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Healthcare resource use and costs of severe, uncontrolled eosinophilic asthma in the UK general population

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ABSTRACT

Background Little is known about the prevalence of severe, uncontrolled eosinophilic asthma (SUEA) and associated costs.

Aims We sought to determine the prevalence of SUEA and compare asthma-related healthcare resource use (HCRU) and associated costs with overall means for a general asthma population.

Methods This cohort study evaluated anonymised medical record data (December 1989 through June 2015) from the Clinical Practice Research Datalink and the Optimum Patient Care Research Database to study UK patients with active asthma (diagnostic code and one or more drug prescriptions in the baseline year), aged 5 years and older, without concomitant COPD, and with recorded eosinophil count. SUEA was defined as two or more asthma attacks during 1 baseline year preceding a high blood eosinophil count (≥0.3×10^9/L) for patients prescribed long-acting β_2-agonist (LABA) and high-dosage inhaled corticosteroids (ICS) during baseline plus 1 follow-up year. We compared asthma-related HCRU and associated direct costs (2015 pounds sterling, £) during the follow-up year for SUEA versus the general asthma population.

Results Of 363 558 patients with active asthma and recorded eosinophil count, 64% were women, mean (SD) age was 49 (21) years; 43% had high eosinophil counts, 7% had two or more attacks in the baseline year and 10% were prescribed high-dosage ICS/LABA for 2 study years. Overall, 2940 (0.81%; 95% CI 0.78% to 0.84%) patients had SUEA. Total mean per-patient HCRU and associated costs were four times greater for SUEA versus all patients (HCRU and cost ratios 3.9; 95% CI 3.7 to 4.1).

Conclusions Less than 1% of patients in a general asthma population had SUEA. These patients accounted for substantially greater asthma-related HCRU and costs than average patients with asthma.

Key messages

What is the key question?

► How prevalent is severe, uncontrolled eosinophilic asthma, and what are the associated healthcare resource use and costs as compared with the average asthma population?

What is the bottom line?

► Severe, uncontrolled eosinophilic asthma is uncommon but is associated with asthma-related healthcare resource use and costs that are four times greater than those for average patients with asthma.

Why read on?

► This study quantifies and contrasts the asthma-related burden, healthcare resource use, and costs during 2 years of observation for patients with severe, uncontrolled eosinophilic asthma compared with a general asthma population in the UK.

INTRODUCTION

Asthma currently affects an estimated 358 million individuals worldwide, posing a substantial burden on healthcare systems.[1] While most asthma can be controlled with available therapies, some patients experience symptoms and severe asthma attacks even with high-intensity therapy (ie, Global Initiative for Asthma (GINA) Step 4/5 therapy with high-dosage inhaled corticosteroids (ICS) plus another controller medication and/or systemic corticosteroids[2]). These patients with severe uncontrolled asthma comprised 2.3%–3.6% of patients with persistent asthma in recent population-based studies using administrative and prescribing databases.[3 4] Uncontrolled asthma accounts for a disproportionate share of asthma-related healthcare resource use (HCRU) and costs.[5 6]

Eosinophilic asthma is a common phenotype of severe asthma,[7–10] and patients with eosinophilic asthma are at heightened risk of asthma attacks.[11–15] Biological agents mepolizumab and reslizumab that target the interleukin-5 molecule directly to reduce eosinophils have been demonstrated to reduce asthma attacks and improve symptoms in patients with severe, uncontrolled eosinophilic asthma (SUEA), with the potential to reduce patient exposure to high dosages of ICS and oral corticosteroids (OCS) and related adverse effects.[16–19] Benralizumab targets the interleukin-5 receptor α and induces direct, rapid and nearly complete depletion of eosinophils. In the phase III SIROCCO and CALIMA trials, benralizumab significantly reduced exacerbations, increased lung function and improved asthma symptoms for patients with severe, uncontrolled asthma with eosinophilic

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inflammation.[20 21] While benralizumab is effective across the full spectrum of patients studied,[20] the best responses to these agents are associated with greater eosinophil counts and asthma attack rates.[16 20] Therefore, information is needed on the prevalence of SUEA and associated HCRU to understand the patient population for which the use of these medications is justified.

Administrative and electronic databases afford the opportunity to study large numbers of patients.[22] In the UK, anonymised databases are available that draw on centralised electronic medical records housed at primary care practices. The aims of this historical follow-up study were to determine the population burden of SUEA and to estimate the asthma-related HCRU and associated costs. Our first objective was to describe the distribution of asthma severity and control, treatment status, high blood eosinophil count and their combinations and to establish the proportion of patients with SUEA in the general UK general population. Our second objective was to determine the asthma-related HCRU and associated costs for SUEA as compared with those for a general asthma population.

METHODS

Data source

This historical follow-up study was performed using datasets extracted from the Clinical Practice Research Datalink (CPRD) and the Optimum Patient Care Research Database (OPCRD), which contain anonymised, longitudinal medical record data from >650 and 500 UK primary care practices, respectively, for patients from throughout the UK. The data include information from general practice (GP) visits as well as secondary care and hospital attendances. The CPRD, formerly known as the General Practice Research Database (GPRD), is a well-maintained and well-regarded database that has been used for public health research since 1987.[23 24] The OPCRD is a bespoke database designed for use in clinical and epidemiological research.[25]

Two datasets were constructed separately using CPRD and OPCRD data in a patient unidentifiable form with harmonised variables. The datasets were checked for overlapping data to exclude any duplicate data (details in online supplementary material). The CPRD dataset contained patient records from June 1994 through January 2015 and was linked for a percentage of patients to Hospital Episode Statistics (HES), a data warehouse containing more complete and reliable information on inpatient hospital admissions.[26] The OPCRD dataset contained patient records from December 1989 through June 2015.

