Original Article

Potential Severe Asthma Hidden in UK Primary Care

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What is already known about this topic? Primary care physicians are often reticent to refer patients with asthma to specialist care, because they are working under the expectation that all asthma can be managed effectively in primary care and/or are unaware of the benefits of referral.

What does this article add to our knowledge? There are large numbers of patients with asthma in the United Kingdom with potential severe asthma (8%) who are managed long-term in primary care who may be eligible for referral to specialist care.

How does this study impact current management guidelines? Our findings may help primary care physicians recognize those with hidden severe asthma in their care. These patients would benefit from a structured assessment by their primary care physician, with possible referral to specialist care.

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International Severe Asthma Registry is conducted by Observational & Pragmatic Research Institute, and cofunded by Optimum Patient Care Global and AstraZeneca. This research study was cofunded by AstraZeneca and Optimum Patient Care Global Limited, including access to the Optimum Patient Care Research Database.

Conflicts of interest: D. Ryan has (in the last 3 years) lectured on behalf of, received sponsorship from, or acted as a paid advisor to Mylan, AstraZeneca, Chiesi, Novartis, GlaxoSmithKline (GSK), Boehringer Ingelheim, and Regeneron. H. Heatley, L. Bulathsinhala, V. Carter, I. Chaudry, N. Eleangovan, and N. Hosseini are employees of Optimum Patient Care, a cofunder of the International Severe Asthma Registry. L. G. Heaney is an Academic Lead for the UK MRC Consortium for Stratified Medicine in Severe Asthma – Industrial Pharma partners Amgen, AstraZeneca, MedImmune, Janssen, Novartis, Roche/Genentech, GSK, and Boehringer Ingelheim; received prior project grant funding from MedImmune, Novartis UK, Roche/Genentech, and GSK; has taken part in advisory boards / lectures supported by Novartis, Roche / Evelo Biosciences, Genentech, GSK, Teva, Theravance, and Vectura; has travel funding support to international respiratory meetings (AstraZeneca, Chiesi, Novartis, Boehringer Ingelheim, Teva, and GSK), and has taken part in asthma clinical trials (GSK, Schering Plough, Synairgen, Novartis, and Roche/Genentech) for which his institution was

Abbreviations used
BEC- blood eosinophil count
GINA- Global INitiative for Asthma
ICS- inhaled corticosteroid
ISAR- International Severe Asthma Registry
LABA- long-acting β_2-agonist
PSA- potential severe asthma
OCS- oral corticosteroid
OPCRD- Optimum Patient Care Research Database
UKSAR- UK Severe Asthma Registry

BACKGROUND: Severe asthma may be underrecognized in primary care.

OBJECTIVE: Identify and quantify patients with potential severe asthma (PSA) in UK primary care, the proportion not referred, and compare primary care patients with PSA with patients with confirmed severe asthma from UK tertiary care.

METHODS: This was a historical cohort study including patients from the Optimum Patient Care Research Database (aged ≥16 years, active asthma diagnosis pre-2014) and UK patients in the International Severe Asthma Registry (UK-ISAR aged ≥18 years, confirmed severe asthma in tertiary care). In the OPCRD, PSA was defined as Global INitiative for Asthma 2018 step 4 treatment and 2 or more exacerbations/y *or* at Global INitiative for Asthma step 5. The proportion of these patients and their referral status in the last year were quantified. Demographic and clinical characteristics of groups were compared.

RESULTS: Of 207,557 Optimum Patient Care Research Database patients with asthma, 16,409 (8%) had PSA. Of these, 72% had no referral/specialist review in the past year. Referred patients with PSA tended to have greater prevalence of inhaled corticosteroid/long-acting β_2-agonist add-ons (54.1 vs 39.8%), and experienced significantly ($P < .001$) more exacerbations per year (median, 3 vs 2/y), worse asthma control, and worse lung function (% predicted postbronchodilator FEV_1/forced vital capacity, 0.69 vs 0.72) versus nonreferred patients. Confirmed patients with severe asthma (ie, UK patients in the International Severe Asthma Registry) were younger (51 vs 65 years; $P < .001$), and significantly ($P < .001$) more likely to have uncontrolled asthma (91.4% vs 62.5%), a higher exacerbation rate (4/y [initial assessment] vs 3/y), use inhaled corticosteroid/long-acting β_2-agonist add-ons (67.7% vs 54.1%), and have nasal polyposis (24.2% vs 6.8) than referred patients with PSA.

CONCLUSIONS: Large numbers of patients with PSA in the United Kingdom are underrecognized in primary care. These patients would benefit from a more systematic assessment in primary care and possible specialist referral. **(J Allergy Clin Immunol Pract 2021;9:1612-23)**

Key words: *Optimum Patient Care Research Database; International Severe Asthma Registry; Potential severe asthma; Referral; Tertiary care*

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INTRODUCTION

Appropriate and timely review of patients with difficult-to-treat asthma in specialist care is a key aspect of asthma management, improving outcomes and access to additional health care resources and advanced therapies.[1,2] A specialist care review facilitates an accurate diagnosis, permits identification and control of comorbidities, triggers, poor adherence and inhaler technique, determination of specific asthma phenotypes, and diagnosis of severe asthma.[3,4] Although much of this can be done in primary care using a structured approach to review patients with uncontrolled asthma,[5] that is often not the case. Asthma management guidelines provide guidance on when patients with asthma should be reviewed.[6] However, despite these guidelines, failure to refer for specialist consultation is evident.[7,8] Indeed, the National Review of Asthma Deaths reported that 19% of deaths attributable to asthma in the United Kingdom were associated with potentially avoidable factors related to access to specialist care, such as failure to refer or delayed referral.[9] Certainly those suspected of having severe asthma should be reviewed in specialist care, but how are these patients with potential severe asthma (PSA) identified?

The true size of the severe asthma population remains unknown. It could be overestimated—a reflection of incorrect inhaler use and poor medication adherence.[10-12] However, it may be underestimated because of differences in definition and diagnostic practices around the world, or it may be a function of how asthma is managed nationally. For example, there may be downward pressure on primary care not to make referrals or some other form of disincentive to refer. Alternatively, patients with severe asthma may have been previously discharged from specialist care back to primary care and managed with long-term maintenance or recurrent courses of oral corticosteroids (OCSs) or at Global INitiative for Asthma (GINA) 2018[4] step 4 treatment with frequent exacerbations. There is a need to identify and understand this potential "hidden" primary care severe asthma population, because these patients may benefit from specialist review and specialist treatments (eg, biologic therapy) but be unable to access it in primary care.

To shed light on this issue, one approach is to identify PSA in a primary care electronic health records database and compare these patients to those with a specialist-confirmed severe asthma diagnosis in the same country. This approach requires existing primary and tertiary care databases with sufficient numbers of patients and a consistent definition of severe asthma. Data should be anonymized and of high quality, and variables collected should be similar between databases to facilitate cross-comparison. This situation exists in the United Kingdom, home to both the Optimum Patient Care Research Database (OPCRD)[13] and the UK Severe Asthma Registry (UKSAR), included in the International Severe Asthma Registry (ISAR).[14]

The OPCRD is a primary care electronic health care records database. It comprises medical records of more than 9.7 million patients (as of April 2020) from more than 700 general practices across the United Kingdom (~13.2% of the total UK population) and integrates with all UK clinical systems (EMIS, TPP SystmOne, InPS Vision, Microtest Evolution).[13] ISAR is the first global, adult, severe asthma registry.[14] It is a multicenter, multinational, observational initiative based in tertiary care that collects a standardized set of variables (agreed by Delphi consensus) prospectively and retrospectively on patients with severe asthma.[15-18]

The aims of this study were to (1) identify patients with PSA managed in UK primary care, (2) estimate how many of these may be effectively "hidden" (ie, not reviewed or currently managed in specialist care), and (3) compare the demographic and clinical characteristics of patients with PSA with those of patients with a confirmed severe diagnosis managed in regional specialist centers in the United Kingdom and included in ISAR.

