR biologics

^b Assuming symptoms less than twice a month

2. Asthma management, based on the most recent prescription of ICS containing inhaler in baseline year
 - No ICS
 - Low-dose ICS monotherapy
 - Low-dose maintenance ICS-LABA, fixed-dose combination (FDC)
 - Medium-dose ICS monotherapy
 - Medium-dose ICS-LABA, FDC
 - High-dose ICS monotherapy
 - High-dose ICS-LABA, FDC
 - A triple inhaler, ICS-LABA-LAMA, FDC
3. Mean daily dose^c of ICS prescribed in the baseline year, fluticasone propionate equivalent in µg/day, as continuous variable and categorised as no ICS, >0 <100, 100-200, >200-500, >500 µg/day
4. ICS, ICS-LABA or triple therapy adherence, measured as:
 - ICS possession ratio, measured as days of supply during the baseline year^d, categorized as <50%, 50-69%, 70-79%, ≥80%
 - The number of inhalers dispensed for 30 days in the baseline year (0, 1-3, 3-5, ≥9 (yes/no))
5. Mean daily dose^c of short-acting reliever medication in the baseline year, short-acting β₂-agonist (SABA) equivalent in µg/day, as continuous variable and categorised as no SABA, 1-100, >100-200, >200-300, >300-400, >400 µg/day
6. Mean daily dose of oral corticosteroids prescribed in the baseline year, prednisolone equivalent in mg/day, as continuous variable and categorised as no OCS, >0<2.5, ≥2.5 <5, ≥5<7.5, ≥7.5 mg/day
7. Any prescription of treatment for (yes/no):
 - a. Short-acting muscarinic antagonist (SAMA) mono-inhaler
 - b. LAMA mono-inhaler
 - c. LABA mono-inhaler
 - d. Theophylline
 - e. LTRA
 - f. Cromones (Sodium cromoglycate or nedocromil sodium)
 - g. Anti-Immunoglobulin (IgE) treatment (Omalizumab (Xolair®))^e
 - h. Anti-IL-5 treatment
 - i. Mepolizumab (Nucala®)
 - ii. Reslizumab (Cinqaro®)
 - iii. Benralizumab (Fasenra®)
 - i. Anti-Interleukin (IL)-4 treatment (Dupilumab (Dupixent®))^f

^c Mean daily dose calculated as: (number of inhalers prescribed in baseline year prior to ID * doses in pack) / 365) * mcg strength)

^d ICS possession ratio = $\sum(\text{number of inhalers per prescription covering the baseline year} * \text{doses per inhaler} / \text{daily dosage}) / 365$

^e Date of first authorisation: 25 October 2005

^f Date of first authorisation: 26 September 2017

Asthma exacerbations and symptom control

The following measures of events are reported as mean number in the baseline year and categorised as 0, 1, 2, 3, ≥ 4

1. Asthma exacerbations, defined as previously described by the American Thoracic Society / European Respiratory Society definition,^{E5} as the occurrence of any of the following events^g:
 - a. Asthma-related hospitalisation or attendance at an accident and emergency department (A&E)^h AND/OR
 - b. Prescription for acute oral corticosteroids
2. Acute oral corticosteroid courses
3. Antibiotics courses in conjunction with an asthma-related primary care consultation, number
4. Acute respiratory events^g, defined as:
 - a. Asthma-related hospitalisation or attendance at an accident and emergency department (A&E)^h AND/OR
 - b. Prescription for acute oral corticosteroids AND/OR
 - c. Prescription for antibiotics in conjunction with an asthma-related primary care consultation

The following measures of asthma control were reported:

5. Asthma symptom control score, ranging from 0 to 3, calculated as the number of “yes-answers” to the following three individual Royal College of Physicians (RCP3) questions for asthmaⁱ recorded within 15 months.^{E6}

In the last month:

 - a. “Have you had difficulty sleeping because of your asthma (including cough)?”
 - b. “Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?”
 - c. “Has your asthma interfered with your usual activities (e.g. housework, work, school, etc.)?”
6. Poor symptom control, yes/no, defined as 3 out of 4 of the following:
 - a. “Yes” to three Royal College of Physicians Questions for asthma.^{E6}
 - b. >2 puffs of SABA prescribed per week on average over baseline year
7. Difficult-to-treat asthma
8. Peak Expiratory Flow (PEF), closest prior to ID within 5 years, reported as %predicted and reported as mean (SD) and categorized as $<50\%$, $50-69\%$, $70-79\%$, $\geq 80\%$
9. Forced Expiratory Flow in one second (FEV₁), closest prior to ID within 5 years, expressed as %predicted and reported as mean (SD) and categorized as $<30\%$, $30-49\%$, $50-79\%$, $\geq 80\%$

^g Events occurring within 14 days of each other are considered to belong to the same exacerbation and counted once

^h Asthma-Related Hospitalisations: consists of either a definite Asthma Emergency Attendance or a definite Asthma Hospital Admission; OR a generic hospitalisation Read code or Medcode which has been recorded on the same day as a Lower Respiratory Consultation.

ⁱ RCP3 questions are routinely recorded during annual asthma review within QOF framework

The following measures of asthma burden and healthcare resource utilisation (HCRU) were described over the last year of EMR data for the CPRD with linked HES data

Number of events occurring in one year are described as mean numbers ($\pm$ SD) and as categorical variables (0, 1, 2, 3, ≥ 4).

Asthma exacerbations and acute respiratory events

1. Asthma exacerbations, defined as previously described by the American Thoracic Society / European Respiratory Society definition,^{E7} as the occurrence of any of the following events^j:
 - a. Hospitalization with asthma as the primary diagnosis^k AND/OR
 - b. Respiratory-related Accident and Emergency department (A&E)^l AND/OR
 - c. Prescription for acute oral corticosteroids
 - d. EMR recording of an acute exacerbation
2. Acute respiratory events, defined as the occurrence of any of the following events:
 - a. Hospitalization with asthma as the primary diagnosis AND/OR
 - b. Respiratory-related Accident and Emergency department (A&E) AND/OR
 - c. Prescription for acute oral corticosteroids AND/OR
 - d. EMR recording of an acute exacerbation AND/OR
 - e. Prescription for antibiotics in conjunction with an asthma-related primary care consultation

Asthma control

The following measures will be used to describe the presence (yes/no) of asthma control:

1. Risk Domain Asthma Control (RDAC), defined as the absence of all of the following events:
 - a. Acute respiratory event (as defined above) AND
 - b. Recording of respiratory-related outpatient visit
2. Overall Asthma Control (OAC), defined as:
 - a. Attainment of RDAC AND
 - b. Average daily dose of ≤ 200 μ g salbutamol / ≤ 500 μ g terbutaline
3. Full asthma control, defined as absence of all of the following in the baseline year:
 - c. ≥ 2 oral corticosteroids courses prescribed AND
 - d. Hospitalization with respiratory disease as the primary diagnosis AND
 - e. Respiratory-related Accident and Emergency department (A&E) AND
 - f. Poor symptom control, yes/no, defined as 3 out of 4 of the following:
 - i. "Yes" to three Royal College of Physicians Questions for asthma.^{E6}
 - ii. > 2 puffs of SABA prescribed per week on average over baseline year

^j Events occurring within 14 days of each other are considered to belong to the same exacerbation and counted once

^k ICD-10 J45/J46 as primary diagnosis of any finished consultant episode;

^l HES variables DIAG2 = 25 (Respiratory conditions) or DIAG = 'AST%' or DIAG2 = 'J4%' or followed by hospital admission with respiratory condition as primary diagnosis (4.2% of A&E attendances)

The three Royal College of Physicians (RCP3) questions for asthma questions for asthma^m, most recent recording within 15 months:^{E6}

In the last month:

- a. "Have you had difficulty sleeping because of your asthma (including cough)?"
- b. "Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?"
- c. "Has your asthma interfered with your usual activities (e.g. housework, work, school, etc.)?"

HCRU variables

1. Physician office visits, categorized as 0, 1-4, 5-8, 9-11, 12-24, ≥25:
 - a. General Practitioner (GP) consultations, all-cause
 - b. Respiratory-related GP consultations
2. Outpatient visits:
 - a. Referrals to specialist, all-cause
 - b. Referrals for asthma or other lower respiratory conditions
3. A&E attendances:
 - a. All-cause,
 - b. Respiratory-relatedⁿ
4. Hospital attendances, number of spells, *including day cases*:
 - a. All-cause
 - b. Asthma (ICD-10 J45/J46) as primary diagnosis
 - c. Asthma (ICD-10 J45/J46) at any diagnostic position
 - d. Respiratory conditions (ICD-10 J00-J99) as primary diagnosis
5. Hospital attendances, number of spells, *excluding day cases*:
 - a. All-cause
 - b. Asthma (ICD-10 J45/J46) as primary diagnosis
 - c. Asthma (ICD-10 J45/J46) at any diagnostic position
 - d. Respiratory conditions (ICD-10 J00-J99) as primary diagnosis
6. Hospital attendance, length of stay, *overall*: cumulative number of days per patient (including values of zero for patients not admitted to hospital)
 - a. All-cause
 - b. Asthma (ICD-10 J45/J46) as primary diagnosis
 - c. Asthma (ICD-10 J45/J46) at any diagnostic position
 - d. Respiratory conditions (ICD-10 J00-J99) as primary diagnosis
7. Hospital attendances, length of stay, *≥1 overnight*: cumulative number of days per patient, only reported for patients who remained overnight
 - a. All-cause
 - b. Asthma (ICD-10 J45/J46) as primary diagnosis
 - c. Asthma (ICD-10 J45/J46) at any diagnostic position
 - d. Respiratory conditions (ICD-10 J00-J99) as primary diagnosis
8. Day cases, number of spells (discharge date = admission date):
 - a. All-cause
 - b. Asthma (ICD-10 J45/J46) as primary diagnosis
 - c. Asthma (ICD-10 J45/J46) at any diagnostic position

^m RCP3 questions are routinely recorded during annual asthma review within QOF framework