The study was performed in compliance with all applicable local and national laws and regulations, including approvals for dataset use and the study protocol, and in accordance with standards suggested for observational studies (see online supplementary material).[27]

Study design and patients

Patients eligible for inclusion in this study were ≥5 years old at the time of their most recent asthma diagnoses, recorded as a diagnostic Read code for asthma qualifying for inclusion in the register of patients with asthma, which general practices in the UK maintain for the Quality Outcomes Framework (QOF).[28] In addition, eligible patients had at least one valid blood eosinophil count after their asthma diagnoses and ≥2 years of continuous data used for this study, including ≥1 year (baseline year for patient characterisation) before their last recorded eosinophil count, and ≥1 year after the eosinophil count (outcome year). The date of the last recorded blood eosinophil count was defined as the *index date*, and eligible patients had to have received at least one prescription for asthma during the baseline year. Patients with asthma and no concomitant diagnosis of chronic obstructive pulmonary disease (COPD) constituted the main study population; and patients ≥40years with both asthma and COPD diagnoses were assessed in separate analyses. Patients with a diagnostic Read code for chronic lower respiratory conditions other than asthma or COPD, such as bronchiolitis obliterans or cystic fibrosis, were excluded from the study.

Study measures and definitions

We defined *severe asthma* as combination maintenance therapy with high-dosage ICS and long-acting β2-agonist (LABA) in both the baseline and the outcome years[29]; *uncontrolled asthma* as two or more asthma attacks in the baseline year[30]; and *eosinophilic asthma* as a blood eosinophil count of $\geq 0.3 \times 10^9$/L at index date.[9 10 31] We defined patients as having SUEA if they were receiving high-dosage ICS plus LABA in both baseline and outcome years, had two or more attacks in the baseline year and had a high blood eosinophil count of $\geq 0.3 \times 10^9$/L at index date.

The three components of the composite definition of SUEA were based on several sources. The definition of severe asthma was based on the definition of high-dosage ICS in the 2014 British guideline on the management of asthma, namely as a cumulative chlorofluorocarbon beclomethasone dipropionate (BDP)–equivalent dosage of ≥800 µg/day for adults and ≥400 µg/day for children 5–12 years.[29] We calculated the ICS daily dosage separately for the baseline and outcome years using the cumulative ICS exposure based on all prescriptions for each year (see online supplementary material). Asthma attacks were defined, according to the consensus European Respiratory Society/American Thoracic Society task force definition of severe asthma exacerbations, as the occurrence of any of the following events: respiratory-related hospital attendance or admission, emergency department (ED) attendance or acute OCS course.[30] A blood eosinophil count of $\geq 0.3 \times 10^9$/L was chosen as reported to be optimal for predicting sputum eosinophilia of ≥3%, reflecting airway eosinophilia.[9 10 31]

Risk-domain asthma control was defined as the absence of asthma attacks and no antibiotic prescribed with evidence of a lower respiratory consultation. Overall asthma control was defined as attainment of risk-domain asthma control plus a mean daily dosage of ≤200 µg salbutamol (or ≤500 µg terbutaline).

We determined asthma treatment step according to the GINA guidelines using the highest step during the baseline year, with the daily dosage of ICS based on the last prescription before the index date (see online supplementary material).[29]

We assessed asthma-related HCRU, including medications, asthma-related GP and hospital-based specialist clinic visits, hospitalisations and lower respiratory-related ED visits during the outcome year. With regard to HCRU that occurred on the index date, we assessed HCRU events (eg, GP visits or hospitalisations) as being part of the baseline year, because exacerbations, for example, might have been a reason for doing a full blood count (including eosinophil count), which defined the index date. Instead, medications prescribed on the index date were included in the outcome year tallies as treatment during the outcome period. Asthma-related direct costs during the outcome year were determined using standard unit costs for the UK National Health Service for 2015 (see online supplementary material).

Statistical analyses

We used summary statistics to describe the distribution of asthma severity and control, treatment status, high blood eosinophil

counts, other asthma determinants and their combinations in the baseline year before the index date, and we described mean asthma-related HCRU and associated direct costs during the outcome year. Although the distributions were skewed, we reported the means for HCRU, costs and cost ratios as recommended.[32–34] The means can be multiplied by a target population to estimate total costs and are therefore of most use to policy-makers and providers.

We performed the analyses separately for patients with and without a concomitant diagnosis of COPD. Analyses for those with concomitant COPD included only patients aged ≥40 years, described in the online supplementary material.

The mean numbers of HCRU events per patient during the outcome year were calculated with SDs. The means were then multiplied by unit costs for the cost year 2015 (expressed as pounds sterling, £) to provide mean (SD) annual, asthma-related healthcare costs for individuals (details in online supplementary material). The HCRU and cost analyses requiring information about inpatient hospitalisations were performed for the subgroup of patients in the CPRD dataset who had linked HES data. Sensitivity analyses on HCRU and costs were performed using different definitions of SUEA based on three additional definitions of high eosinophil count, namely $\geq 0.2\times10^9$/L, $\geq 0.4\times10^9$/L and $\geq 0.5\times10^9$/L. The HCRU and costs were described also for patients with prescriptions for maintenance oral corticosteroids. Cost ratios were estimated by calculating the ratios of the mean costs for the subgroup of patients with SUEA to those for the reference group of all patients with asthma. All 95% CIs were estimated based on 1000 bootstrap replicates (see online supplementary material).

Analyses were performed using IBM SPSS Statistics V.23 (IBM SPSS Statistics, Feltham, Middlesex, UK) and R V.3.0.2 (The R Project for Statistical Computing; https://www.r-project.org/).