METHODS

Study design

This was a historical cohort study, using data from the OPCRD[13] and from UK patients in ISAR.[14] Patients in primary care with PSA (see patient cohort definitions) were identified from the OPCRD. Asthma-related outcome measures within the OPCRD have been validated using patient-reported outcomes.[19] Patients in tertiary care with confirmed severe asthma were those registered in the UKSAR and included in the ISAR (http://isaregistries.org/). UKSAR has received ethics approval to provide deidentified data to ISAR in compliance with UK-specific international data transfer laws and legislation.[17,18] ISAR captures 95 core variables agreed by Delphi consensus.[15] The current study protocol was approved by the Anonymised Data Ethics Protocols And Transparency committee (ADEPT0319) and registered with the European Union electronic Register of Post-Authorization studies (EUPAS28611).[20]

Inclusion criteria

Patients included from the OPCRD (ie, primary care) were required to be 16 years or older, have an active current diagnosis of asthma (before 2014 and no subsequent recorded asthma resolved Read Code after the latest asthma diagnosis), have received 1 or more asthma medication during the 1-year follow-up period, and have 1 or more year of data from 2014 onward (to align with the ISAR data collection period). Patients with physician-confirmed diagnosis of other respiratory conditions were excluded. Those with a confirmed severe asthma diagnosis included all UK patients registered in ISAR. Inclusion in ISAR requires that patients are 18 years or older *and* are receiving GINA (2018)[4] step 5 treatment *or* have uncontrolled asthma at GINA 2018 step 4 (eg, ≥2 exacerbations/y). These patients have been assessed by a specialist to ensure correct diagnosis and optimum management (including identification of triggers, drug therapy, correct use of device(s), adherence, and comorbidities).

Patient cohort definitions

The following patient cohorts were defined:

1. PSA reviewed/referred from the OPCRD cohort. These were patients (aged ≥16 years) in primary care receiving GINA 2018[4] step 4 treatment *and* experiencing 2 or more exacerbations/y *or* receiving GINA 2018 step 5 treatment *and* who had been reviewed by, or received a referral to, a respiratory specialist in the last year.
2. PSA NOT reviewed/referred from the OPCRD cohort. As for above, but these patients had *not* been reviewed by, or referred to, a respiratory specialist in the last year.
3. Confirmed patients with severe asthma from the ISAR cohort. Patients (aged ≥18 years) managed in regional specialist centers, registered in the UKSAR and included in ISAR.

TABLE I. Description of key outcome variables presented

Variable	Description
Comorbidities	• For UK-ISAR, comorbidities are captured in free text, and so are likely underreported (particularly when compared with the patients' long-term primary care record) • OPCRD: comorbidities are coded
Exacerbation	• Worsening of asthma requiring systemic corticosteroids
Asthma control	• OPCRD: assessed 5 ways: 1. Royal College of Physicians questionnaire[21] 2. Asthma Control Test[22] 3. Risk Domain Asthma Control[19] 4. Overall Asthma Control 5. Short-acting β_2-agonist use • UK-ISAR: assessed by the Asthma Control Questionnaire[23]
Adherence	• OPCRD: assessed using the medication possession ratio, with good adherence to treatment defined as a ratio ≥70% (based on ICS prescription refills).[24] • UK-ISAR: assessed by asking the question, "is there evidence of poor adherence?" during systematic assessments, which was answered as "clinical impression," "prescription records," "objective measures," or "no."

Study outcomes

OPCRD patients with active asthma (aged ≥16 years) with 1 or more asthma medication were categorized according to GINA 2018[4] treatment step and number of exacerbations experienced/y. The proportion of patients in the OPCRD with PSA (with/without specialist review/referral in the last year) was quantified. Demographic and clinical characteristics were described for each patient cohort, using data from the latest available year for all outcomes. Demographic outcomes included age, sex, race, body mass index, and smoking history. Clinical outcomes included exacerbations/y, asthma control, lung function, asthma treatments, adherence, comorbidities (ie, allergic rhinitis, eczema, nasal polyps), and blood eosinophil count (BEC). Definitions of outcomes assessed are presented in Table I (full details in Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Statistics

Primary analyses. OPCRD data were assessed using Stata MP/6 version 15.1 (StataCorp LLC, College Station, Texas) and data for UK patients in the International Severe Asthma Registry (UK-ISAR) using Stata version 14 (College Station, Texas) or SAS version 9.4/9.5 (Cary, NC). Descriptive statistics for demographic and clinical characteristics for each patient cohort from the OPCRD and UK-ISAR were provided for continuous and categorical variables as either n (%) or mean (95% CI) and median (25th, 75th percentile), as appropriate. Mean values were compared using a *t* test, median values using Wilcoxon-Mann-Whitney, and categorical values suing χ^2 or Fishers exact for variables with small (ie, <5) values. A *P* value of less than .05 was considered statistically significant. The proportion of patients with PSA (n, %) (1) referred/reviewed in the last year and (2) *not* referred/reviewed in the last year was also calculated. Referral was defined as a referral code in OPCRD to a respiratory specialist.

Sensitivity analyses. The proportion of patients with 0, 1, 2, 3, 4, and 5 or more exacerbations/y was calculated for the PSA referred patient cohort, for those 16 years and older and 18 years and older, in the year before a referral to better understand referral drivers. In addition, for those OPCRD patients who were *not* referred/reviewed in the last year, a *post hoc* analysis was conducted to quantify the proportion of patients *not* referred/reviewed ever during the OPCRD look-back period (mean, 19.2 years; 95% CI, 19.1-19.3). Finally, the demographic and clinical characteristics of patients in each OPCRD cohort were described for patients 18 years and older and for those with a more than 5-year OPCRD look-back period. The former analysis was conducted to align with UK-ISAR age inclusion criterion and to facilitate cross-comparison between OPCRD and ISAR data. The latter analysis was a sensitivity analysis to determine whether the look-back period had an impact on demographic and clinical characteristic outcomes. Highest BEC recorded was also assessed for each patient cohort *post hoc*.

RESULTS

Study population

From an initial 900,785 patients in the OPCRD with a diagnosis of asthma before 2014 (and no other respiratory diagnosis), 207,557 patients met all inclusion criteria and were included in the analysis (Figure 1). Overall, 17.5%, 41.6%, and 2.6% of patients were receiving treatment at GINA 2018[4] step 3, 4, and 5, respectively. The number of exacerbations per year increased with treatment step (Figure 2). As expected, most patients receiving GINA step 5 treatment experienced 2 or more exacerbations/y, but many patients at lower GINA steps also experienced multiple exacerbations per year. A summary of asthma treatment by GINA 2018[4] step is provided in Table E2 in this article's Online Repository at www.jaci-inpractice.org.

Quantification and referral status of patients with PSA managed in UK primary care

A total of 8% (16,409 of 207,557) of patients with active asthma in UK primary care (aged ≥16 years) were found to have PSA (Figure 3); or 4% of patients (16,409 of 416,125) if one considers all patients (aged ≥16 years) with a diagnosis of asthma (not necessarily active). Overall, 10,963 of these 16,409 patients were at GINA 2018 step 4 and 2 or more exacerbations and 5446 were at GINA 2018 step 5. Of the 8% of patients with PSA, 72% (11,741 of 16,4096) had not been reviewed by or referred to a specialist in the past year; 56% (9,113) had no record of specialist referral or review ever during the OPCRD look-back period (mean, 19.2 years; 95% CI, 19.1-19.3). The remaining 16% of patients (n = 2628) had been referred or reviewed in specialist care, but more than 1 year ago (mean time since last review, 1.89 years) (Figure 3; see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

There were other patient cohorts within the OPCRD active asthma population that, despite not meeting the strict PSA criteria, nevertheless continued to experience 2 or more exacerbations/y at GINA 2018 step 3 (1%; n = 1,889 of 207,557) or were at GINA 2018 step 4 with 0 exacerbation/y (29%; 60,425 of 207,557) or 1 exacerbation/y (7%; n = 14,917 of 207,557).