ⁿ HES variables DIAG2 = 25 (Respiratory conditions) or DIAG = 'AST%' or DIAG2 = 'J4%' or followed by hospital admission with respiratory condition as primary diagnosis (4.2% of A&E attendances)

- d. Respiratory conditions (ICD-10 J00-J99) as primary diagnosis

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Table E1: calculation the standard mean difference (SMD) for continuous, binary and categorical data

Covariate type	Formula
Continuous	$SMD = 100 * \frac{(\bar{x}_t - \bar{x}_r)}{\sqrt{\frac{s_t^2 + s_r^2}{2}}},$ where $\bar{x}_t, \bar{x}_r$ denote the sample means and s_t, s_r the standard deviations
Binary	$SMD = 100 * \frac{(\hat{p}_t - \hat{p}_r)}{\sqrt{\frac{\hat{p}_t(1-\hat{p}_t) + \hat{p}_r(1-\hat{p}_r)}{2}}},$ where $\hat{p}_t, \hat{p}_r$ denote the proportion of patients in each category
Categorical (>2 categories)	$SMD = 100 * \sqrt{(T - C)' S^{-1} (T - C)}$ where S is a $(k - 1) \times (k - 1)$ covariance matrix: $S = [S_{kl}] = \begin{cases} \frac{\hat{p}_{1k}(1 - \hat{p}_{1k}) + \hat{p}_{2k}(1 - \hat{p}_{2k})}{2}, & k = l \\ \frac{\hat{p}_{1k}\hat{p}_{1l} + \hat{p}_{2k}\hat{p}_{2l}}{2}, & k \neq l \end{cases}$, $T = (\hat{p}_{12}, \dots, \hat{p}_{1k})'$, $C = (\hat{p}_{22}, \dots, \hat{p}_{2k})'$ and $\hat{p}_{jk} = P(\text{category } k \text{treatment arm } j)$, $j = 1, 2$, $k = 2, 3, \dots, k$

Table E2. Distribution of characteristics used to define eosinophilic phenotype grades (OPCRD + CPRD)

Variable		0 (N= 13,521)	1 (N= 52,741)	2 (N= 53,431)	3 (N= 121,313)	Total (N= 241,006)	P	SMD 0→3	SMD 1→ 3	SMD 2→ 3
Highest eosinophil count (cells/ μ L)	Mean (SD)	97.1 (29.6)	195.4 (76.4)	236.4 (50.7)	660.0 (889.5)	432.8 (673.3)	<0.0001	89.4	73.6	67.2
	Geometric mean (SD)	79.4 (2.0)	158.5 (1.6)	251.2 (1.3)	501.2 (1.6)	316.2 (2.0)	<0.0001	321.8	220.9	230.0
	Median (IQR)	100.0 (100.0;110.0)	200.0 (120.0;270.0)	220.0 (200.0;300.0)	500.0 (400.0;700.0)	300.0 (200.0;500.0)				
	<150, n (%)	13,521 (100.0)	15,840 (30.0)	477 (0.9)	0 (0.0)	29,838 (12.4)	<0.0001	2280.6	382.9	907.1
	150-300, n (%)	0 (0.0)	36,901 (70.0)	52,954 (99.1)	1,866 (1.5)	91,721 (38.1)				
Age of asthma onset	>300, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	119,447 (98.5)	119,447 (49.6)				
	Mean (SD)	13.0 (8.4)	24.3 (19.5)	49.9 (13.9)	34.2 (22.2)	34.3 (21.9)	<0.0001	126.5	47.5	84.7
	Median (IQR)	12.0 (5.0;20.0)	19.0 (8.0;36.0)	49.0 (39.0;60.0)	34.0 (13.0;52.0)	35.0 (14.0;52.0)				
	Childhood-onset (<18), n (%)	9,630 (71.2)	25,455 (48.3)	534 (1.0)	37,808 (31.2)	73,427 (30.5)	<0.0001	135.5	49.4	110.0
	Adult-onset(18-29), n (%)	3,891 (28.8)	11,446 (21.7)	289 (0.5)	14,824 (12.2)	30,450 (12.6)				
Maintenance OCS in baseline year	Late-onset ($\geq$ 30), n (%)	0 (0.0)	15,840 (30.0)	52,608 (98.5)	68,681 (56.6)	137,129 (56.9)				
	Yes, n (%)	<5	<5	97 (0.2)	1,446 (1.2)	1,543 (0.6)	<0.0001	15.5	15.5	12.3
Anti-IL5 therapy ever	Yes, n (%)	<5	<5	<5	12 (0.0)	12 (0.0)	0.0080	1.4	1.4	1.4
Nasal polyps	Ever, n (%)	<5	<5	1,043 (2.0)	9,089 (7.5)	10,132 (4.2)	<0.0001	40.2	40.2	26.3

P = P-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate

Grade 0: non-eosinophilic; Grade 1: least likely eosinophilic; Grade 2: likely eosinophilic; Grade 3 most likely eosinophilic (see Figure 1 for definition of eosinophil phenotype grades). CPRD: Clinical Practice Research Datalink; IL: interleukin; IQR: interquartile range; OCS: oral corticosteroid; OPCR: Optimum Patient Care Research Database; SD: standard deviation; SMD: standardized mean difference

Categorical variables: p-values were calculated using Pearson's chi-square tests of independent categories.

Continuous or ordinal variables: p-values were calculated using the non-parametric Kruskal-Wallis equality of populations rank test.

Table E3. Distribution of co-morbidities; age-standardised percentages with 95% confidence intervals: total population (OPCRD + CPRD; n=241,006)

Variable, % (95% CI)		0 (N= 13,521)	1 (N= 52,741)	2 (N= 53,431)	3 (N= 121,313)
Eczema	No	74.0 (72.6; 75.4)	73.1 (72.7; 73.5)	74.7 (73.4; 76.1)	68.2 (67.9; 68.4)
	Yes	20.2 (18.9; 21.4)	20.2 (19.8; 20.6)	17.8 (16.6; 18.9)	21.8 (21.6; 22.0)
	Yes, active	5.9 (5.1; 6.6)	6.7 (6.5; 6.9)	7.5 (6.5; 8.5)	10.1 (9.9; 10.2)
Allergic rhinitis	No	67.5 (66.2; 68.9)	67.9 (67.5; 68.3)	66.8 (65.4; 68.2)	61.7 (61.5; 62.0)
	Yes	26.7 (25.4; 28.0)	26.3 (26.0; 26.7)	26.0 (24.6; 27.5)	30.9 (30.6; 31.2)
	Yes	5.7 (5.0; 6.5)	5.8 (5.6; 6.0)	7.2 (6.2; 8.2)	7.4 (7.2; 7.5)
Urticaria	Ever	6.5 (5.8; 7.2)	7.5 (7.2; 7.7)	8.3 (7.5; 9.1)	9.7 (9.5; 9.9)
Food allergy	Ever	2.8 (2.4; 3.3)	2.6 (2.5; 2.7)	1.6 (1.3; 2.0)	3.5 (3.4; 3.6)
Anaphylaxis	Ever	0.7 (0.4; 0.9)	0.6 (0.5; 0.6)	0.4 (0.3; 0.4)	0.8 (0.8; 0.9)
Aspirin sensitivity	Ever	1.0 (0.5; 1.5)	0.9 (0.8; 1.0)	1.0 (0.9; 1.1)	1.2 (1.2; 1.3)
Chronic rhinosinusitis	No	92.3 (91.5; 93.1)	91.1 (90.8; 91.3)	87.4 (86.2; 88.5)	86.7 (86.5; 86.9)
	Yes, without nasal polyps	7.7 (6.9; 8.5)	8.9 (8.7; 9.2)	9.1 (8.8; 9.4)	10.6 (10.4; 10.7)
	Yes, with nasal polyps	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	3.6 (2.4; 4.7)	2.7 (2.7; 2.8)
COPD	Ever	5.7 (4.7; 6.8)	6.7 (6.4; 6.9)	8.1 (7.9; 8.3)	8.0 (7.9; 8.1)
GERD	Ever	14.0 (12.8; 15.1)	16.6 (16.2; 16.9)	18.7 (17.9; 19.4)	18.6 (18.4; 18.8)
Diabetes Mellitus	Ever	4.7 (3.9; 5.5)	7.6 (7.3; 7.8)	10.4 (10.1; 10.6)	12.9 (12.7; 13.1)
Osteoporosis	Ever	4.5 (3.5; 5.6)	3.9 (3.7; 4.2)	4.0 (3.9; 4.2)	4.2 (4.1; 4.3)
Hypertension	Ever	22.1 (20.5; 23.6)	25.4 (25.0; 25.8)	29.3 (29.0; 29.6)	29.8 (29.6; 30.0)
Cardiovascular disease	Ever	11.7 (10.4; 13.1)	14.3 (14.0; 14.7)	17.0 (16.5; 17.6)	17.9 (17.7; 18.1)
Ischaemic heart disease	Ever	3.5 (2.7; 4.4)	5.4 (5.1; 5.6)	7.2 (7.1; 7.4)	8.3 (8.1; 8.4)
Heart failure	Ever	0.6 (0.1; 1.1)	1.3 (1.2; 1.5)	1.7 (1.6; 1.7)	2.0 (1.9; 2.1)
Myocardial infarction	Ever	1.4 (0.9; 2.0)	1.9 (1.8; 2.1)	2.7 (2.6; 2.8)	3.6 (3.5; 3.7)
Chronic kidney disease, stage 3-5	Ever	3.4 (2.5; 4.3)	5.0 (4.7; 5.2)	6.7 (6.4; 7.0)	7.7 (7.6; 7.8)
Anxiety / Depression	Ever	38.6 (37.1; 40.1)	44.1 (43.7; 44.6)	46.8 (45.5; 48.2)	45.1 (44.9; 45.4)

Variable, % (95% CI)		0 (N= 13,521)	1 (N= 52,741)	2 (N= 53,431)	3 (N= 121,313)
Apnea	Ever	0.7 (0.5; 0.9)	1.2 (1.1; 1.3)	1.6 (1.3; 1.9)	1.8 (1.7; 1.8)
Pneumonia diagnosis	Ever	5.2 (4.4; 6.0)	4.8 (4.6; 5.0)	4.9 (4.4; 5.3)	5.9 (5.8; 6.0)
Charlson Comorbidity Index	0-1	81.2 (79.7; 82.7)	78.6 (78.2; 79.0)	75.0 (74.6; 75.4)	72.5 (72.3; 72.7)
	2-4	15.2 (13.8; 16.7)	16.5 (16.1; 16.8)	18.4 (18.0; 18.8)	19.7 (19.5; 19.9)
	≥4	3.5 (2.7; 4.4)	4.9 (4.7; 5.2)	6.6 (6.4; 6.8)	7.8 (7.7; 8.0)

Grade 0: non-eosinophilic; Grade 1: least likely eosinophilic; Grade 2: likely eosinophilic; Grade 3 most likely eosinophilic (see Figure 1 for definition of eosinophil phenotype grades). CI: confidence interval; COPD: chronic obstructive pulmonary disease; CPRD: Clinical Practice Research Datalink; GERD: gastroesophageal reflux disease; OPCR: Optimum Patient Care Research Database

Categorical variables: p-values were calculated using Pearson's chi-square tests of independent categories.