RESULTS

Patient populations

In the two databases, 1 016 696 of 2 117 427 patients (48%) with asthma diagnostic code had recorded eosinophil counts. Of these, we identified a total of 401 261 (39%) patients with active asthma who met all eligibility criteria (figure 1). The main study population (those without a concomitant COPD diagnosis) included 363 558 (91%) patients with active asthma who had index dates from 6 December 1990 to 23 June 2014, with a median (IQR) index date year of 2011 (2008–2012); 0.7% of patients had an index date before the year 2000. Our findings for the 37 703 (9%) patients ≥40 years old with concomitant diagnosis of COPD are reported in the online supplementary material.

Demographic and clinical characteristics and asthma burden

In the main study population, 24 047 (7%) patients experienced two or more attacks during the baseline year; 34 898 (10%) received high-dosage ICS plus LABA during both baseline and outcome years; and 6326 (1.7%) received high-dosage ICS plus LABA during both baseline and outcome years and also experienced two or more attacks during the baseline year. Of the 6326 patients, a total of 2940 patients (46.5%), or 0.81% (95% CI 0.78% to 0.84%) of the main study population, met the study definition of SUEA, namely high-dosage ICS plus LABA in both baseline and outcome years, two or more attacks in the baseline year and high blood eosinophil count of $\geq 0.3\times10^9$/L at the index date.

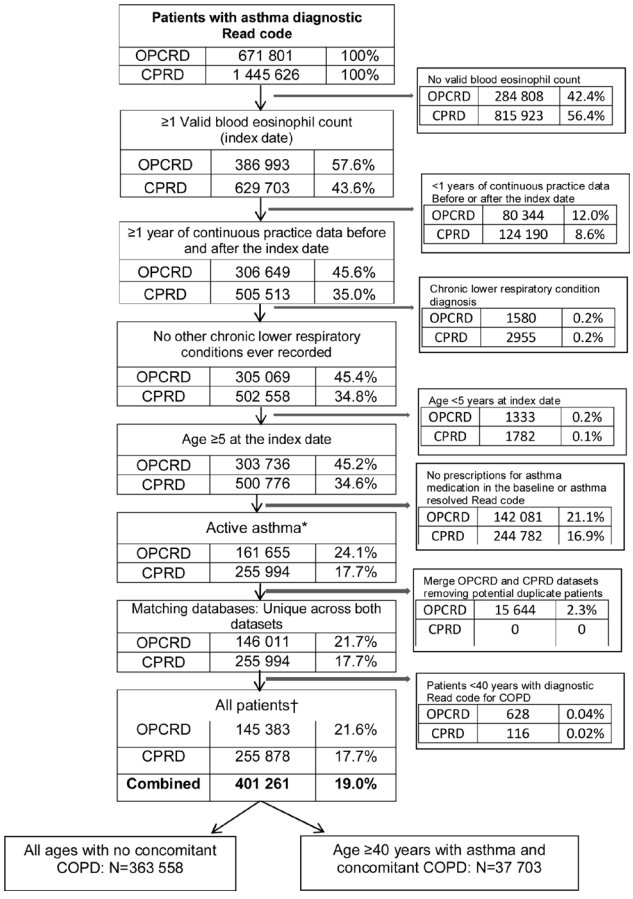

Figure 1 Patient flow chart. *Active asthma was defined as one or more prescriptions for asthma medication in the baseline year and asthma not resolved. †Includes those aged ≥40 years with concomitant COPD diagnosis. COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; OPCRD, Optimum Patient Care Research Database.

Tables 1 and 2 summarise demographics and baseline clinical characteristics for all ages combined (≥5 years) and for adults (18–64 and ≥65 years) in the SUEA population and the main study population. The median (IQR) index date years were 2011 (2009–2013) for SUEA and 2011 (2008–2012) for the total population. Most patients with SUEA were ≥18 years. Only 57 patients (2%) were <18 years, including 14 children who were 5–11 years old and 43 who were 12–17 years old (online supplementary table S1). Overall, the SUEA population was older than the main study population—983 (33%) and 95 189 (26%) were ≥65 years, respectively—but included roughly the same proportion of female patients (1952 (66%) and 233 210 (64%) female, respectively) (table 1). On the index date, blood eosinophil counts of $\geq 0.3\times10^9$/L were recorded for 156 136 (43%) patients, including 91 865/233 210 (39%) female patients and 64 271/130 348 (49%) male patients (table 2).

The 2940 patients in the SUEA population and those in each of the adult SUEA cohorts, compared with patients in the main study population, were less likely to have been normal weight, more likely to have been obese, and more likely to have had recorded comorbidities, with the greatest differences between SUEA and main populations overall in the recorded frequency of nasal polyps, followed by non-allergic rhinitis, chronic sinusitis, gastro-oesophageal reflux disease, cardiovascular

Table 1 Demographics and baseline clinical characteristics of the main study population (including patients with SUEA) and the SUEA population: all ages (≥5 years) and the adult cohorts