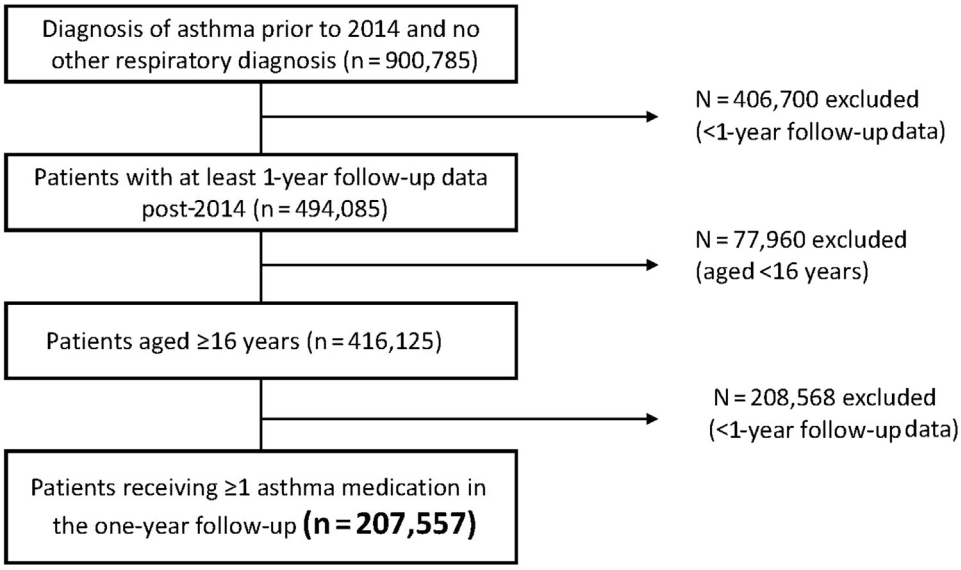

FIGURE 1. OPCRD subject disposition.

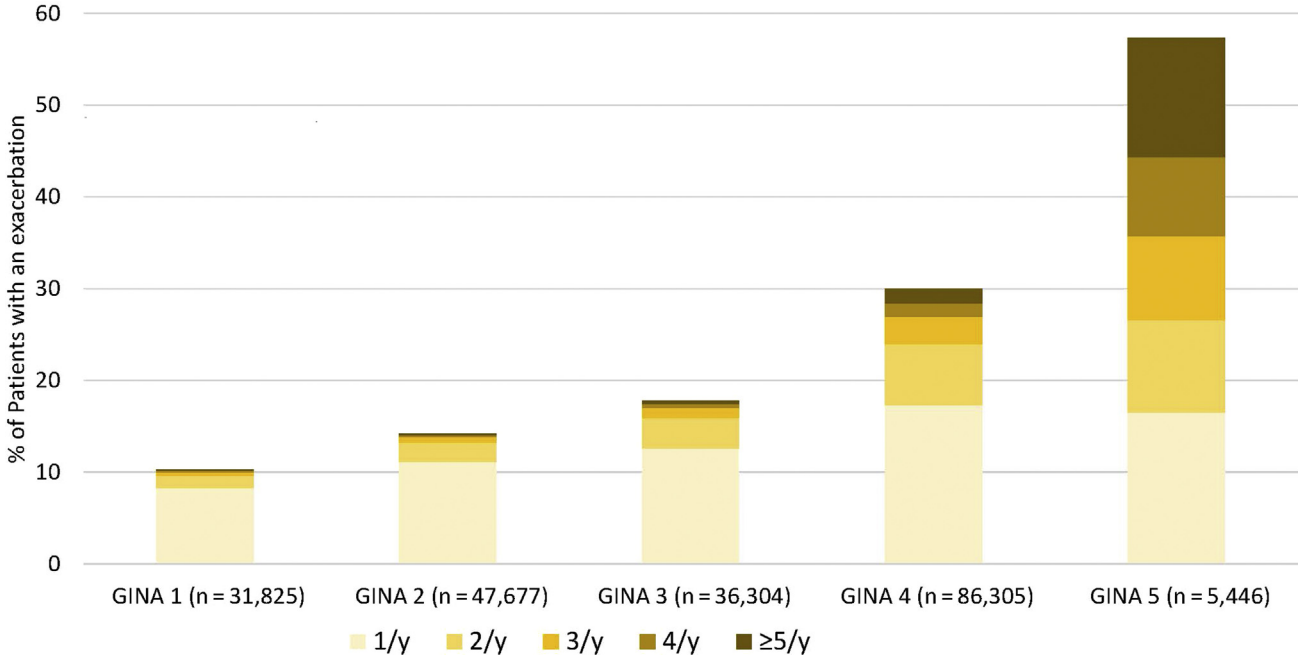

FIGURE 2. Number of exacerbations experienced by OPCRD patients (n = 207,557) by GINA 2018 treatment step.

Demographic and clinical characteristics

Characteristics of patients with PSA in primary care. Patients with PSA managed in UK primary care tended to be female, in their 60s, and overweight/obese (Table II). More than 70% of them were current or ex-smokers. These patients exhibited significant morbidity. Lung function was poor. More than 50% of patients had evidence of irreversible obstruction (ie, postbronchodilator FEV_1/forced vital capacity <0.7), and more than 60% of patients had a postbronchodilator peak expiratory flow rate less than 80% predicted. Although patients with PSA experienced a median of 2 to 3 exacerbations/y (Table II), not all patients with PSA experienced multiple exacerbations/y prereferral (Figure 4). Most had poorly controlled disease (>60% of patients were prescribed ≥4 short-acting β_2-agonist inhalers in the past year), despite treatment with ICS/long-acting β_2-agonist (ICS/LABA) (>40% patients) and add-on therapy (ie, leukotriene receptor antagonist and/or long-acting muscarinic receptor antagonist) for more than 40% of patients (Table II; Figure 5). Multimorbidity was also a feature of this population, most commonly allergic rhinitis and eczema (one-third of patients for each) (Table II).