Continuous or ordinal variables: p-values were calculated using the non-parametric Kruskal-Wallis equality of populations rank test.

Table E4: Distribution of asthma control and lung function variables; age-standardised percentages with 95% confidence intervals: total population (OPCRD + CPRD; n=241,006)

Variable	0 (N= 13,521)	1 (N= 52,741)	2 (N= 53,431)	3 (N= 121,313)
Asthma exacerbations				
Mean (95% CI)	0.31 (0.28; 0.35)	0.35 (0.34; 0.36)	0.42 (0.40; 0.45)	0.54 (0.53; 0.55)
0, % (95% CI)	82.8 (81.6; 84.1)	81.0 (80.6; 81.3)	77.4 (76.2; 78.5)	75.2 (75.0; 75.5)
1, % (95% CI)	10.6 (9.7; 11.5)	12.6 (12.3; 12.9)	14.3 (13.3; 15.3)	14.3 (14.1; 14.5)
2, % (95% CI)	3.6 (2.9; 4.3)	3.3 (3.2; 3.5)	4.2 (3.6; 4.7)	4.7 (4.6; 4.8)
3, % (95% CI)	1.3 (0.9; 1.8)	1.3 (1.2; 1.4)	1.8 (1.5; 2.2)	2.1 (2.0; 2.2)
≥4, % (95% CI)	1.6 (1.1; 2.1)	1.8 (1.7; 1.9)	2.3 (2.0; 2.6)	3.7 (3.6; 3.8)
Acute oral corticosteroids courses				
Mean (95% CI)	0.29 (0.25; 0.32)	0.31 (0.30; 0.32)	0.38 (0.36; 0.40)	0.48 (0.47; 0.49)
0, % (95% CI)	84.2 (83.0; 85.4)	82.7 (82.3; 83.0)	79.1 (77.9; 80.2)	77.3 (77.1; 77.5)
1, % (95% CI)	10.0 (9.1; 10.9)	11.5 (11.2; 11.8)	13.4 (12.4; 14.5)	13.3 (13.1; 13.5)
2, % (95% CI)	3.2 (2.5; 3.8)	3.0 (2.9; 3.2)	3.8 (3.3; 4.3)	4.3 (4.2; 4.4)
3, % (95% CI)	1.3 (0.9; 1.7)	1.2 (1.1; 1.3)	1.7 (1.3; 2.0)	1.9 (1.8; 2.0)
≥4, % (95% CI)	1.4 (0.9; 1.8)	1.6 (1.4; 1.7)	2.0 (1.7; 2.3)	3.2 (3.1; 3.3)
Antibiotic courses				
Mean (95% CI)	0.29 (0.27; 0.32)	0.33 (0.33; 0.34)	0.38 (0.36; 0.39)	0.38 (0.38; 0.39)
0, % (95% CI)	79.9 (78.6; 81.3)	77.5 (77.1; 77.9)	75.1 (73.9; 76.3)	75.7 (75.5; 76.0)
1, % (95% CI)	14.1 (12.9; 15.2)	15.8 (15.5; 16.1)	17.1 (16.0; 18.2)	16.1 (15.9; 16.3)
2, % (95% CI)	4.1 (3.4; 4.8)	4.3 (4.1; 4.5)	5.0 (4.5; 5.5)	5.0 (4.8; 5.1)
3, % (95% CI)	1.1 (0.7; 1.4)	1.4 (1.3; 1.6)	1.6 (1.5; 1.7)	1.8 (1.7; 1.9)
≥4, % (95% CI)	0.8 (0.5; 1.2)	1.0 (0.9; 1.1)	1.2 (1.1; 1.3)	1.4 (1.4; 1.5)
Acute lower respiratory events				
Mean (95% CI)	0.36 (0.32; 0.39)	0.39 (0.38; 0.40)	0.47 (0.44; 0.49)	0.54 (0.53; 0.54)
0, % (95% CI)	77.5 (76.1; 78.9)	74.8 (74.4; 75.2)	71.5 (70.2; 72.7)	70.8 (70.6; 71.1)

Variable	0 (N= 13,521)	1 (N= 52,741)	2 (N= 53,431)	3 (N= 121,313)
1, % (95% CI)	15.5 (14.3; 16.6)	17.9 (17.5; 18.2)	19.1 (18.0; 20.2)	18.5 (18.2; 18.7)
2, % (95% CI)	4.5 (3.7; 5.2)	4.5 (4.3; 4.7)	5.6 (5.0; 6.3)	5.7 (5.5; 5.8)
3, % (95% CI)	1.2 (0.9; 1.6)	1.5 (1.4; 1.6)	1.9 (1.6; 2.1)	2.2 (2.1; 2.3)
≥4, % (95% CI)	1.3 (0.9; 1.8)	1.3 (1.2; 1.4)	1.9 (1.6; 2.2)	2.8 (2.7; 2.9)
RCP3 score				
0, % (95% CI)	32.0 (29.9; 34.1)	29.6 (29.0; 30.2)	27.4 (25.9; 28.9)	28.4 (28.1; 28.8)
1, % (95% CI)	39.7 (37.6; 41.8)	40.3 (39.7; 41.0)	41.3 (39.6; 42.9)	39.7 (39.4; 40.1)
2, % (95% CI)	20.8 (19.1; 22.6)	21.8 (21.3; 22.3)	22.5 (21.1; 23.9)	22.2 (21.9; 22.5)
3, % (95% CI)	7.5 (6.3; 8.6)	8.2 (7.9; 8.6)	8.8 (8.3; 9.3)	9.6 (9.4; 9.8)
Poor symptom control				
Yes, % (95% CI)	25.4 (23.6; 27.3)	27.2 (26.6; 27.7)	27.7 (26.5; 29.0)	29.2 (28.8; 29.5)
Difficult-to-treat asthma, GINA 2020				
Yes, % (95% CI)	23.0 (21.0; 25.0)	24.6 (24.0; 25.1)	26.9 (25.8; 28.0)	31.1 (30.7; 31.4)
FEV ₁ % predicted				
Mean (95% CI)	82.3 (80.7; 83.9)	85.2 (84.8; 85.7)	85.4 (83.8; 86.9)	82.9 (82.6; 83.2)
Peak Expiratory Flow (PEF) % predicted				
Mean (95% CI)	82.6 (81.8; 83.3)	83.8 (83.6; 84.0)	83.8 (83.2; 84.3)	82.2 (82.1; 82.3)

Grade 0: non-eosinophilic; Grade 1: least likely eosinophilic; Grade 2: likely eosinophilic; Grade 3 most likely eosinophilic (see Figure 1 for definition of eosinophil phenotype grades). CI: confidence interval; CPRD: Clinical Practice Research Datalink; FEV₁: forced expiratory volume in one second; GINA: Global Initiative for Asthma; OPCR: Optimum Patient Care Research Database; RCP: Royal College of Physicians

Categorical variables: p-values were calculated using Pearson's chi-square tests of independent categories.

Continuous or ordinal variables: p-values were calculated using the non-parametric Kruskal-Wallis equality of populations rank test.

Table E5: Distribution of asthma therapy; age-standardised percentages with 95% confidence intervals: total population (OPCRD + CPRD; n=241,006)