	All patients (age ≥5 years)*		18–64 years old		≥65 years old	
Variable	All ages (n=3 63 558)	SUEA (n=2940)	All 18–64 years old (n=2 42 714)	SUEA (n=1900)	All ≥65 years old (n=95 189)	SUEA (n=983)
Female sex, n (%)	233 210 (64.1)	1952 (66.4)	158 507 (65.3)	1269 (66.8)	61 990 (65.1)	650 (66.1)
Age at index date, mean (SD)	49.4 (20.6)	55.8 (17.6)	43.0 (12.8)	47.1 (11.6)	75.5 (7.5)	74.9 (7.1)
Body mass index, n (%)†						
Underweight	10 152 (3.3)	47 (1.8)	3948 (1.9)	18 (1.0)	1642 (1.9)	20 (2.2)
Normal	96 309 (31.0)	674 (25.1)	64 852 (30.7)	406 (23.4)	24 984 (29.0)	254 (27.6)
Overweight	100 937 (32.4)	828 (30.8)	67 176 (31.8)	489 (28.2)	32 116 (37.3)	333 (36.2)
Obese	103 738 (33.3)	1135 (42.3)	75 319 (35.6)	821 (47.3)	27 470 (31.9)	312 (33.9)
Unknown, n	52 422	256	31 419	166	8977	64
Smoking status, n (%)†						
Current smoker	64 350 (18.0)	530 (18.3)	56 194 (23.4)	476 (25.3)	6218 (6.6)	45 (4.6)
Ex-smoker	93 359 (26.2)	899 (31.0)	56 807 (23.7)	523 (27.8)	35 941 (38.2)	376 (38.6)
Never smokers	199 299 (55.8)	1475 (50.8)	126 664 (52.9)	879 (46.8)	51 906 (55.2)	554 (56.8)
Unknown, n	6550	36	3049	22	1124	8
Charlson comorbidity index, n (%)						
0	166 280 (45.7)	669 (22.8)	118 122 (48.7)	424 (22.3)	35 111 (36.9)	232 (23.6)
1–4	170 791 (47.0)	1941 (66.0)	114 735 (47.3)	1337 (70.4)	43 500 (45.7)	560 (57.0)
≥5	26 487 (7.3)	330 (11.2)	9857 (4.1)	139 (7.3)	16 578 (17.4)	191 (19.4)
Ever-recorded comorbidity, n (%)						
Eczema	105 659 (29.1)	999 (34.0)	68 507 (28.2)	661 (34.8)	25 188 (26.5)	302 (30.7)
Allergic rhinitis	62 490 (17.2)	608 (20.7)	45 790 (18.9)	427 (22.5)	12 789 (13.4)	163 (16.6)
Non-allergic rhinitis	32 285 (8.9)	422 (14.4)	19 918 (8.2)	245 (12.9)	10 825 (11.4)	172 (17.5)
Chronic sinusitis	35 708 (9.8)	456 (15.5)	24 940 (10.3)	287 (15.1)	10 351 (10.9)	169 (17.2)
Nasal polyps	12 949 (3.6)	376 (12.8)	7070 (2.9)	218 (11.5)	5802 (6.1)	158 (16.1)
Gastro-oesophageal reflux disease	42 154 (11.6)	515 (17.5)	25 129 (10.4)	293 (15.4)	16 323 (17.1)	221 (22.5)
Cardiovascular disease	93 443 (25.7)	1080 (36.7)	44 393 (18.3)	507 (26.7)	48 411 (50.9)	572 (58.2)

*All patients with SUEA included 14 children who were 5–11 years old and 43 adolescent patients 12–17 years old.
†The percentages for BMI and for smoking status were calculated for patients with available data. Overall, patients with missing data for BMI represented 14% of patients and for smoking status, 2% of patients. The BMI categories, determined from data closest to the index date, were defined as follows: underweight, <18.5 kg/m^2; normal weight, ≥18.5 kg/m^2 to <25 kg/m^2); overweight, ≥25 kg/m^2 to <30 kg/m^2; and obese, ≥30 kg/m^2 for patients ≥18 years old. (For children BMI was not calculated because accurate information on age in months required to calculate BMI z-scores was not provided for privacy reasons.)
BMI, body mass index; SUEA, severe, uncontrolled eosinophilic asthma.

disease and evidence of atopy (eczema and allergic rhinitis; see table 1).

Patients with SUEA also had lower mean percent predicted peak expiratory flow rate (67% vs 77%) and, on average, a much greater asthma medication burden than did patients in the main study population (table 2). Almost all patients with SUEA (2881 (98%)]) were at GINA step 4 or 5 based on the ICS prescription preceding the index date, while approximately one-third of patients (113 543 (31%)) in the main population were at step 4 or 5. The median (IQR) ICS dosage exposures during the baseline year in SUEA and main populations were 1425 (1068–1967 µg/day) and 329 µg/day (132–658 µg/day), respectively; and maintenance OCS were prescribed for 488 (17%) and 10 522 (3%) patients, respectively.

Demographics and baseline clinical characteristics of patients with SUEA defined using different definitions of high blood eosinophil count are described in online supplementary table S2. The prevalence of SUEA ranged from 1.2% at an eosinophil count of ≥0.2×10^9/L to 0.3% at a count of ≥0.5×10^9/L.

Healthcare resource use and costs

The mean HCRU and direct, asthma-related costs for each HCRU-related category were from 2.5 to 7.6 times greater for the SUEA cohort than for the main study population with active asthma, as summarised in table 3. The mean number of GP visits was 2.7 for the SUEA cohort and 1.4 for the main population, and the mean numbers of hospital-based specialist visits were 0.30 versus 0.04, respectively. During the outcome year, 627 of the 2940 patients in the SUEA cohort (21.3%) experienced two asthma attacks, and 387 (13.2%) and 393 (13.4%) experienced three and four or more attacks, respectively. Corresponding numbers for the main population of 363 558 patients with active asthma were 13 556 (3.7%), 5165 (1.4%) and 2987 (0.8%), respectively (online supplementary table S3).