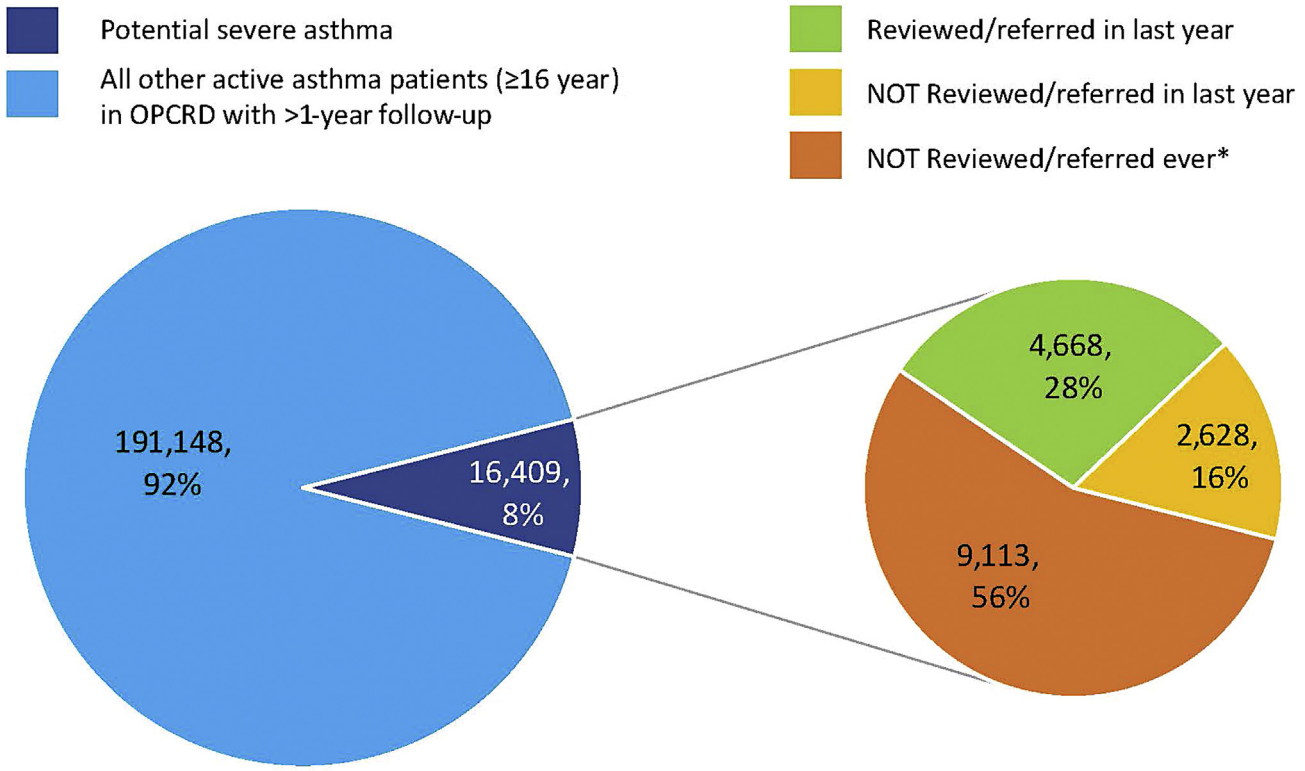

FIGURE 3. Proportion of patients with active asthma (age ≥16 years) managed in UK primary care with potential severe disease and their referral status. *During the OPCRD look-back period (mean, 19.2 years; 95% CI, 19.1-19.3).

Characteristics of patients with PSA in primary care *not* referred/reviewed in specialist care. Compared with patients with PSA who were referred to or reviewed by a specialist in the preceding year, those without a referral/review experienced significantly fewer exacerbations (median 2 vs 3/y; $P < .001$) in the last year (after referral) and had fewer prescriptions for add-ons to ICS/LABA therapy (39.8% vs 54.1% of patients; Figure 5). However, many referred patients with PSA (45.3%) experienced 0 exacerbations before referral (Figure 4). There was no significant difference in postbronchodilator FEV_1/forced vital capacity ratios between patients with PSA with and without a referral/review. Although patients with PSA without a referral/review also experienced significantly ($P < .001$) worse asthma control and lung function, were more likely ($P < .001$) to suffer from allergic rhinitis and anxiety/depression, and were less likely ($P < .05$) to have chronic rhinitis, diabetes, osteoporosis, and heart failure compared with referred patients with PSA, these differences were small (Table II; see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

PSA in primary care vs confirmed severe asthma in tertiary care. Compared with patients with PSA (aged ≥18 years) in primary care who were referred/reviewed by a specialist in the preceding year, patients with confirmed severe asthma (aged ≥18 years) managed in tertiary care were significantly ($P < .001$) younger, significantly ($P < .001$) more likely to have never smoked and to be of wider race diversity (Table II), reported more exacerbations and frequency (at first assessment) (Table II; Figure 4), have uncontrolled asthma (Table II; Figure E2), be prescribed add-ons to ICS/LABA therapy (Figure 5), and have nasal polyps and anxiety/depression, but less likely to have AR or eczema (Table II). Interestingly, those in tertiary care and referred patients with PSA from primary care had almost identical lung function and the proportions of patients with irreversible obstruction were similar in both groups. A total of 55% of patients with severe asthma managed in tertiary care were treated with biologics (Table II).

Sensitivity analyses

The results were similar for OPCRD cohorts 18 years or older (vs ≥16 years) and did not markedly differ from those with an OPCRD look-back period of more than 5 years (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

In this study we have introduced a classification of PSA for patients with asthma managed in primary care and quantified this population in the UK on the basis of well-defined primary care electronic medical records, described their demographic and clinical characteristics, and analyzed the respiratory specialist referral/review landscape. Using this approach, 8% of patients with active asthma managed in UK primary care had strong evidence of severe asthma and could benefit from referral to/review by an asthma specialist. However, 72% had neither been referred nor received specialist care for over a year, and 56% of patients had never been referred to or reviewed by a specialist from their inclusion in the OPCRD (mean, 19 years look-back period). Other primary care patient cohorts were also identified; patients with active asthma at GINA 2018 step 4

TABLE II. Demographic and clinical characteristics of patients with PSA (aged ≥16 years) in UK primary care (OPCRD) vs those UK patients with confirmed severe asthma in tertiary care (UK-ISAR)

	Primary care (OPCRD)			Primary care (OPCRD)	Tertiary care (UK-ISAR)	
Population	PSA *not* reviewed or referred in specialist care (age ≥16 y)	PSA reviewed/referred in specialist care in last year (age ≥16 y)	*P* value	PSA reviewed/referred in specialist care in last year (age ≥18 y)	Confirmed severe asthma (age ≥18 y)	*P* value
Demographic characteristic						
	N = 11,741	N = 4,668		N = 4,634	N = 714	
Age (y)						.001
Mean (95% CI)	62 (62.0-62.7)	63 (62.1-63.2)	NS	63 (62.4-63.4)	50 (48.8-50.8)	
Median (25th, 75th percentile)	65 (51, 76)	65 (51, 76)		65 (51, 76)	51 (40, 60)	
Female, n (%)	7,672 (65.3)	3,040 (65.1)	NS	3,019 (65.1)	458 (64.1)	NS
Race, n (%)	N = 5,093	N = 2,984	NS	N = 2,961		.001
White	3,144 (61.7)	1,821 (61.0)		1,806 (61.0)	488 (68.3)	
Black	46 (0.9)	47 (1.6)		46 (1.5)	50 (7.0)	
Asian	1 (0.0)	2 (0.1)		2 (0.1)	82 (11.5)	
Other	22 (0.4)	14 (0.5)		14 (0.5)	94 (13.2)	
Unknown	1,880 (36.9)	1,100 (36.9)		1,093 (36.9)	0 (0.0)	
Body mass index	N = 10,417	N = 3,962	NS	N = 3,933		NS
Mean (95% CI)	29.2 (29.1-29.4)	29.4 (29.2-29.7)		29.5 (29.2-29.7)	30.7 (30.2-31.3)	
Median (25th, 75th percentile)	28.2 (24.3, 33.1)	28.3 (24.2, 33.3)		28.3 (24.2, 33.4)	29.5 (25.8, 34.6)	
Underweight (<18.5), n (%)	321 (3.1)	133 (3.4)		130 (3.3)	5 (0.7)	
Normal weight (≥18.5-<25), n (%)	2,743 (26.2)	1,039 (26.2)		1,026 (26.1)	144 (20.2)	
Overweight (≥25-<30), n (%)	3,249 (31.0)	1,192 (30.1)		1,186 (30.1)	226 (31.6)	
Obese (≥30), n (%)	4,104 (39.2)	1,598 (40.3)		1,591 (40.5)	339 (47.5)	
Smoking status, n (%)	N = 11,674	N = 4,637	.001	N = 4,603	N = 712	.001
Never	2,945 (25.2)	1,021 (22.0)		1,001 (21.7)	492 (69.1)	
Current	2,459 (21.1)	914 (19.7)		910 (19.8)	29 (4.1)	
Ex-smoker	6,270 (53.7)	2,702 (58.3)		2,692 (58.5)	191 (26.8)	
Exacerbations						
Exacerbations/y (after referral)			.001			.001
Mean (95% CI)	2.36 (2.33-2.39)	3.22 (3.15-3.28)		3.21 (3.15-3.28)	5.13 (4.83-5.44)*	
Median (25th, 75th percentile)	2 (2, 3)	3 (2, 4)		2 (3,4)	4 (2, 7)	
Asthma control						
Asthma control RCP, n (%)	N = 5,000	N = 2,941	.001	N = 2,920		—
Controlled	2,312 (46.2)	1,015 (34.5)		1,008 (34.5)	—	
Partial control	—	—		—	—	
Not controlled	2,688 (53.8%)	1,926 (65.5%)		1,912 (65.5%)	—	
Asthma control ACT, n (%)	N = 664	N = 448	.001	N = 445	N = 690†	.001
Well controlled	58 (8.7)	19 (4.2)		19 (4.3)	33 (4.8)	
Reasonably	262 (39.5)	151 (33.7)		148 (33.2)	26 (3.8)	
Not controlled	344 (51.8)	278 (62.1)		278 (62.5)	631 (91.4)	
Asthma control RDAC, n (%)			.001			
Controlled	1,586 (13.5)	337 (7.2)		330 (7.1)	—	—
Not controlled	10,155 (86.5)	4,331 (92.8)		4,304 (92.9)	—	
Asthma control OAC, n (%)			.001			—