Variable		0 (N= 13,521)	1 (N= 52,741)	2 (N= 53,431)	3 (N= 121,313)
GINA step of asthma management (2020), % (95% CI)	1	14.8 (13.8; 15.8)	13.2 (12.9; 13.5)	10.7 (9.6; 11.9)	9.8 (9.6; 10.0)
	2	33.3 (31.8; 34.8)	32.0 (31.5; 32.4)	31.3 (29.9; 32.7)	28.2 (28.0; 28.5)
	3	17.8 (16.5; 19.0)	17.9 (17.5; 18.3)	18.0 (17.0; 19.1)	17.8 (17.6; 18.0)
	4	21.5 (20.1; 22.9)	22.9 (22.5; 23.3)	24.0 (22.8; 25.2)	25.2 (24.9; 25.4)
	5	12.7 (11.4; 13.9)	14.0 (13.7; 14.4)	15.9 (15.2; 16.7)	19.0 (18.8; 19.2)
Last ICS management step, % (95% CI)	No ICS	15.1 (14.1; 16.2)	13.8 (13.5; 14.1)	11.5 (10.4; 12.7)	10.4 (10.2; 10.5)
	Low dose ICS monotherapy	35.2 (33.7; 36.8)	33.6 (33.2; 34.0)	32.7 (31.3; 34.1)	30.0 (29.8; 30.3)
	Low dose ICS/LABA	9.4 (8.5; 10.4)	9.4 (9.2; 9.7)	10.1 (9.1; 11.2)	10.5 (10.3; 10.7)
	Medium ICS monotherapy	9.1 (8.1; 10.2)	8.7 (8.4; 9.0)	8.9 (8.2; 9.6)	8.0 (7.8; 8.1)
	Medium dose ICS/LABA	23.3 (21.9; 24.8)	25.3 (24.9; 25.7)	26.4 (25.4; 27.5)	28.8 (28.5; 29.0)
	High dose ICS monotherapy	0.5 (0.3; 0.7)	0.5 (0.5; 0.6)	0.5 (0.4; 0.6)	0.8 (0.7; 0.8)
	High dose ICS/LABA	7.1 (6.2; 7.9)	8.4 (8.1; 8.7)	9.5 (8.9; 10.1)	11.2 (11.0; 11.4)
ICS, mean daily dose FP equivalent (mcg)	Triple therapy inhaler	0.2 (0.0; 0.4)	0.2 (0.2; 0.3)	0.3 (0.3; 0.3)	0.4 (0.3; 0.4)
	Mean (95% CI)	240 (229; 250)	249 (246; 252)	252 (247; 258)	274 (272; 275)
	0, % (95% CI)	15.1 (14.1; 16.2)	13.8 (13.5; 14.1)	11.5 (10.4; 12.7)	10.4 (10.2; 10.5)
	>0; <100, % (95% CI)	27.3 (26.0; 28.6)	25.6 (25.2; 26.0)	26.8 (25.4; 28.2)	24.6 (24.4; 24.9)
	100-200, % (95% CI)	17.9 (16.7; 19.1)	19.4 (19.0; 19.8)	20.4 (19.3; 21.5)	20.0 (19.7; 20.2)
	>200-500, % (95% CI)	25.9 (24.5; 27.4)	27.6 (27.2; 28.0)	27.6 (26.7; 28.5)	29.7 (29.5; 30.0)
ICS Possession Ratio baseline year (%)	>500, % (95% CI)	13.7 (12.4; 15.1)	13.6 (13.3; 13.9)	13.7 (13.1; 14.3)	15.3 (15.1; 15.5)
	Mean (95% CI)	70.0 (68.1; 71.9)	70.0 (69.4; 70.5)	68.2 (67.0; 69.4)	69.2 (68.9; 69.6)
	<50, % (95% CI)	42.2 (40.6; 43.9)	41.9 (41.5; 42.4)	43.3 (42.0; 44.7)	41.5 (41.2; 41.7)
	50-69, % (95% CI)	13.9 (12.7; 15.1)	14.8 (14.4; 15.1)	14.8 (13.9; 15.8)	15.6 (15.3; 15.8)
	70-79, % (95% CI)	6.1 (5.2; 7.0)	6.3 (6.0; 6.5)	6.2 (5.4; 6.9)	6.6 (6.4; 6.7)
	≥80, % (95% CI)	37.8 (36.0; 39.6)	37.0 (36.5; 37.5)	35.6 (34.7; 36.6)	36.4 (36.1; 36.7)
Mean (95% CI)		7 (7; 7)	7 (7; 7)	7 (7; 7)	7 (7; 7)

Variable		0 (N= 13,521)	1 (N= 52,741)	2 (N= 53,431)	3 (N= 121,313)
Number of ICS	0, % (95% CI)	9.1 (8.3; 10.0)	8.4 (8.1; 8.6)	6.7 (5.8; 7.6)	6.1 (5.9; 6.2)
inhalers of 30 days	1-3, % (95% CI)	23.7 (22.5; 24.8)	23.3 (22.9; 23.7)	24.0 (22.7; 25.4)	22.9 (22.7; 23.2)
dispensed in baseline	4-6, % (95% CI)	17.7 (16.5; 19.0)	18.5 (18.1; 18.8)	20.3 (19.1; 21.5)	20.2 (20.0; 20.4)
year	7-9, % (95% CI)	12.7 (11.6; 13.8)	13.8 (13.5; 14.2)	14.1 (13.2; 15.0)	15.3 (15.1; 15.5)
	>9, % (95% CI)	30.8 (29.2; 32.4)	30.6 (30.2; 31.0)	30.1 (29.3; 30.9)	31.2 (30.9; 31.4)
SABA, mean daily	Mean (95% CI)	257 (236; 279)	244 (240; 248)	234 (228; 240)	283 (280; 286)
dose salbutamol	0, % (95% CI)	15.1 (14.0; 16.2)	15.9 (15.6; 16.3)	16.5 (15.7; 17.4)	15.7 (15.5; 15.9)
equivalent(mcg)	1-100, % (95% CI)	21.8 (20.6; 23.0)	20.6 (20.2; 20.9)	20.3 (19.0; 21.6)	17.1 (16.9; 17.3)
	101-200, % (95% CI)	24.4 (23.0; 25.7)	24.1 (23.7; 24.5)	24.2 (22.9; 25.5)	22.6 (22.4; 22.8)
	201-300, % (95% CI)	11.4 (10.4; 12.4)	12.8 (12.5; 13.1)	13.4 (12.2; 14.5)	13.1 (12.9; 13.3)
	301-400, % (95% CI)	8.1 (7.1; 9.1)	7.9 (7.7; 8.2)	8.1 (7.4; 8.8)	8.7 (8.5; 8.9)
	>400, % (95% CI)	19.2 (17.8; 20.6)	18.8 (18.4; 19.1)	17.5 (16.7; 18.2)	22.8 (22.6; 23.0)
OCS, mean daily dose	Mean (95% CI)	0.22 (0.19; 0.26)	0.25 (0.24; 0.27)	0.31 (0.28; 0.33)	0.43 (0.42; 0.44)
(mg)	0, % (95% CI)	83.2 (82.0; 84.5)	81.5 (81.1; 81.8)	77.9 (76.7; 79.0)	75.5 (75.3; 75.8)
	>0 <2.5, % (95% CI)	15.0 (13.9; 16.2)	16.7 (16.3; 17.0)	19.7 (18.5; 20.8)	20.4 (20.1; 20.6)
	≥2.5 <5, % (95% CI)	1.0 (0.6; 1.4)	1.1 (0.9; 1.2)	1.4 (1.2; 1.7)	2.3 (2.2; 2.4)
	≥5 <7.5, % (95% CI)	0.5 (0.2; 0.7)	0.3 (0.3; 0.4)	0.4 (0.4; 0.5)	0.9 (0.8; 0.9)
	≥7.5, % (95% CI)	0.3 (0.1; 0.4)	0.4 (0.4; 0.5)	0.6 (0.3; 0.9)	1.0 (0.9; 1.0)
SAMA prescribed in	≥1 prescription, % (95% CI)	1.2 (0.8; 1.6)	1.6 (1.5; 1.8)	1.6 (1.5; 1.7)	1.7 (1.6; 1.8)
last 12 months					
LAMA prescribed in	≥1 prescription, % (95% CI)	5.7 (4.7; 6.8)	5.3 (5.0; 5.5)	6.3 (6.0; 6.6)	6.6 (6.5; 6.8)
last 12 months					
LABA prescribed in	≥1 prescription, % (95% CI)	3.9 (3.2; 4.6)	3.3 (3.2; 3.5)	2.9 (2.7; 3.0)	3.2 (3.1; 3.3)
last 12 months					
Theophylline	≥1 prescription, % (95% CI)	1.5 (0.9; 2.0)	0.9 (0.8; 1.0)	0.9 (0.8; 1.0)	1.5 (1.4; 1.6)
prescribed in last 12					
months					

Variable		0 (N= 13,521)	1 (N= 52,741)	2 (N= 53,431)	3 (N= 121,313)
LTRA prescribed in last 12 months	≥1 prescription, % (95% CI)	6.6 (5.8; 7.4)	6.8 (6.6; 7.1)	8.1 (7.1; 9.1)	8.9 (8.7; 9.0)
Cromones prescribed in last 12 months	≥1 prescription, % (95% CI)	0.1 (0.0; 0.1)	0.0 (0.0; 0.1)	0.0 (0.0; 0.1)	0.0 (0.0; 0.0)
Biologics prescribed in last 12 months	≥1 prescription, % (95% CI)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Anti-IgE therapy ever	Yes, % (95% CI)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Anti-IL5 therapy ever	Yes, % (95% CI)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)
Anti-IL4 therapy ever	Yes, % (95% CI)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)

Grade 0: non-eosinophilic; Grade 1: least likely eosinophilic; Grade 2: likely eosinophilic; Grade 3 most likely eosinophilic (see Figure 1 for definition of eosinophil phenotype grades). CI: confidence interval; CPRD: Clinical Practice Research Database; FP: fluticasone propionate; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; IL: interleukin; LABA: long-acting β_2 -agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; OPCR: Optimum Patient Care Research Database; SABA: short-acting β_2 -agonist; SAMA: short-acting muscarinic antagonist

Categorical variables: p-values were calculated using Pearson's chi-square tests of independent categories.

Continuous or ordinal variables: p-values were calculated using the non-parametric Kruskal-Wallis equality of populations rank test.