The total mean asthma-related costs were £861 for the SUEA cohort versus £222 for the main study population, for a cost ratio of 3.9 (95% CI 3.7 to 4.1). The asthma-related HCRU and associated cost ratios for patients with SUEA appeared to increase with the increasing blood eosinophil counts used to

Table 2 Clinical characteristics and asthma disease burden of the main study population (including patients with SUEA) and the SUEA population: all ages (≥5 years) and the adult cohorts

	All patients (age ≥5 years)*		18–64 years old		≥65 years old	
Variable	All ages (n=3 63 558)	SUEA (n=2940)	All 18–64 years old (n=2 42 714)	SUEA (n=1900)	All ≥65 years old (n=95 189)	SUEA (n=983)
Blood eosinophil count, median (IQR)	0.20 (0.11–0.35)	0.40 (0.30–0.60)	0.20 (0.12–0.34)	0.40 (0.30–0.60)	0.20 (0.10–0.30)	0.40 (0.30–0.55)
Blood eosinophil count ≥0.3×10^9/L, n (%)	156 136 (42.9)	2940 (100)	103 298 (42.6)	1900 (100)	37 629 (39.5)	983 (100)
Female patients, n (% of females)	91 865 (39.4)	1952 (100)	63 086 (39.8)	1269 (100)	22 010 (35.5)	650 (100)
Male patients, n (% of males)	64 271 (49.3)	988 (100)	40 212 (47.8)	631 (100)	15 619 (47.0)	333 (100)
% Predicted PEF						
Available data, n (%)	277 334 (76.3)	2614 (88.9)	199 539 (82.2)	1762 (92.7)	77 795 (81.7)	852 (86.7)
Mean (SD)	77.4 (17.4)	66.6 (18.6)	79.2 (16.7)	67.2 (18.5)	72.8 (18.4)	65.3 (18.8)
Mean daily SABA dosage (µg/day), n (%)†						
0	74 637 (20.5)	610 (20.7)	46 517 (19.2)	354 (18.6)	25 475 (26.8)	250 (25.4)
1–200	148 727 (40.9)	315 (10.7)	102 914 (42.4)	180 (9.5)	31 601 (33.2)	132 (13.4)
201–400	72 073 (19.8)	504 (17.1)	47 377 (19.5)	286 (15.1)	19 035 (20.0)	211 (21.5)
>400	68 121 (18.7)	1511 (51.4)	45 906 (18.9)	1080 (56.8)	19 078 (20.0)	390 (39.7)
Asthma therapy: GINA step, n (%)‡						
Step 1	58 159 (16.0)	0	43 676 (18.0)	0	8723 (9.2)	0
Step 2	115 346 (31.7)	0	77 732 (32.0)	0	26 297 (27.6)	0
Step 3	76 510 (21.0)	59 (2.0)	49 070 (20.2)	40 (2.1)	21 874 (23.0)	17 (1.7)
Step 4	103 019 (28.3)	2393 (81.4)	67 661 (27.9)	1547 (81.4)	32 511 (34.2)	798 (81.2)
Step 5	10 524 (2.9)	488 (16.6)	4575 (1.9)	313 (16.5)	5784 (6.1)	168 (17.1)
Prescribed ICS during the baseline year, n (%)	300 920 (82.8)	2940 (100)	196 640 (81.0)	1900 (100)	84 615 (88.9)	983 (100)
Cumulative ICS dosage (µg/day), baseline year, median (IQR)†	329 (132–658)	1425 (1068–1967)	301 (110–656)	1421 (1068–1967)	460 (230–874)	1479 (1066–1967)
Last ICS dosage prescribed, per GINA classification, n (%)‡						
No ICS prescribed	62 638 (17.2)	0	46 074 (19.0)	0	10 574 (11.1)	0
Low ICS dosage	159 858 (44.0)	114 (3.9)	105 503 (43.5)	75 (3.9)	39 438 (41.4)	35 (3.6)
Medium ICS dosage	107 207 (29.5)	943 (32.1)	69 839 (28.8)	569 (29.9)	33 094 (34.8)	330 (33.6)
High ICS dosage	33 855 (9.3)	1883 (64.0)	21 298 (8.8)	1256 (66.1)	12 083 (12.7)	618 (62.9)
≥1 prescription during baseline, n (%)						
Omalizumab	3 (0)	0 (0)	3 (0)	0	0	0
LTRA	21 436 (5.9)	1001 (34.0)	14 209 (5.9)	743 (39.1)	5092 (5.3)	216 (22.0)
Theophylline	6073 (1.7)	397 (13.5)	3333 (1.4)	276 (14.5)	2676 (2.8)	116 (11.8)
Cumulative high-dosage ICS, n (%)†	59 953 (16.5)	2940 (100)	34 463 (14.2)	1900 (100)	24 327 (25.6)	983 (100)
Cumulative high-dosage ICS+LABA, n (%)†	46 687 (12.8)	2940 (100)	27 526 (11.3)	1900 (100)	18 419 (19.3)	983 (100)
Cumulative high-dosage ICS+LABA for 2 years, n (%)†§	34 898 (9.6)	2940 (100)	20 336 (8.4)	1900 (100)	14 128 (14.8)	983 (100)
Maintenance OCS, n (%)¶	10 522 (2.9)	488 (16.6)	4573 (1.9)	313 (16.5)	5784 (6.1)	168 (17.1)
Asthma attacks, mean (SD)	0.31 (0.76)	2.89 (1.32)	0.30 (0.74)	2.93 (1.35)	0.36 (0.84)	2.80 (1.27)
Median (range)	0 (0–15)	2 (2–14)	0 (0–15)	3 (2–14)	0 (0–14)	2 (2–13)
0 attacks, n (%)	288 836 (79.4)	0	193 674 (79.8)	0	73 362 (77.1)	0
1 attack, n (%)	50 675 (13.9)	0	33 621 (13.9)	0	14 229 (14.9)	0
2–3 attacks, n (%)**	20 793 (5.7)	2307 (78.5)	13 415 (5.5)	1464 (77.1)	6434 (6.8)	800 (81.4)
≥4 attacks, n (%)**	3254 (0.9)	633 (21.5)	2004 (0.8)	436 (22.9)	1164 (1.2)	183 (18.6)
Risk-domain asthma control, n (%)	232 944 (64.1)	244 (8.3)	157 232 (64.8)	151 (7.9)	58 070 (61.0)	90 (9.2)
Overall asthma control, n (%)	149 349 (41.1)	77 (2.6)	100 694 (41.5)	43 (2.3)	36 490 (38.3)	33 (3.4)
Cumulative high-dosage ICS+LABA and ≥2 attacks, n (%)	8164 (2.2)	2940 (100)	5098 (2.1)	1900 (100)	2919 (3.1)	983 (100)