(continued)

TABLE II. *(Continued)*

Population	Primary care (OPCRD)			Primary care (OPCRD)	Tertiary care (UK-ISAR)	
	PSA *not* reviewed or referred in specialist care (age ≥16 y)	PSA reviewed/referred in specialist care in last year (age ≥16 y)	*P* value	PSA reviewed/referred in specialist care in last year (age ≥18 y)	Confirmed severe asthma (age ≥18 y)	*P* value
Controlled	928 (7.9)	150 (3.2)		144 (3.1)	—	
Not controlled	10,813 (92.1)	4,518 (96.8)		4,490 (96.9)	—	
SABA use, n (%)			.001			—
<4 inhalers	4,284 (36.5)	1,428 (30.6)		1,424 (30.7)	—	
≥4 inhalers (not controlled)	7,457 (63.5)	3,240 (69.4)		3,210 (69.3)	—	
Lung function			.001			NS
% predicted postbronchodilator FEV_1	N = 5,149	N = 2,405		N = 2,398	N = 653	
Mean (95% CI)	0.72 (0.71-0.72)	0.69 (0.68-0.70)		0.69 (0.68-0.70)	0.70 (0.68-0.72)	
Patients with postbronchodilator FEV_1 >80%, n (%)	6,599 (56.2)	2,256 (48.4)	NS	2,236 (48.3)	—	—
% predicted postbronchodilator FVC	N = 4,021	N = 1,931	.001	N = 1,926	N = 643	NS
Mean (95% CI)	0.85 (0.84-0.85)	0.82 (0.81-0.83)		0.82 (0.81-0.83)	0.87 (0.85-0.88)	
Postbronchodilator FEV_1/FVC‡	N = 5,249	N = 2,503	NS	N = 1,709	N = 697	NS
Mean (95% CI)	0.78 (0.72-0.90)	0.78 (0.72-0.92)		0.78 (0.72-0.90)	0.66 (0.65-0.68)	
<0.70, %	52.4	53.4		53.4	56.4	
% predicted PEF rate	N = 2,498	N = 1,678	NS	N = 1,678	—	—
Mean (95% CI)	0.75 (0.74-0.76)	0.73 (0.72-0.74)		0.73 (0.72-0.74)		
≥80%, n (%)	964 (38.3)	636 (37.6)		629 (37.5)		
BEC						
	N = 11,147	N = 4,458	NS	N = 4,442	N = 712	
Median BEC (25th, 75th percentile)	230 (152-350)	231 (154-343)		231 (154-343)	NA	—
Median highest BEC (25th, 75th percentile)	260 (160-400)	270 (170-400)		270 (170-400)	278 (269-287)	NS
Other treatments, n (%)						
Theophylline	935 (8.0)	640 (13.7)	NS	636 (13.7)	173 (24.2)	NS
Biologics	0 (0.0)	19 (0.2)		10 (0.2)	393 (55.0)	
Adherence, n (%)						
	N = 4,303	N = 4,303	.001	N = 4,279	N = 708§	.001
≥70% MPR of ICS	5,176 (51.6)	2,416 (56.1)		2,403 (56.2)	520 (73.4)	
Comorbidities, n (%)‖						
Allergic rhinitis	3,660 (31.2)	1,245 (26.7)	.001	1,238 (26.7)	33 (4.6)	.001
Chronic rhinosinusitis	495 (4.2)	241 (5.2)	.05	239 (5.1)	NA	—
Eczema	3,822 (32.5)	1,456 (31.3)	NS	1,445 (31.2)	20 (2.8)	.001
Nasal polyps	801 (6.8)	317 (6.8)	NS	316 (6.8)	173 (24.2)	.001
Anxiety/depression	191 (1.6)	39 (0.8)	.001	39 (0.8)	20 (2.8)	.001
Diabetes	1,058 (9.0)	585 (12.6)	.001	585 (12.6)	2 (0.3)	.001
GERD	2,324 (19.7)	970 (20.7)	NS	968 (20.8)	NA	NS
Osteoporosis	928 (7.9)	431 (9.3)	.05	431 (9.3)	2 (0.3)	.001
Heart failure	424 (3.6)	212 (4.6)	.05	212 (4.6)	1 (0.1)	.001

ACT, Asthma Control Test; *FVC*, forced vital capacity; *MPR*, medication possession ratio; *NA*, not applicable/available; *NS*, not significant; *OAC*, overall asthma control; *PEF*, peak expiratory flow; *RCP*, Royal College of Physicians; *RDAC*, Risk Domain Asthma Control; *SABA*, short-acting β_2-agonist.

*At first assessment.

†Assessed by the Asthma Control Questionnaire.

‡Age-standardized FEV_1/FVC ratios.

§Adherence assessed via the probe question, "is there evidence of poor adherence."

‖OPCRD: based on having a diagnosis at any point in time; ISAR: patient self-reported.