Table E6: Demographic and clinical characteristics according to eosinophilic and non-eosinophilic phenotype in a subset of a primary care UK cohort with active asthma (OPCRD + CPRD) and a recent assessment of asthma control using the three RCP questions (n=137,969) – age standardised

Variable		0 (N= 6,878)	1 (N= 28,560)	2 (N= 31,295)	3 (N= 71,236)
Demographic characteristics					
Male	Yes, % (95% CI)	42.8 (40.6; 45.0)	35.3 (34.7; 35.9)	30.3 (28.9; 31.7)	39.1 (38.7; 39.5)
Age at last extraction date	Mean (SD)	37.5 (14.8)	48.2 (17.6)	64.8 (12.8)	55.3 (19.3)
	13-17, n (%)	540 (7.9)	961 (3.4)	13 (0.0)	2,459 (3.5)
	18-64, n (%)	6,003 (87.3)	21,982 (77.0)	15,113 (48.3)	43,082 (60.5)
	≥65, n (%)	335 (4.9)	5,617 (19.7)	16,169 (51.7)	25,695 (36.1)
Smoking status	Never smoker, % (95% CI)	47.0 (44.8; 49.2)	42.5 (41.9; 43.1)	41.4 (40.1; 42.8)	40.6 (40.3; 41.0)
	Current smoker, % (95% CI)	10.5 (9.5; 11.5)	13.5 (13.2; 13.9)	14.0 (12.9; 15.0)	13.4 (13.2; 13.7)
	Ex-smoker, % (95% CI)	42.5 (40.3; 44.7)	44.0 (43.3; 44.6)	44.6 (43.5; 45.7)	46.0 (45.6; 46.3)
BMI (kg/m ²)	Mean (95% CI)	27.4 (27.2; 27.6)	28.3 (28.2; 28.4)	29.1 (28.8; 29.3)	28.8 (28.7; 28.8)
	<18.5, % (95% CI)	2.3 (1.7; 3.0)	2.3 (2.1; 2.5)	2.6 (1.4; 3.8)	2.2 (2.1; 2.3)
	≥18.5 <25, % (95% CI)	32.9 (30.8; 35.1)	29.3 (28.7; 29.9)	25.2 (23.5; 26.8)	26.9 (26.6; 27.2)
	≥25 <30, % (95% CI)	37.3 (35.0; 39.6)	34.6 (34.0; 35.2)	33.1 (31.6; 34.6)	33.6 (33.2; 33.9)
	≥30, % (95% CI)	27.5 (25.5; 29.4)	33.8 (33.2; 34.4)	39.2 (38.0; 40.3)	37.3 (37.0; 37.7)
Age of asthma onset	Mean (SD)	13.0 (8.5)	24.9 (19.9)	50.3 (13.8)	35.1 (22.1)
	Childhood (<118 yrs), n (%)	4,898 (71.2)	13,549 (47.4)	307 (1.0)	21,096 (29.6)
	Adult (18-29 yrs), n (%)	1,980 (28.8)	6,054 (21.2)	175 (0.6)	8,300 (11.7)
	Late (≥30), n (%)	<5	8,957 (31.4)	30,813 (98.5)	41,840 (58.7)
Co-morbidities					
Eczema	Yes, % (95% CI)	20.0 (18.4; 21.7)	20.6 (20.1; 21.1)	18.2 (16.9; 19.5)	22.4 (22.1; 22.7)
	Yes, active, % (95% CI)	6.1 (5.0; 7.1)	7.1 (6.8; 7.4)	7.3 (6.2; 8.3)	10.3 (10.1; 10.6)
Allergic rhinitis	Yes, % (95% CI)	26.8 (25.1; 28.6)	26.4 (25.9; 27.0)	26.1 (24.4; 27.7)	31.1 (30.8; 31.5)
	Yes, active, % (95% CI)	5.8 (4.7; 6.8)	5.7 (5.4; 6.0)	7.1 (5.8; 8.3)	7.3 (7.1; 7.5)

Variable		0 (N= 6,878)	1 (N= 28,560)	2 (N= 31,295)	3 (N= 71,236)
Chronic rhinosinusitis, % (95% CI)	Yes, without nasal polyps	7.4 (6.3; 8.6)	8.6 (8.3; 9.0)	9.2 (8.8; 9.5)	10.7 (10.4; 10.9)
	Yes, with nasal polyps	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	3.3 (2.0; 4.7)	3.0 (2.9; 3.1)
Charlson Comorbidity Index	0-1, % (95% CI)	78.9 (76.9; 81.0)	77.1 (76.5; 77.6)	72.8 (72.3; 73.4)	70.3 (70.0; 70.6)
	2-4, % (95% CI)	16.9 (14.9; 18.9)	17.5 (17.0; 18.1)	19.9 (19.3; 20.4)	21.3 (21.0; 21.6)
	≥4, % (95% CI)	4.1 (2.9; 5.4)	5.4 (5.1; 5.7)	7.3 (7.0; 7.5)	8.4 (8.2; 8.6)
Asthma control					
Asthma attacks (EMR data)	Mean (95% CI)	0.31 (0.27; 0.36)	0.36 (0.35; 0.37)	0.42 (0.40; 0.45)	0.55 (0.54; 0.56)
	0, % (95% CI)	81.9 (80.2; 83.6)	79.9 (79.4; 80.4)	76.9 (75.5; 78.2)	74.2 (73.9; 74.5)
	1, % (95% CI)	11.4 (10.1; 12.8)	13.3 (12.9; 13.8)	14.6 (13.5; 15.7)	15.1 (14.8; 15.3)
	2, % (95% CI)	3.8 (2.9; 4.8)	3.6 (3.4; 3.9)	4.4 (3.7; 5.1)	4.9 (4.8; 5.1)
	3, % (95% CI)	1.4 (0.8; 2.1)	1.3 (1.2; 1.5)	2.0 (1.5; 2.6)	2.1 (2.0; 2.2)
	≥4, % (95% CI)	1.4 (0.8; 2.0)	1.8 (1.6; 2.0)	2.1 (2.0; 2.3)	3.7 (3.6; 3.8)
RCP3 score	0, % (95% CI)	32.0 (29.9; 34.1)	29.6 (29.0; 30.2)	27.4 (25.9; 28.9)	28.4 (28.1; 28.8)
	1, % (95% CI)	39.7 (37.6; 41.8)	40.3 (39.7; 41.0)	41.3 (39.6; 42.9)	39.7 (39.4; 40.1)
	2, % (95% CI)	20.8 (19.1; 22.6)	21.8 (21.3; 22.3)	22.5 (21.1; 23.9)	22.2 (21.9; 22.5)
	3, % (95% CI)	7.5 (6.3; 8.6)	8.2 (7.9; 8.6)	8.8 (8.3; 9.3)	9.6 (9.4; 9.8)
Poor symptom control	Yes, % (95% CI)	25.4 (23.6; 27.3)	27.2 (26.6; 27.7)	27.7 (26.5; 29.0)	29.2 (28.8; 29.5)
Difficult-to-treat asthma, GINA 2020	Yes, % (95% CI)	23.0 (21.0; 25.0)	24.6 (24.0; 25.1)	26.9 (25.8; 28.0)	31.1 (30.7; 31.4)
Lung function					
FEV ₁ % predicted	Mean (95% CI)	82.7 (80.6; 84.7)	86.0 (85.4; 86.6)	85.5 (83.6; 87.4)	83.7 (83.3; 84.0)
Peak Expiratory Flow (PEF) % predicted	Mean (95% CI)	83.1 (82.2; 84.1)	84.4 (84.1; 84.7)	84.3 (83.6; 84.9)	82.7 (82.5; 82.8)
Asthma therapy					
	1, % (95% CI)	9.9 (8.7; 11.1)	8.9 (8.5; 9.2)	7.6 (6.4; 8.8)	6.7 (6.5; 6.9)

Variable		0 (N= 6,878)	1 (N= 28,560)	2 (N= 31,295)	3 (N= 71,236)
GINA step of asthma management (2020)	2, % (95% CI)	33.4 (31.4; 35.5)	32.4 (31.8; 33.0)	32.1 (30.4; 33.7)	28.1 (27.8; 28.5)
	3, % (95% CI)	18.2 (16.5; 19.9)	18.6 (18.1; 19.1)	18.2 (17.0; 19.4)	18.2 (17.9; 18.5)
	4, % (95% CI)	24.9 (23.0; 26.9)	25.0 (24.4; 25.5)	25.3 (24.0; 26.6)	26.7 (26.4; 27.0)
	5, % (95% CI)	13.6 (11.9; 15.2)	15.2 (14.7; 15.6)	16.8 (15.9; 17.7)	20.3 (20.0; 20.6)
ICS, mean daily dose (mcg)*	Mean (95% CI)	240 (229; 250)	249 (246; 252)	252 (247; 258)	274 (272; 275)
ICS, mean daily dose (mcg)	% (95% CI)	10.2 (9.0; 11.4)	9.4 (9.0; 9.7)	8.3 (7.1; 9.5)	7.2 (7.0; 7.4)
0		26.8 (25.0; 28.6)	23.8 (23.3; 24.3)	24.8 (23.1; 26.4)	22.6 (22.3; 22.9)
>0 to <100		18.2 (16.6; 19.8)	20.0 (19.5; 20.5)	20.9 (19.5; 22.2)	20.6 (20.3; 20.9)
100-200		28.4 (26.4; 30.4)	30.8 (30.2; 31.3)	30.6 (29.4; 31.8)	32.3 (32.0; 32.7)
>200 to 200		16.4 (14.5; 18.2)	16.0 (15.5; 16.5)	15.5 (14.9; 16.0)	17.3 (17.9; 17.6)
>500					
Number of ICS inhalers†	Mean (95% CI)	7 (7; 7)	7 (7; 7)	7 (7; 7)	7 (7; 7)
SABA daily dose (mcg)‡	Mean (95% CI)	257 (236; 279)	244 (240; 248)	234 (228; 240)	283 (280; 286)
OCS daily dose (mg)	Mean (95% CI)	0.22 (0.19; 0.26)	0.25 (0.24; 0.27)	0.31 (0.28; 0.33)	0.43 (0.42; 0.44)
SAMA§	% (95% CI)	1.1 (0.6; 1.5)	1.2 (1.1; 1.4)	1.3 (1.2; 1.4)	1.4 (1.3; 1.5)
LAMA§	% (95% CI)	6.5 (5.1; 8.0)	5.4 (5.1; 5.8)	6.3 (6.0; 6.5)	7.0 (6.8; 7.2)
LABA§	% (95% CI)	3.9 (2.9; 4.9)	3.1 (2.8; 3.3)	2.5 (2.3; 2.6)	2.8 (2.7; 2.9)
Theophylline§	% (95% CI)	1.5 (0.8; 2.3)	0.9 (0.7; 1.0)	0.9 (0.8; 1.0)	1.4 (1.4; 1.5)
LTRA§	% (95% CI)	7.5 (6.4; 8.6)	8.1 (7.7; 8.4)	9.3 (8.1; 10.4)	10.5 (10.3; 10.7)

* FP equivalent; † of 30 days dispensed in baseline year; ‡ salbutamol equivalent; § ≥1 prescription in last 12 months

Grade 0: non-eosinophilic; Grade 1: least likely eosinophilic; Grade 2: likely eosinophilic; Grade 3 most likely eosinophilic (see Figure 1 for definition of eosinophil phenotype grades). BMI: body mass index; CI: confidence interval; CPRD: Clinical Practice Research Datalink; EMR: electronic medical record; FEV₁: forced expiratory volume in one second; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; LABA: long-acting β₂-agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; OPCR: Optimum Patient Care Research Database; RCP: Royal College of Physicians; SABA: short-acting β₂-agonist; SAMA: short-acting muscarinic antagonist; SD: standard deviation Categorical variables: p-

Variable	0 (N= 6,878)	1 (N= 28,560)	2 (N= 31,295)	3 (N= 71,236)
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values were calculated using Pearson's chi-square tests of independent categories. Continuous or ordinal variables: p-values were calculated using the non-parametric Kruskal-Wallis equality of populations rank test.