Continued

Table 2 Continued

Variable	All patients (age ≥5 years)*		18–64 years old		≥65 years old	
	All ages (n=3 63 558)	SUEA (n=2940)	All 18–64 years old (n=2 42 714)	SUEA (n=1900)	All ≥65 years old (n=95 189)	SUEA (n=983)
Cumulative high-dosage ICS+LABA and ≥4 attacks, n (%)	1569 (0.4)	633 (21.5)	1011 (0.4)	436 (22.9)	533 (0.6)	183 (18.6)

*All patients with SUEA included 14 children who were 5–11 years old and 43 adolescent patients 12–17 years old.
†SABA and cumulative ICS dosage exposure during the baseline year were calculated as the mean of recorded prescriptions over 365 days. High-dosage ICS was defined, using chlorofluorocarbon beclomethasone dipropionate-equivalent dose, according to 2014 British asthma guidelines as a cumulative beclomethasone-equivalent dosage of ≥800 µg/day for adults and ≥400 µg/day for children 5–12 years.[29]
‡GINA treatment steps were defined using the last prescribed ICS dosage before the index date and applying low-dosage, medium-dosage and high-dosage ICS definitions per GINA guidelines (details in the online supplementary material).[2]
§Study definition of severe asthma, that is, cumulative high-dosage ICS+LABA during both baseline and outcome years.
¶Maintenance OCS at some time during the baseline year.
**The study definition of uncontrolled asthma was 2 or more attacks during the baseline year.
GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting β2-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; PEF, peak expiratory flow; SABS, short-acting β2-agonist; SUEA, severe, uncontrolled eosinophilic asthma.

define SUEA, ranging from 3.8 (95% CI 3.7 to 4.0) for an eosinophil count of $\geq 0.2\times10^9$/L to 4.2 (95% CI 3.8 to 4.7) for a count of $\geq 0.5\times10^9$/L (online supplementary table S4).

For the 10 552 patients in the main study population who received maintenance OCS during the baseline year, the total mean costs, including medication costs, were £552, for a cost ratio of 2.5 (95% CI 2.4 to 2.6) relative to all patients with asthma (table 3).

Patients ≥40 years old with concomitant COPD

Demographics and baseline clinical characteristics of patients ≥40 years with asthma and concomitant COPD are described in the online supplementary table S5. The percentage of these patients who had SUEA (blood eosinophil count $\geq 0.3\times10^9$/L) was greater than in the main study population (1596/37 703 or 4.2% vs 0.8% (2940/363 558) in the main population) (online supplementary table S1).

The mean asthma-related HCRU and costs for the total population of patients with concomitant COPD were much higher than those for the main study population with asthma but without concomitant COPD (total mean costs of £530 vs £222, respectively). Patients with SUEA and concomitant COPD had total mean costs of £866. Thus, the cost ratio for patients ≥40 years old with SUEA and concomitant COPD versus patients ≥40

Table 3 Mean asthma-related HCRU, associated direct costs (2015 pounds sterling, £), and HCRU and cost ratios during the outcome year for patients with SUEA and those receiving maintenance oral corticosteroids compared with all patients with active asthma (including patients with SUEA) in the UK general population

Asthma-related HCRU outcome	All patients (n=3 63 558/146 485*)	SUEA (n=2940/1206*)	HCRU and cost ratios (95% CI)†	≥1 OCS maintenance (n=10 522/4140*)	HCRU and cost ratios (95% CI)†
GP visit‡					
Number	1.36 (1.57)	2.67 (2.80)	2.5 (2.4 to 2.6)	1.93 (2.43)	1.7 (1.7 to 1.8)
Costs	£30.8 (49.8)	£77.0 (107.5)		£53.2 (90.8)	
Costs, median (IQR)	£14.5 (0.0–43.4)	£44.0 (14.5–101.7)	–	£28.9 (14.5–58.5)	–
Hospital-based specialist visit					
Number	0.04 (0.33)	0.30 (0.96)	6.8 (6.0 to 7.7)	0.31 (0.96)	5.7 (5.3 to 6.2)
Costs	£6.9 (52.2)	£46.7 (149.2)		£39.4 (138.6)	
Asthma-related ED attendance					
Number	0.01 (0.11)	0.04 (0.25)	4.1 (3.2 to 5.3)	0.03 (0.23)	3.4 (3.0 to 4.0)
Costs	£1.6 (18.8)	£6.6 (44.7)		£5.5 (38.2)	
Hospitalisation*					
Number	0.01 (0.12)	0.05 (0.38)	7.6 (4.7 to 11.6)	0.04 (0.37)	6.7 (5.0 to 8.9)
Costs	£10.4 (194.7)	£78.7 (660.3)		£69.6 (653.5)	
Medication cost	£170.1 (218.2)	£645.4 (285.4)	3.8 (3.7 to 3.9)	£363.6 (338.6)	2.1 (2.1 to 2.2)
Cost, median (IQR)	£87.8 (18.0–244.9)	£595.3 (451.8–760.5)	–	£285.2 (111.4–527.0)	–
Total costs*	£222.0 (337.2)	£861.0 (811.9)	3.9 (3.7 to 4.1)	£552.1 (842.8)	2.5 (2.4 to 2.6)
Total costs, median (IQR)	£125.6 (43.1–297.9)	£707.0 (523.0–951.0)	–	£370.0 (159.6–689.7)	–