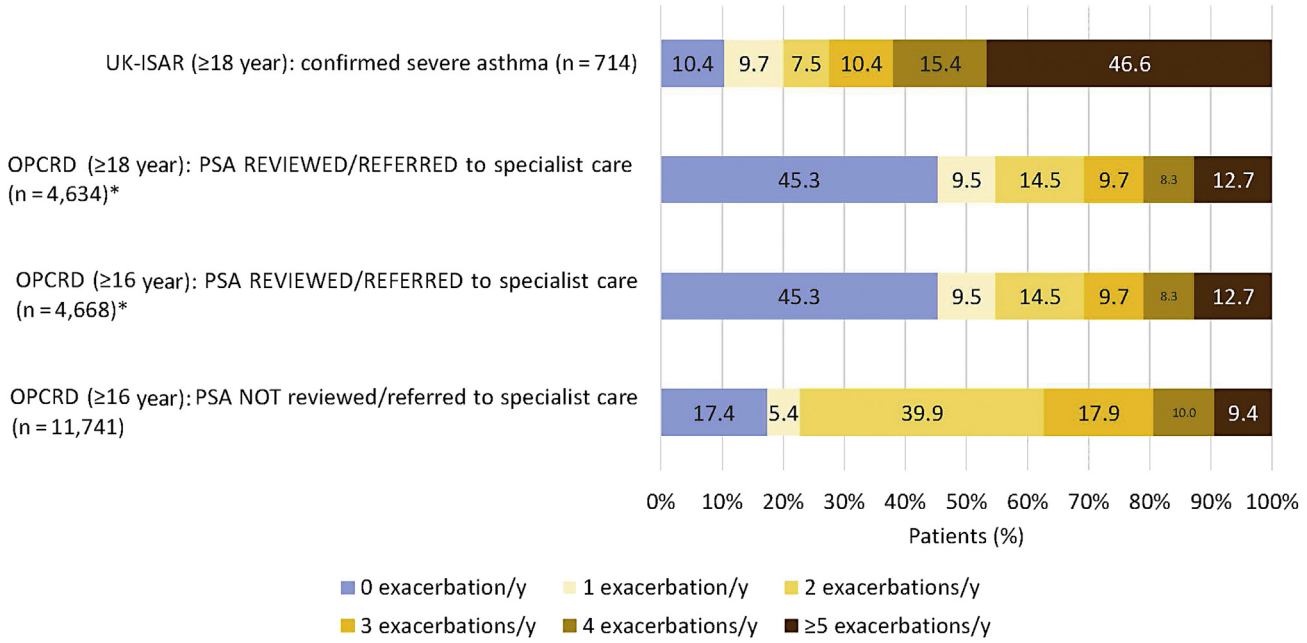

FIGURE 4. Proportion of patients in each cohort according to number of exacerbations experienced per year. *UK-ISAR*, UK patients in the ISAR. *For those patients referred to specialist care, the exacerbation rate is the rate in the year before referral.

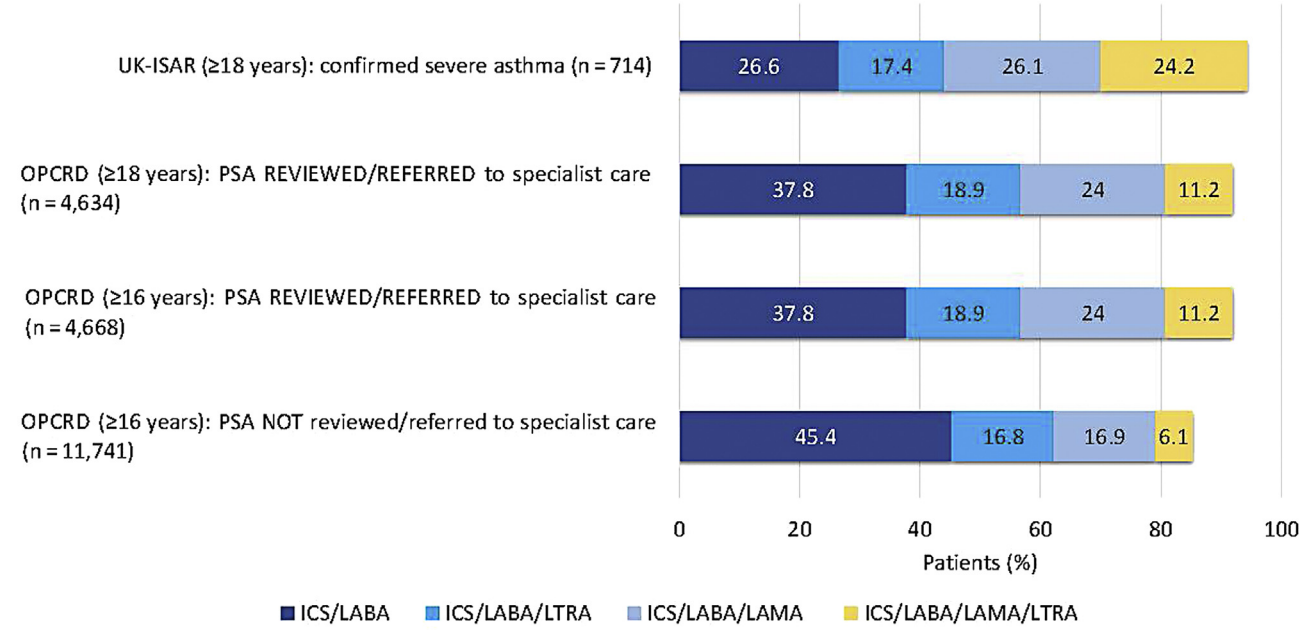

FIGURE 5. Proportion of patients in each cohort on a multiple asthma treatment regimen. *LAMA*, Long-acting muscarinic receptor antagonist; *LTRA*, leukotriene receptor antagonist; *UK-ISAR*, UK patients in the ISAR.

treatment but experienced 0 exacerbation/y (29%). These patients may be overtreated and could benefit from treatment step-down pending review of control status. Furthermore, 8% of patients were either receiving GINA 2018 step 3 treatment with 2 or more exacerbations/y or receiving GINA 2018 step 4 treatment with 1 exacerbation/y. This group should be considered for careful assessment/reassessment in primary care to determine whether a specialist referral/review is warranted, but further research is needed to confirm this.

Patients with PSA managed in UK primary care tended to be female, in their 60s, either current or ex-smokers, and characterized by high rescue short-acting β_2-agonist use, add-on medications to ICS/LABA therapy, poor lung function and asthma control, frequent exacerbations, and high

multimorbidity rates (Table II; see Table E4 in this article's Online Repository at www.jaci-inpractice.org). Taken together, these characteristics may help primary care physicians recognize those with hidden severe asthma in their care, and prompt referral. Although the older age and smoking history of patients with PSA may have suggested that some of them had chronic obstructive pulmonary disease or asthma-chronic obstructive pulmonary disease overlap, the mean FEV_1/forced vital capacity ratio was 0.78, higher than that reported in the ISAR cohort (0.66) where asthma has been confirmed. In either case, it is important to refer these patients with PSA to confirm an asthma diagnosis, exclude chronic obstructive pulmonary disease, manage comorbidities, and treat appropriately. Furthermore, the low rate of current/ex-smokers in the confirmed severe asthma ISAR cohort may indicate a bias against referring smokers to severe asthma services. These clinical characteristics match very well with those reported for patients with severe asthma managed in secondary and tertiary care in other countries,[25-27] and in the UKSAR,[28] providing confidence in the definition of PSA used in our study. For example, a survey of 104 French pulmonologists, including information from 1502 patients with severe asthma managed in secondary care, found that these patients were typically in their 50s, more frequently female, had poorly controlled asthma (despite common ICS therapy add-ons, eg, leukotriene receptor antagonist and anticholinergics), a high OCS burden, and commonly presented with ear, nose, and throat comorbidities and a high BEC.[25] Similarly, in the United Kingdom, patients with severe asthma had significantly higher comorbidity rates than those with mild to moderate disease, for conditions associated with systemic corticosteroid exposure (eg, type II diabetes mellitus, osteoporosis, dyspeptic disorders, and cataracts).[28] However, in the current study, although patients with asthma referred to tertiary care were at the severe end of the primary care asthma population, their asthma was not as severe as those managed in tertiary care (ie, UK-ISAR). This is most likely driven by the National Institute for Health and Care Excellence requirement for 4 or more exacerbations in the previous 12 months to qualify for biologic therapy.