Table E7: Demographic and clinical characteristics according to eosinophilic and non-eosinophilic phenotype in a sub-set of a primary care UK cohort with difficult-to-treat (severe) asthma: GINA 2020 treatment step definition (OPRCD + CPRD n=39,357) – age standardised

Variable		0 (N= 1,259)	1 (N= 6,596)	2 (N= 9,350)	3 (N= 22,152)
Demographic characteristics					
Male	Yes, % (95% CI)	45.7 (39.3; 52.1)	32.2 (30.6; 33.9)	29.5 (26.8; 32.2)	37.6 (36.9; 38.4)
Age at last extraction date (yrs)	Mean (SD)	41.4 (14.5)	51.8 (16.8)	65.7 (12.5)	59.6 (17.7)
	13-17, n (%)	37 (2.9)	85 (1.3)	0 (0.0)	276 (1.2)
	18-64, n (%)	1,131 (89.8)	4,898 (74.3)	4,241 (45.4)	12,084 (54.6)
	≥65, n (%)	91 (7.2)	1,613 (24.5)	5,109 (54.6)	9,792 (44.2)
Smoking status	Never smoker, % (95% CI)	41.3 (34.8; 47.7)	35.5 (33.8; 37.2)	30.3 (27.5; 33.1)	34.2 (33.4; 34.9)
	Current smoker, % (95% CI)	18.0 (13.3; 22.7)	18.8 (17.6; 20.1)	20.9 (18.2; 23.6)	17.2 (16.6; 17.8)
	Ex-smoker, % (95% CI)	40.7 (34.3; 47.2)	45.7 (43.9; 47.4)	47.2 (45.9; 48.5)	48.7 (47.9; 49.5)
BMI (kg/m ²)	Mean (95% CI)	28.4 (27.7; 29.1)	29.4 (29.2; 29.6)	30.6 (30.2; 31)	29.9 (29.8; 30)
	<18.5, % (95% CI)	1.8 (0.5; 3.1)	2.2 (1.6; 2.7)	1.1 (0.8; 1.4)	1.8 (1.6; 2.0)
	≥18.5 <25, % (95% CI)	29.2 (23.2; 35.2)	25.4 (23.8; 27.0)	19.9 (18.8; 21.0)	22.9 (22.2; 23.5)
	≥25 <30, % (95% CI)	35.3 (28.7; 41.8)	32.5 (30.8; 34.2)	30.4 (27.7; 33.1)	32.2 (31.5; 33.0)
	≥30, % (95% CI)	33.7 (27.8; 39.6)	39.9 (38.1; 41.7)	47.2 (44.4; 49.9)	43.1 (42.3; 43.9)
Age of asthma onset (yrs)	Mean (SD)	13.9 (8.6)	27.6 (20.6)	51.1 (13.9)	38.5 (21.8)
	Childhood-onset (<18), n (%)	848 (67.4)	2,740 (41.5)	90 (1.0)	5,205 (23.5)
	Adult-onset (18-29), n (%)	411 (32.6)	1,422 (21.6)	49 (0.5)	2,468 (11.1)
	Late-onset (≥30), n (%)	<5	2,434 (36.9)	9,211 (98.5)	14,479 (65.4)

Variable		0 (N= 1,259)	1 (N= 6,596)	2 (N= 9,350)	3 (N= 22,152)
Co-morbidities					
Eczema	Yes, % (95% CI)	18.0 (14.6; 21.5)	20.1 (19.1; 21.2)	19.3 (17.4; 21.2)	21.7 (21.2; 22.3)
	Yes, active, % (95% CI)	6.4 (4.1; 8.6)	7.5 (6.8; 8.1)	6.4 (5.9; 7.0)	11.6 (11.2; 12.0)
Allergic rhinitis	Yes, % (95% CI)	22.8 (19.2; 26.5)	24.7 (23.6; 25.8)	22.4 (20.4; 24.3)	29.7 (29.1; 30.3)
	Yes, active, % (95% CI)	7.6 (4.9; 10.3)	6.3 (5.7; 6.9)	6.9 (5.3; 8.6)	8.2 (7.8; 8.5)
Chronic rhinosinusitis	Yes, without nasal polyps, % (95% CI)	7.6 (5.0; 10.3)	9.5 (8.7; 10.3)	10.1 (9.4; 10.8)	11.5 (11.1; 11.9)
	Yes, with nasal polyps, % (95% CI)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	2.4 (0.8; 3.9)	3.9 (3.6; 4.1)
Charlson Comorbidity Index	0-1, % (95% CI)	72.5 (68.0; 77.1)	71.4 (70.2; 72.6)	64.4 (63.5; 65.3)	62.9 (62.3; 63.5)
	2-4, % (95% CI)	20.6 (16.4; 24.9)	21.5 (20.3; 22.6)	24.2 (23.4; 25.0)	26.1 (25.6; 26.7)
	≥4, % (95% CI)	6.9 (3.8; 9.9)	7.1 (6.3; 7.9)	9.7 (9.2; 10.3)	11.0 (10.6; 11.4)
Asthma control					
Asthma exacerbations	Mean (95% CI)	0.84 (0.70; 0.98)	0.88 (0.83; 0.92)	0.94 (0.89; 0.99)	1.24 (1.21; 1.26)
	0, % (95% CI)	61.2 (56.6; 65.8)	59.1 (57.8; 60.5)	56.5 (54.4; 58.5)	52.5 (51.8; 53.2)
	1, % (95% CI)	17.6 (14.2; 21.0)	21.2 (20.1; 22.3)	19.8 (18.8; 20.7)	20.5 (20.0; 21.1)
	2, % (95% CI)	11.6 (8.2; 14.9)	9.9 (9.1; 10.7)	11.5 (9.7; 13.3)	11.4 (10.9; 11.8)
	3, % (95% CI)	4.4 (2.4; 6.4)	4.1 (3.6; 4.6)	4.6 (4.1; 5.0)	5.6 (5.3; 5.9)
	≥4, % (95% CI)	5.3 (3.0; 7.6)	5.7 (5.0; 6.3)	6.1 (5.6; 6.6)	10.0 (9.6; 10.4)
RCP3 score	0, % (95% CI)	16.9 (13.1; 20.7)	15.6 (14.6; 16.6)	13.6 (12.8; 14.3)	16.2 (15.7; 16.7)
	1, % (95% CI)	28.9 (24.6; 33.2)	28.4 (27.2; 29.6)	29.5 (27.5; 31.4)	29.1 (28.5; 29.7)
	2, % (95% CI)	35.8 (31.3; 40.3)	38.1 (36.8; 39.4)	35.8 (33.8; 37.8)	35.1 (34.5; 35.8)
	3, % (95% CI)	18.4 (14.9; 21.9)	17.9 (16.9; 18.9)	19.5 (18.6; 20.4)	19.6 (19.1; 20.1)
Poor symptom control	Yes, % (95% CI)	51.0 (46.3; 55.6)	53.8 (52.5; 55.1)	53.3 (51.3; 55.3)	52.7 (52.0; 53.3)
Difficult-to-treat asthma, GINA 2020	Yes, % (95% CI)	71.8 (67.5; 76.1)	72.4 (71.2; 73.6)	72.2 (70.2; 74.1)	74.9 (74.3; 75.5)
Lung function					

Variable		0 (N= 1,259)	1 (N= 6,596)	2 (N= 9,350)	3 (N= 22,152)
FEV ₁ % predicted	Mean (95% CI)	76.1 (73.9; 78.3)	78.3 (77.7; 79.0)	78.1 (77.1; 79.2)	76.9 (76.6; 77.2)
GINA step of asthma management (2019)	4, % (95% CI)	66.7 (60.6; 72.8)	61.2 (59.5; 63.0)	62.0 (59.2; 64.7)	57.4 (56.6; 58.2)
	5, % (95% CI)	33.3 (27.2; 39.4)	38.8 (37.0; 40.5)	36.5 (33.8; 39.3)	42.6 (41.8; 43.4)
Asthma therapy					
ICS daily dose (mcg)*	Mean (95% CI)	523 (489; 557)	547 (535; 560)	529 (512; 547)	535 (529; 541)
ICS daily dose (mcg)*	% (95% CI)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.2 (0.2; 0.3)
0		9.9 (7.6; 12.2)	7.2 (6.6; 7.8)	7.1 (6.4; 7.7)	7.3 (6.9; 7.6)
<0 to < 100		8.8 (6.4; 11.1)	12.3 (11.4; 13.1)	13.0 (11.3; 14.8)	12.0 (11.5; 12.4)
100-200		41.5 (36.9; 46.1)	39.7 (38.4; 41.0)	40.7 (38.7; 42.7)	41.3 (40.6; 41.9)
>200 to 500		39.9 (35.1; 44.6)	40.8 (39.5; 42.1)	37.5 (35.9; 39.1)	39.3 (38.6; 39.9)
>500					
Number of ICS inhalers†	Mean (95% CI)	10 (10; 11)	10 (9; 10)	9 (9; 9)	9 (9; 9)
SABA daily dose (mcg)‡	Mean (95% CI)	424 (364; 484)	409 (394; 424)	380 (364; 396)	455 (447; 464)
OCS daily dose (mg)	Mean (95% CI)	0.64 (0.48; 0.81)	0.68 (0.61; 0.76)	0.70 (0.66; 0.75)	1.05 (1.02; 1.09)
SAMA§	% (95% CI)	3.9 (2.0; 5.9)	3.1 (2.6; 3.6)	3.0 (2.6; 3.3)	3.1 (2.9; 3.4)
LAMA§	% (95% CI)	26.6 (22.2; 30.9)	19.4 (18.2; 20.5)	20.6 (19.8; 21.4)	20.5 (20.0; 21.0)
LABA§	% (95% CI)	5.8 (3.3; 8.4)	4.3 (3.7; 4.8)	3.4 (3.0; 3.8)	3.8 (3.6; 4.1)
Theophylline§	% (95% CI)	5.8 (3.1; 8.6)	3.2 (2.7; 3.7)	2.9 (2.6; 3.3)	4.3 (4.0; 4.6)
LTRA§	% (95% CI)	25.8 (21.8; 29.7)	26.1 (25.0; 27.2)	25.4 (23.5; 27.4)	28.3 (27.7; 28.9)