Data are reported as mean (SD) unless otherwise noted. The medians (IQRs) that are not included in the table were all 0 (0–0).
*The second number of patients in the column headers represents those in the Clinical Practice Research Datalink who had linked Hospital Episode Statistics (HES), used to determine hospitalisations and associated costs, as factored into total costs. The SUEA cohort with HES data included 26 (2.2%) patients <18 years old.
†95% CI, based on 1000 bootstrap replicates.
‡GP visits included consultations with primary care physicians and asthma nurses.
ED, emergency department; GP, general practice; HCRU, healthcare resource use; OCS, oral corticosteroids; SUEA, severe, uncontrolled eosinophilic asthma.

years with asthma and concomitant COPD was 1.6 (95% CI 1.6 to 1.7) (online supplementary table S6).

DISCUSSION

We identified a total of 2940 patients, representing <1% of patients in a general UK asthma population without concomitant COPD, as having SUEA, which we defined as at least two asthma attacks in the year before a recorded high blood eosinophil count ($\geq 0.3\times10^9$/L) while receiving treatment with high-dosage ICS plus LABA during the 2 consecutive years bracketing the eosinophil count. Sixty-six percent of the patients with SUEA were women. They were older on average (56 vs 49 years old), and they had more frequent comorbidities than other patients with asthma. Moreover, the individuals with SUEA had greater asthma-related disease burden, consulting their general practitioners for asthma twice as frequently, and visiting the hospital-based specialist clinics seven times as frequently as the general asthma population. During the outcome year after the eosinophil count, they presented substantially greater asthma-related HCRU and associated direct costs, four times greater than those for the main study population of patients with active asthma.

Costs for HCRU in the UK are relatively lower than in some other countries. Therefore, the absolute difference in total costs between patients with SUEA and all patients with asthma may be greater in countries with more expensive healthcare systems, such as the USA.[35] In a recent US study, the total mean, annual asthma-related costs for 101 patients with severe, uncontrolled asthma and eosinophil count of $\geq 0.3\times10^9$/L were US$3030 (2013 US dollars), roughly four times greater than the analogous costs in our study.[36] We found that asthma medications comprised approximately 75% of total mean costs incurred by patients in each of the SUEA and general asthma populations and, thus, were the largest category of asthma-related costs in this study, similar to findings in other studies of severe uncontrolled asthma in the USA and UK.[4 5 36] A 2009 systematic review of 68 studies evaluating the economic burden of asthma identified medications or hospitalisations, depending on the study, as being the major drivers of asthma-related direct costs.[6]

We found greater asthma-related disease burden also in the subgroup of patients with concomitant COPD and elevated blood eosinophils, as reported by others.[37] The total mean asthma-related costs were similar for the two SUEA populations (those with and without concomitant COPD, £865 and £861, respectively). However, the cost ratio for those with SUEA and concomitant COPD was just 1.6 because of greater total mean costs (£530) for all patients with concomitant COPD, likely because they were older (all ≥40 years) and had more frequent comorbidities. Others have found that asthma-related healthcare costs for patients with asthma and concomitant COPD are nearly double those for matched patients with asthma without COPD.[38] The subgroup of patients on maintenance OCS had mean total costs 2.5 times greater than those for the main study population.

Strengths of this study include the large general asthma population (>350 000 patients with active asthma) and the use of well-maintained databases of electronic medical records that are used frequently for observational research. We examined 1 baseline year, a standard interval used to clinically characterise patients, followed by 1 full outcome year to account for seasonal variation in asthma symptoms and considered a minimum interval for follow-up, as used in prior observational studies.[11–13 35–39] Over 99% of patients in both main and SUEA populations had index dates after 1999, the year when the first fixed-dose combination ICS/LABA was introduced in the UK. Moreover, 91% of the main study population (and 94% of the SUEA population) had index dates in 2005 or later; therefore, most of the data were post-2004 and thus after the introduction on 1 April 2004 of the UK Quality Outcomes Framework (QOF) establishing incentives for improved data recording at GP practices.[28] Indeed, smoking status, for example, was recorded for all but 2% of patients. Nonetheless, information on spirometry was limited, especially with regard to bronchodilator reversibility, which was available for only approximately 1% of patients. The datasets represent information collected for clinical and routine use rather than specifically for research purposes. Moreover, reports from hospital registrars and referrals to chest physicians, in addition to eosinophil counts determined in hospital or the ED, may not have been consistently incorporated in patients' general practitioner records. For this reason, we restricted the calculation of hospitalisations and associated costs to the subset of patients in the CPRD who were also included in the HES dataset.

Our choice of $\geq 0.3\times10^9$/L blood eosinophils as the primary definition of high blood eosinophil count is in line with prior reports that found eosinophil thresholds of 0.27×10^9/L and 0.26×10^9/L to be optimal for predicting sputum eosinophilia of ≥3%.[9 10 31] Our definition of high-dosage ICS used in the SUEA definition was less than that defined as the high dosage in ERS/ATS guidelines defining severe asthma (ie, BDP ≥2000 µg/day for adults and ≥800 µg/day for children).[8] However, the mean daily ICS dosages during the baseline and outcome years were calculated using all prescriptions averaged over 365 days (rather than a single prescribed dose) and thus represent total ICS exposure during the year.