In the current study, only 28% of patients in the PSA group had received specialist care in the previous year. The fate of these patients warrants further study (eg, % referred back to primary care; % with severe asthma confirmed). The use of more asthma therapies, including triple and quadruple therapy regimens, appeared to be the main driver of referral/review. Interestingly, asthma control status, lung function, ICS adherence (measured by medication possession ratio), and BEC profile did not markedly differ between those with and without a referral. Furthermore, exacerbation rate was not a referral driver for all patients with PSA, because many of those referred had not experienced an exacerbation in the year before referral. Other studies conducted in the United Kingdom have shown a similar reticence to refer to specialist care.[7,9] The Observational cohort study to investigate the unmet need and time waiting for referral for specialist opinion in adult asthma in England study found that of 19,837 patients with asthma (age 18-65 years) eligible for referral in the United Kingdom according to British Thoracic Society/Scottish Intercollegiate Guidelines Network 2016 criteria,[28] only 4% were referred during follow-up, with a median waiting time to specialist care of 2.4 years.[7] In addition, the National Review of Asthma Deaths report (2014) found that of patients who had died because of asthma in the United Kingdom, 47% had not been under specialist supervision during the 12 months before death.[9] Similar findings have been reported in other countries.[8,29-31] For example, the Prevalence, characteristics and management of frequently exacerbating asthma patients: an observational study in Sweden that included 790 patients with severe asthma in primary care in Sweden found that more than half of these patients had poor asthma control, but 4 of 5 patients had no contact with secondary care in the previous year.[30] Similarly, results from the Asthma Insight and Management Survey conducted in the United States in 2009 including 2500 patients with asthma found that 48% had never visited a specialist (although some of these may have had mild disease).[8]

These data indicate an apparent reluctance to refer (and/or be referred), but further work is needed to understand this behavior. Possible reasons for lack of referral include clinical inertia; underestimation of asthma severity and the long-term effects of OCS, high-dose ICS, and high use of short-acting β_2-agonist[32,33]; lack of a confirmed asthma diagnosis (many primary care physicians do not perform confirmatory spirometry); perception that asthma is a primary care disease; and lack of awareness, both of newer treatments available at specialist care (eg, biologics) and of asthma referral guidelines.[6] Other barriers include high referral hurdles (ie, only those with very severe disease qualify), lack of coordination between different parts of the health care system,[34] patient attitudes/expectations,[35] financial pressures,[36] and underresourcing; currently, there are 1.86 adult respiratory physicians/100,00 people in the United Kingdom compared with the European average of 4.4/100,000.[37]

Numerous guidelines are available that provide guidance on when a patient with asthma should be referred to a specialist.[4,28,38] According to the British Thoracic Society guidelines (2016),[28] adults with asthma should be referred to specialist care in cases of diagnostic uncertainty, if they are high risk (eg, marked blood eosinophilia, poor response to asthma treatment at GINA step 4, and/or suffer a severe asthma exacerbation), if they have a high corticosteroid burden (eg, on high-dose ICS or continuous/frequent use of OCS), and if biologics are considered. More than half the patients with PSA in the current study had never received a specialist referral/review (since inclusion in OPCRD), despite meeting these criteria, suggesting there remains a high prevalence of hidden severe asthma in the United Kingdom. Unfortunately, in real life, patients with severe asthma often experience several exacerbations and emergency department admissions before specialist referral,[6,9] and referral can be further delayed by long waiting times.[7] For example, the average time since last referral (for those patients with PSA who were referred) was 1.89 years in our study. During this time patients may not receive optimal therapy for asthma or may be poorly adherent to an optimal treatment regimen and are often prescribed maintenance OCS or repeated steroid bursts to treat exacerbations, with potential deleterious effects.[39,40] Although both ICS and OCS have a positive impact on controlling symptoms and exacerbations,[41,42] cumulative OCS use is associated with increased risk of acute and chronic adverse events (eg, increased risk of diabetes and osteoporosis),[43] increased health care resource use, and increased costs.[39] Indeed, a recently published Swedish study found that the total health care cost was 3 times greater for patients taking OCS regularly (€5615) and twice as high for patients taking OCS

intermittently (€2948), compared with non-OCS users (€1980).[44] Similarly, in the United Kingdom, general practice average annual costs for adverse outcomes and asthma were 42% greater for patients with active asthma exposed to systemic corticosteroids (vs those who were not).[45]

The benefits of a timely and appropriate referral/review by an asthma specialist are well documented, and include a diagnostic review, treatment optimization (including immunotherapy and biologics and improved adherence), and improved self-management education (eg, inhaler technique). Specialist review of difficult-to-treat and severe asthma has been associated not only with an improvement in asthma control, quality of life, lung function, and exacerbation rate but also with reduced OCS burden.[46,47] Higher costs associated with specialist review could, thus, be offset against these benefits. However, not all patients with uncontrolled asthma on standard-of-care therapy should be referred or have severe asthma. This is evident in the current study by observed differences in the demographic and clinical characteristics of patients with PSA who were referred from primary care in the last year and those with a confirmed severe asthma diagnosis managed in tertiary care. Before referral, primary care physicians should play a key role in "referral triage," assessing their patients with asthma using a structured methodology (eg, **S**moking status, **I**nhaler technique, **M**onitoring, **P**harmacotherapy, **L**ifestyle, **E**ducation, **S**upport approach)[5] and selecting only those with an accurate asthma diagnosis who continue to have poor control despite guideline-directed therapy, good adherence and inhaler technique, and appropriate management of any comorbidities.[5,48] Such an approach would avoid unnecessary treatment step-up, streamline asthma assessment at the primary care level, and optimize referrals to specialist care. Shared decision making should be encouraged to facilitate patient-centered care that ensures patients with severe asthma get the right treatment, at the right time, and for the right reason(s).

One limitation of the current study is the use of prescription data to define PSA with the assumptions that medications were (1) prescribed correctly in line with GINA 2018 recommendations and (2) taken as directed. Furthermore, OCS burden was not used to define severity due to difficulties in differentiating between long-term and acute use in the OPCRD. In addition, although the presence of a referral code in the OPCRD provided a clear indication of the referral status of patients (and time since last referral), no data were captured on the reason(s) for referral, pathway to referral (eg, from primary care and A&E department), and/or whether the patient attended. Knowledge of referral reasons would allow cross-reference with British Thoracic Society/Scottish Intercollegiate Guidelines Network referral criteria[28] to assess compliance with recommendations. Knowledge of the referral pathway and "did not attend" prevalence could provide a more accurate estimation of the true prevalence of hidden severe asthma in UK primary care. Finally, information on the type of respiratory specialist referred to (and their level of asthma expertise) is not captured by OPCRD. To counterbalance these limitations, it should be noted that, because of its size, the OPRCD enabled us to identify and study a large cohort of patients with PSA managed in UK primary care. Data contained within the OPCRD come from electronic medical records and have been used frequently for observational research.[49-51] These data provide a snapshot of patients with asthma managed in real life in practices all over the United Kingdom. Finally, by virtue of the number of disease-specific variables collected by OPRCD, we were able to compare patient cohorts using a comprehensive list of demographic and clinical characteristics.

CONCLUSIONS

There are large numbers of patients with asthma in the United Kingdom with PSA who are managed long-term in primary care who, after specialist assessment, may be eligible for biologic therapy. These patients would benefit from a structured assessment by their primary care physician (**S**moking status, **I**nhaler technique, **M**onitoring, **P**harmacotherapy, **L**ifestyle, **E**ducation, **S**upport),[5] with referral to specialist care if appropriate. A standard national asthma template would be useful to facilitate a structured asthma review at the primary care level (with input from other health care providers, eg, pharmacists and asthma nurses) to help identify those patients who would most benefit from specialist review. Further work is necessary to determine reasons for, and barriers to, specialist referral in the United Kingdom, how many of those patients referred have severe asthma, and the fate of patients discharged from specialist care, or who continue to be managed long-term in primary care. Combining primary and tertiary care data in severe asthma registries is one way to answer these questions. This would enable better monitoring of patients over their disease life cycle, facilitate tracking through the health care system—from primary to tertiary care and back again—improve communication between primary physicians and tertiary specialists, and improve the quality of care for patients with severe asthma.