* FP equivalent; † of 30 days dispensed in baseline year; ‡ salbutamol equivalent; § ≥1 prescription in last 12 months

Grade 0: non-eosinophilic; Grade 1: least likely eosinophilic; Grade 2: likely eosinophilic; Grade 3 most likely eosinophilic (see Figure 1 for definition of eosinophil phenotype grades). BMI: body mass index; CI: confidence interval; CPRD: Clinical Practice Research Datalink; EMR: electronic medical record; FEV₁: forced expiratory volume in one second; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; LABA: long-acting β 2-agonist; LAMA: long-

Variable	0 (N= 1,259)	1 (N= 6,596)	2 (N= 9,350)	3 (N= 22,152)
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acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid; OPCR: Optimum Patient Care Research Database; RCP:

Royal College of Physicians; SABA: short-acting β_2 -agonist; SAMA: short-acting muscarinic antagonist; SD: standard deviation

Categorical variables: p-values were calculated using Pearson's chi-square tests of independent categories.

Continuous or ordinal variables: p-values were calculated using the non-parametric Kruskal-Wallis equality of populations rank test.

Table E8 Asthma disease burden and health care resource utilisation (HCRU) variables of patients from CPRD with HES available (n=113,148): age standardised

Variable		0 (N= 6,855)	1 (N= 26,866)	2 (N= 25,323)	3 (N= 54,104)
Asthma burden variables					
Asthma exacerbations, using HES	Mean (SD)	0.31 (0.26; 0.36)	0.36 (0.35; 0.38)	0.42 (0.40; 0.45)	0.56 (0.55; 0.57)
	0, n (%)	82.9 (81.2; 84.6)	80.6 (80.1; 81.1)	77.6 (76.2; 79.0)	75.0 (74.7; 75.4)
	1, n (%)	11.1 (9.8; 12.5)	12.7 (12.3; 13.2)	14.3 (13.1; 15.5)	14.2 (13.9; 14.5)
	2, n (%)	3.3 (2.5; 4.2)	3.4 (3.2; 3.6)	4.0 (3.4; 4.5)	4.6 (4.4; 4.7)
	3, n (%)	0.9 (0.5; 1.4)	1.3 (1.1; 1.4)	1.8 (1.3; 2.3)	2.2 (2.1; 2.3)
	≥4, n (%)	1.7 (1.0; 2.4)	2.0 (1.8; 2.2)	2.3 (2.1; 2.5)	4.0 (3.8; 4.1)
Acute lower respiratory events, using HES	Mean (SD)	0.50 (0.44; 0.56)	0.59 (0.57; 0.61)	0.67 (0.64; 0.70)	0.79 (0.78; 0.81)
	0, n (%)	71.2 (69.1; 73.2)	67.4 (66.8; 68.0)	63.0 (61.2; 64.8)	62.9 (62.5; 63.3)
	1, n (%)	18.3 (16.7; 20.0)	20.8 (20.3; 21.3)	23.3 (21.6; 25.1)	21.0 (20.6; 21.3)
	2, n (%)	6.7 (5.5; 7.9)	6.3 (6.0; 6.6)	7.1 (6.3; 7.8)	7.5 (7.3; 7.7)
	3, n (%)	1.6 (1.0; 2.2)	2.6 (2.4; 2.8)	3.2 (2.6; 3.7)	3.4 (3.2; 3.5)
	≥4, n (%)	2.1 (1.3; 2.9)	2.9 (2.7; 3.2)	3.4 (3.2; 3.6)	5.3 (5.1; 5.5)
Risk Domain Asthma Control	Yes, n (%)	70.1 (68.1; 72.2)	66.3 (65.6; 66.9)	61.5 (59.7; 63.3)	61.7 (61.3; 62.1)
Overall Asthma Control	Yes, n (%)	44.6 (42.4; 46.7)	42.2 (41.5; 42.8)	40.0 (38.1; 41.9)	36.9 (36.5; 37.3)
Full Asthma Control	Yes, n (%)	34.5 (32.3; 36.6)	34.6 (34.0; 35.3)	34.8 (32.8; 36.7)	33.6 (33.2; 34.0)
HCRU variables					
All-cause GP consultations	Mean (SD)	8.73 (8.31; 9.15)	9.69 (9.58; 9.81)	10.59 (10.32; 10.85)	10.68 (10.61; 10.76)
Respiratory-related GP consultations	Mean (SD)	4.13 (3.90; 4.36)	4.40 (4.34; 4.46)	4.58 (4.45; 4.70)	4.52 (4.48; 4.56)
All cause outpatient visits	Mean (SD)	2.53 (2.29; 2.76)	2.83 (2.76; 2.90)	3.24 (3.08; 3.41)	3.38 (3.33; 3.43)
Respiratory outpatient visits	Mean (SD)	0.08 (0.05; 0.11)	0.08 (0.07; 0.09)	0.09 (0.08; 0.10)	0.12 (0.11; 0.13)
All cause A&E attendances	Mean (SD)	0.44 (0.38; 0.50)	0.41 (0.40; 0.43)	0.44 (0.40; 0.48)	0.46 (0.45; 0.47)
Respiratory A&E attendances	Mean (SD)	0.04 (0.02; 0.05)	0.03 (0.03; 0.03)	0.03 (0.03; 0.04)	0.05 (0.04; 0.05)

Variable		0 (N= 6,855)	1 (N= 26,866)	2 (N= 25,323)	3 (N= 54,104)
Hospital admissions, asthma primary diagnosis	Mean (SD)	0.01 (0.00; 0.03)	0.01 (0.01; 0.01)	0.01 (0.01; 0.01)	0.01 (0.01; 0.02)
Hospital admissions, respiratory condition primary diagnosis	Mean (SD)	0.03 (0.01; 0.04)	0.03 (0.03; 0.03)	0.03 (0.03; 0.04)	0.05 (0.04;0.05)
Length of stay ≥ 1 overnight, asthma primary diagnosis	Mean (SD)	7.03 (4.19; 9.86)	6.44 (4.82; 8.06)	5.88 (4.49;7.28)	5.98 (5.07;6.88)
Length of stay ≥ 1 overnight, respiratory condition primary diagnosis	Mean (SD)	5.61 (3.93; 7.29)	7.16 (6.16;8.15)	6.43 (5.63; 7.24)	7.23 (6.58; 7.89)
Grade 0: non-eosinophilic; Grade 1: least likely eosinophilic; Grade 2: likely eosinophilic; Grade 3 most likely eosinophilic (see Figure 1 for definition of eosinophil phenotype grades). A&E: Accident & Emergency; CPRD: Clinical Practice Research Datalink; GP: general practitioner; HES: hospital episode statistics; SD: standard deviation; Categorical variables: p-values were calculated using Pearson's chi-square tests of independent categories. Continuous or ordinal variables: p-values were calculated using the non-parametric Kruskal-Wallis equality of populations rank test.					

Table E9. Age-standardized distribution of HCRU utilization in patients from CPRD with HES available with difficult-to-treat (severe) asthma (2020 definition)