Working retrospectively from databases limited our ability to separate severe treatment-resistant (refractory) asthma (ie, asthma that remains uncontrolled despite GINA Step 4/5 therapy) from difficult-to-control asthma (ie, uncontrolled asthma resulting from poor adherence, poor inhalation technique or treatable comorbidities, for example).[8] In addition, our definition of asthma control was limited to items recorded in the database that reflected asthma control or lack thereof, such as acute OCS prescriptions; we were not able to assess asthma symptoms.

We included patients with SUEA in the main study population without concomitant COPD (as well as in the total population with concomitant COPD), because our aim was to report costs for a general asthma population, which, by definition, also includes patients with SUEA. Therefore, the main study and SUEA cohorts were not mutually exclusive, which caused a slight underestimation of the difference between cohorts. In post hoc calculations, the mean total costs for the main study population excluding SUEA were £216.7 (vs £222.0 when including SUEA), giving a cost ratio of 4.0, a difference of only 0.1 versus our reported ratio of 3.9.

Our general asthma population may not be fully representative of all patients with active asthma because we included only patients who had a recorded eosinophil count, limiting the generalisability of our findings. Eosinophil counts are usually performed for a reason, for example, for a health-related reason that may not be related to asthma. Indeed, previous studies report that patients with asthma and recorded eosinophil count tend to be older, more commonly female, and with greater asthma-related burden than the general asthma population.[12 13] Finally, there are several other limitations of working retrospectively from databases. Because we restricted our analyses to HCRU with a primary code of asthma, it is possible that not all asthma-related direct costs were captured. Some

consultations for conditions occurring as a result of asthma treatment, for example, steroid-induced morbidity, or consultations not primarily related to asthma that involved discussion and management of asthma may not have been coded as being asthma-related. Moreover, when assigning costs, although most annual asthma reviews in the UK are performed by nurses,[40] we could not be certain whether all asthma reviews were indeed done by nurses and all other consultations by primary care physicians. In addition, we could not assess indirect costs, such as lost school and work time,[6] because these data are not included in patients' medical records.

We note that patients with SUEA had fewer attacks in the outcome year compared with the baseline year (48% vs 100% with two or more attacks). This difference could be explained by regression to the mean.[41] Alternatively, for some patients, perhaps their asthma was more aggressively or appropriately managed during the outcome year, or the natural history of severe asthma could include the transition to less severe asthma over time.[42]

In conclusion, we found that 0.8% of patients in a general UK asthma population have SUEA, and 4.2% of those with asthma and concomitant COPD have SUEA, defined as having two or more asthma attacks in the year before a recorded high blood eosinophil count ($\geq 0.3 \times 10^9$/L) and while under treatment for 2 years with high-dosage ICS plus LABA. Individuals who have SUEA despite treatment with high dosages of ICS combined with LABA therapy account for substantially greater asthma-related HCRU and associated direct costs than average patients with asthma.

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Competing interests MK is an employee of the Observational and Pragmatic Research Institute Pte Ltd (OPRI), which conducted this study with funding from AstraZeneca and which has conducted paid research in respiratory disease on behalf of the following other organizations: Aerocrine, AKL Research and Development Ltd, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, Takeda, Teva Pharmaceuticals, Theravance, UK National Health Service and Zentiva. TNT, SG and DG are employees of AstraZeneca. JBS is a consultant to OPRI and has received pharmaceutical company grants from GSK in 2011 and Chiesi in 2012 via CIMERA his former home institution, and in 2014 and 2015 from Linde via Hospital Universitario de La Princesa; JBS participated in speaking activities, advisory committees and consultancies during the period 2011-2016 sponsored by: Almirall, AstraZeneca, Boehringer-Ingelheim, Chiesi, ERS, GEBRO, Grifols, GSK, Linde, Lipopharma, Mundipharma, Novartis, Pfizer, RiRL, Rovi, SEPAR, Takeda and Teva. EVH is a consultant to OPRI and has received fees for medical writing assistance from Merck. DBP has board membership with Aerocrine, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Mundipharma, Napp, Novartis and Teva Pharmaceuticals; consultancy agreements with Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Napp, Novartis, Pfizer, Teva Pharmaceuticals and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from Aerocrine, AKL Research and Development Ltd, AstraZeneca, Boehringer Ingelheim, British Lung Foundation, Chiesi, Mylan, Mundipharma, Napp, Novartis, Pfizer, Respiratory Effectiveness Group, TevaPharmaceuticals, Theravance, UK National Health Service, Zentiva; payment for lectures/speaking engagements from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Merck, Mundipharma, Novartis, Pfizer, Skyepharma, and Teva Pharmaceuticals; payment for manuscript preparation from Mundipharma and Teva Pharmaceuticals; payment for the development of educational materials from Mundipharma and Novartis; payment for travel/accommodation/meeting expenses from Aerocrine, AstraZeneca, Boehringer Ingelheim, Mundipharma, Napp, Novartis and Teva Pharmaceuticals; funding for patient enrolment or completion of research from Chiesi, Novartis, Teva Pharmaceuticals and Zentiva; stock/stock options from AKL Research and Development Ltd which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia, Singapore, and UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); and is peer reviewer for grant committees of the Efficacy and Mechanism Evaluation programme and Health Technology Assessment.

Ethics approval CPRD Independent Scientific Advisory Committee gave approval for use of the GPRD (ISAC registration number, 15_141) and the OPCRD is approved by the Health Research Authority of the UK NHS for clinical research use (REC reference: 15/EM/0150).

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