Variable		0 (N= 603)	1 (N= 3,241)	2 (N= 4,056)	3 (N= 8,964)
All-cause GP consultations	Mean (SD)	12.14 (10.74; 13.54)	12.13 (11.76; 12.50)	13.48 (13.06; 13.89)	13.88 (13.66; 14.10)
	0, n (%)	1.4 (0.0; 2.9)	0.6 (0.4; 0.9)	0.5 (0.3; 0.7)	0.4 (0.3; 0.6)
	1-4, n (%)	21.0 (16.0; 26.0)	17.0 (15.6; 18.4)	13.0 (11.7; 14.3)	13.3 (12.6; 14.0)
	5-8, n (%)	22.9 (17.9; 27.9)	24.9 (23.3; 26.5)	21.8 (20.2; 23.4)	21.8 (21.0; 22.7)
	9-11, n (%)	15.4 (10.7; 20.1)	15.8 (14.4; 17.2)	17.0 (14.5; 19.4)	15.6 (14.9; 16.4)
	12-24, n(%)	25.7 (19.9; 31.6)	32.8 (31.0; 34.5)	34.8 (32.1; 37.4)	36.0 (35.0; 37.0)
	≥25, n (%)	12.2 (7.2; 17.3)	8.9 (7.8; 9.9)	11.3 (10.2; 12.5)	12.8 (12.1; 13.5)
	Mean (SD)	7.72 (6.74; 8.69)	7.79 (7.56; 8.03)	7.72 (7.47; 7.97)	7.75 (7.63; 7.88)
Respiratory-related GP consultations	0, n (%)	11.8 (7.5; 16.1)	13.4 (12.1; 14.7)	12.9 (11.5; 14.2)	12.7 (12.0; 13.4)
	1-4, n (%)	17.7 (12.9; 22.6)	16.2 (14.9; 17.6)	14.1 (12.9; 15.3)	15.6 (14.8; 16.3)
	5-8, n (%)	35.7 (29.6; 41.9)	31.4 (29.7; 33.1)	33.7 (31.3; 36.1)	33.7 (32.7; 34.7)
	9-11, n (%)	11.6 (7.8; 15.5)	16.5 (15.1; 17.9)	15.1 (13.8; 16.3)	16.0 (15.3; 16.8)
	12-24, n(%)	19.7 (14.2; 25.3)	20.9 (19.3; 22.4)	21.4 (19.1; 23.6)	20.5 (19.7; 21.4)
	≥25, n (%)	2.0 (0.0; 4.1)	1.6 (1.1; 2.1)	1.2 (0.8; 1.5)	1.5 (1.2; 1.7)
	Mean (SD)	3.51 (2.83; 4.18)	3.95 (3.71; 4.19)	4.32 (3.97; 4.68)	4.73 (4.58; 4.88)
All-cause outpatient visits	0, n (%)	37.5 (31.9; 43.2)	37.4 (35.6; 39.2)	33.1 (30.4; 35.8)	30.4 (29.5; 31.3)
	1, n (%)	12.1 (7.4; 16.8)	11.8 (10.6; 13.0)	10.5 (9.3; 11.7)	11.1 (10.5; 11.8)
	2, n (%)	10.5 (6.3; 14.7)	10.0 (8.9; 11.2)	8.8 (7.8; 9.9)	9.7 (9.1; 10.3)
	3, n (%)	5.0 (2.0; 8.1)	6.6 (5.6; 7.5)	7.3 (6.4; 8.3)	8.1 (7.5; 8.7)
	≥4, n (%)	33.6 (27.1; 40.0)	34.2 (32.4; 35.9)	38.5 (35.9; 41.2)	40.6 (39.6; 41.6)
	Mean (SD)	0.26 (0.11; 0.41)	0.25 (0.21; 0.30)	0.27 (0.23; 0.31)	0.35 (0.31; 0.38)
Respiratory outpatient visits	0, n (%)	88.6 (84.1; 93.0)	91.4 (90.3; 92.4)	89.1 (87.9; 90.3)	89.1 (88.5; 89.8)
	1, n (%)	6.2 (2.5; 9.9)	3.1 (2.4; 3.8)	3.0 (2.3; 3.7)	4.1 (3.6; 4.5)
	2, n (%)	0.3 (0.0; 0.6)	2.4 (1.8; 3.0)	2.5 (1.8; 3.1)	2.3 (2.0; 2.6)
	3, n (%)	1.9 (0.2; 3.6)	1.4 (1.0; 1.8)	1.3 (0.8; 1.8)	1.7 (1.4; 1.9)
	≥4, n (%)	1.7 (0.0; 3.6)	1.7 (1.3; 2.2)	2.4 (1.8; 3.1)	2.9 (2.5; 3.2)
	Mean (SD)	0.64 (0.40; 0.89)	0.57 (0.53; 0.62)	0.55 (0.50; 0.59)	0.65 (0.62; 0.68)
All-cause A&E attendances	0, n (%)	69.3 (63.2; 75.5)	69.1 (67.4; 70.8)	67.3 (64.6; 69.9)	65.8 (64.8; 66.8)
	1, n (%)	19.1 (13.7; 24.5)	18.7 (17.3; 20.1)	19.7 (17.2; 22.3)	20.6 (19.8; 21.4)

Variable		0 (N= 603)	1 (N= 3,241)	2 (N= 4,056)	3 (N= 8,964)
Respiratory A&E attendances	2, n (%)	4.2 (1.9; 6.5)	6.9 (5.9; 7.8)	6.0 (5.2; 6.8)	7.6 (7.0; 8.1)
	3, n (%)	3.3 (0.5; 6.1)	2.8 (2.2; 3.4)	2.8 (2.1; 3.5)	2.8 (2.4; 3.1)
	≥4, n (%)	2.7 (1.0; 4.4)	2.5 (2.0; 3.1)	2.6 (2.0; 3.1)	3.3 (2.9; 3.7)
	Mean (SD)	0.13 (0.02; 0.24)	0.09 (0.07; 0.11)	0.09 (0.07; 0.10)	0.11 (0.09; 0.12)
	0, n (%)	93.4 (90.6; 96.2)	94.0 (93.1; 94.8)	91.9 (90.9; 92.8)	92.7 (92.2; 93.3)
	1, n (%)	3.6 (1.2; 6.0)	4.6 (3.9; 5.4)	5.2 (4.3; 6.1)	5.7 (5.2; 6.2)
	2, n (%)	0.9 (0.0; 2.1)	0.7 (0.4; 1.0)	0.7 (0.5; 1.0)	1.0 (0.8; 1.2)
Hospital admissions with asthma as primary diagnosis	3, n (%)	0.1 (0.0; 0.2)	0.4 (0.2; 0.7)	0.3 (0.1; 0.4)	0.2 (0.1; 0.3)
	≥4, n (%)	0.7 (0.0; 1.7)	0.3 (0.1; 0.5)	0.2 (0.1; 0.4)	0.4 (0.3; 0.5)
	Mean (SD)	0.04 (0.01; 0.07)	0.03 (0.02; 0.04)	0.02 (0.01; 0.03)	0.04 (0.03; 0.05)
	0, n (%)	97.1 (95.9; 98.2)	98.3 (97.9; 98.8)	96.6 (96.1; 97.1)	97.3 (96.9; 97.6)
	1, n (%)	0.8 (0.3; 1.4)	1.1 (0.7; 1.5)	1.5 (1.0; 1.9)	2.1 (1.8; 2.4)
	2, n (%)	0.5 (0.0; 1.5)	0.3 (0.2; 0.5)	0.1 (0.0; 0.3)	0.4 (0.3; 0.5)
	3, n (%)	0.0 (0.0; 0.0)	0.0 (0.0; 0.1)	0.0 (0.0; 0.1)	0.1 (0.0; 0.1)
Hospital admissions with respiratory condition as primary diagnosis	≥4, n (%)	0.2 (0.0; 0.5)	0.2 (0.1; 0.3)	0.1 (0.0; 0.2)	0.2 (0.1; 0.2)
	Mean (SD)	0.08 (0.04; 0.13)	0.08 (0.06; 0.10)	0.10 (0.07; 0.12)	0.10 (0.09; 0.11)
	0, n (%)	93.2 (89.8; 96.6)	95.0 (94.1; 95.8)	91.6 (89.8; 93.5)	93.1 (92.6; 93.6)
	1, n (%)	4.4 (1.2; 7.6)	3.5 (2.8; 4.2)	5.3 (3.4; 7.1)	5.3 (4.8; 5.8)
	2, n (%)	0.8 (0.0; 1.9)	1.0 (0.6; 1.4)	0.9 (0.6; 1.1)	1.0 (0.8; 1.2)
	3, n (%)	0.0 (0.0; 0.0)	0.1 (0.0; 0.3)	0.3 (0.1; 0.4)	0.2 (0.1; 0.3)
	≥4, n (%)	0.2 (0.0; 0.5)	0.4 (0.2; 0.6)	0.3 (0.1; 0.4)	0.4 (0.2; 0.5)
Length of stay, ≥1 overnight asthma primary	≥4, n (%)	0.1 (0.0; 0.2)	0.0 (0.0; 0.1)	0.1 (0.0; 0.2)	0.1 (0.0; 0.2)
	Mean (SD)	9.91 (4.39; 15.43)	9.46 (6.47; 12.46)	6.44 (4.09; 8.79)	7.30 (5.79; 8.80)
	1, n (%)		22.1 (10.9; 33.3)		22.3 (16.6; 28.0)
	2-7, n (%)	Not estimated	38.4 (26.5; 50.3)	Not estimated	57.2 (50.3; 64.2)
	8-13, n (%)		12.0 (1.4; 22.6)		8.4 (4.5; 12.3)
	≥14, n (%)		27.5 (14.3; 40.7)		12.1 (7.6; 16.6)
	≥14, n (%)	0.3 (0.1; 0.6)	1.3 (0.9; 1.8)	1.0 (0.7; 1.3)	1.4 (1.2; 1.6)
Length of stay, ≥1 overnight respiratory	Mean (SD)	7.56 (4.50; 10.62)	10.07 (7.82; 12.31)	7.89 (6.30; 9.47)	7.91 (6.82; 8.99)
	1, n (%)	16.5 (3.8; 29.1)	16.6 (9.7; 23.5)	20.7 (16.0; 25.3)	21.7 (18.1; 25.3)
	2-7, n (%)	53.1 (40.9; 65.3)	38.4 (29.2; 47.6)	45.7 (39.8; 51.7)	48.0 (43.5; 52.4)

Variable		0 (N= 603)	1 (N= 3,241)	2 (N= 4,056)	3 (N= 8,964)
condition as primary	8-13, n (%)	17.4 (1.1; 33.6)	19.9 (11.5; 28.4)	14.8 (10.4; 19.1)	13.6 (10.6; 16.6)
diagnosis	≥14, n (%)	9.0 (2.9; 15.0)	25.1 (16.9; 33.3)	16.8 (12.2; 21.5)	16.6 (13.3; 19.9)

Grade 0: non-eosinophilic; Grade 1: least likely eosinophilic; Grade 2: likely eosinophilic; Grade 3 most likely eosinophilic (see Figure 1 for definition of eosinophil phenotype grades). A&E: Accident & Emergency; CPRD: Clinical Practice Research Datalink; GP: general practitioner; HES: hospital episode statistics; SD: standard deviation; Continuous or ordinal variables: p-values were calculated using the non-parametric Kruskal-Wallis equality of populations rank test.

Legend to figures**Figure E1**

Subject disposition of asthma patients from the Optimum Patient Care Research Database (OPCRD) and the Clinical Practice Research Datalink (CPRD). BEC: blood eosinophil count; HES: hospital episode statistics; OCS: oral corticosteroid

Figure E2

Number of patients included by year and data source (n=241,006)

Figure E3

Frequency distribution of age of asthma onset of the study population (OPCRD + CPRD, n=241,006)

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