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ONLINE REPOSITORY

Appendix

Optimum Patient Care Research Database. At the time this study was conducted, OPCRD contained anonymous, longitudinal records from June 1930 to March 2019. Quality of care for patients with asthma is encouraged for General Practitioner practices in the United Kingdom through the quality and outcomes framework initiative, by incentivizing collection of key clinical metrics (including asthma review and assessment of asthma control).[E1] OPCRD benefits from a long retrospective period (mean time in the database is 13 years, going back to birth for summary diagnostic data in 44% of cases), and contains linked patient-completed respiratory questionnaires for approximately 10% of patients with asthma included.[E2] The OPCRD is approved by the UK National Health Service for clinical research use (Research Ethics Committee reference 15/EM/0150).

The OPCRD is approved by the Health Research Authority for clinical research use and governed by the Anonymized Data Ethics and Protocols Transparency Committee.[E3] The Anonymized Data Ethics and Protocols Transparency Committee is an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group to govern the standard of research conducted on internationally recognized databases.[E4]

TABLE E1. Definition of demographic and clinical outcomes

Variable name	Description
Demographic outcomes	
Age	Age in years Defined at the start of the most recent year of data
Sex	Female or male
Ethnicity	Patients classified by ethnicity as categorized within clinical records as specified by the GLI 2012 definitions.[E5] Categorized as • Caucasian • Black • South East Asian • North East Asian • Not specified
Height	Defined as the patient's most recent height data recorded in their clinical records
BMI	The ratio of weight (kg) to height^2 (m^2). Defined by either a BMI recorded as part of the patient's clinical record or calculated using the most recent height and weight data. Categorized as • underweight (<18.5 kg/m^2) • normal weight (≥18.5 kg/m^2 and <25 kg/m^2) • overweight (≥25 kg/m^2 and <30 kg/m^2) • obese (≥30 kg/m^2)
Smoking status	Patient's most recent smoking status. Defined by most recent patient's clinical smoking recording. Patients' records with a "never" recording after ex or current will be disregarded. Categorized as • Nonsmoker • Current smoker • Ex-smoker
Clinical characteristics	
No. of exacerbations	No. of asthma exacerbations requiring OCSs during the study period
Exacerbation in the year	A count of exacerbations/y
Asthma control	OPCRD Patients 1. RCP Asthma 3-Questions.[E6] Defined by clinical records of RCP control within the latest year of data. Patients are classified as having poor control if 2 or 3 of the measures denote poor control or if patients experience difficulty sleeping because of their asthma symptoms 2. ACT[E7] Defined by clinical records using the ACT questionnaire within the latest year of data. • ACT score ≤19—Not controlled • ACT score 20-24—Reasonably controlled • ACT score 25—Controlled 3. Control measured by SABA use: Use of >3.65 SABA canisters in a year indicates poor asthma control[E8] 4. Risk Domain Asthma Control: Uncontrolled if any of the following occur in a 12-mo assessment period[E9]: • Primary care exacerbation Read Code • Acute use of OCS with evidence of lower respiratory tract consultation • Antibiotics prescribed with evidence of lower respiratory tract consultation ISAR patients Categorized according to the ACQ.[E10] The 7-item ACQ was developed to measure the primary goals of asthma management as identified by international guidelines. Categorized as: • ACQ score ≤0.75—Controlled • ACQ score >0.75-1.25—Partial control • ACQ score >1.25—Not controlled
BEC	BEC (average) measured in cells per liter (10^9/L) recorded within the last year of data, not within 14 d of an OCS prescription. Categorized as • ≤0.15 • >0.15-≤0.3 • >0.3-≤0.45 • >0.45

(continued)

TABLE E1. *(Continued)*

Variable name	Description
FEV_1 (taken at the same time as an asthma review)	Maximum forced expiratory volume (FEV_1) in the first second of expiration within the last 5 y of available data
% Predicted FEV_1	Predicted value of FEV_1 standardized according to ethnicity, age, sex, and height using GLI 2012
FVC (taken at the same time as an asthma review)	Maximum FVC within the last 5 y of available data
% Predicted FVC	Predicted value of FVC standardized according to ethnicity, age, sex, and height using GLI 2012
FEV_1/FVC ratio (taken at the same time as an asthma review)	Measured FEV_1 as a ratio of measured FVC
PEF (taken at the same time as an asthma review)	PEF (L/min) recorded using Read Code within the last year of available data
% Predicted PEF	Predicted value of PEF standardized according to ethnicity, age, sex, and height. Categorized as • % Predicted PEF—0%-50% • % Predicted PEF—>50%-80% • % Predicted PEF—>80%
FENO test	Measurements of FENO concentration in exhaled breath, measured in ppb at a flow rate of 50 mL/s within the last 5 y of available data. Categorized as • low (<25 ppb) • intermediate (25-50 ppb) • high (>50 ppb)
MPR (surrogate marker for adherence in OPCRD only)	Good adherence to treatment defined as an MPR ≥70%, measure based on ICS prescription refills
Adherence in ISAR	In response to the question, "Is there evidence of poor adherence?," which is answered as either • clinical impression • prescription records • objective measures (eg, evidence of FENO suppression) or • no
Respiratory treatments	• ICS/LABA • ICS/LABA/LTRA • ICS/LABA/LAMA • ICS/LABA/LAMA/LTRA • SABA • Theophylline • Biologic treatments
Comorbidities (all comorbidities are considered at any point in time except for anxiety/depression, which is considered only if within the last year)	• Allergic rhinitis • Eczema • Nasal polyps • Anxiety/depression • Diabetes • Osteoporosis • Heart failure

ACQ, Asthma Control Questionnaire; *ACT*, Asthma Control Test; *BMI*, body mass index; *FENO*, fractional exhaled nitric oxide; *FVC*, forced vital capacity; *LAMA*, long-acting muscarinic receptor antagonist; *LTRA*, leukotriene receptor antagonist; *MPR*, medication possession ratio; *PEF*, peak expiratory flow; *ppb*, parts per billion; *RCP*, Royal College of Physicians; *SABA*, short-acting β_2-agonist.

TABLE E2. Summary of asthma treatments by GINA (2018) step

GINA (2018) treatment step	Asthma treatment
Step 1	• Only β-agonist or • Only muscarinic agonist
Step 2	• Low-dose ICS without other controllers or • LTRA without other controllers or • Low-dose theophylline all without other controllers
Step 3	• Medium- or high-dose ICS without other controllers or • Low-dose ICS/LABA or • Low-dose ICS/LAMA or • Low-dose ICS (without LABA/LAMA) and/or theophylline or • LABA and/or LAMA (without ICS) or • LTRA plus theophylline (without ICS)
Step 4	• Medium- or high-dose ICS/LABA or • Medium- or high-dose ICS/LAMA or • Medium- or high-dose ICS plus LTRA and/or theophylline or • ≥3 controllers (without ICS)
Step 5	• Maintenance OCS plus any other asthma treatment or • Anti-IgE therapy

LAMA, Long-acting muscarinic antagonist; *LTRA*, leukotriene receptor antagonist.

TABLE E3. Demographic and clinical characteristics of patients with asthma in primary care (OPCRD) for those patients 18 y or older with and without a >5-y OPCRD look-back period

	OPCRD potential severe asthma NOT REFERRED to specialist care		OPCRD potential severe asthma REFERRED to specialist care	
	Without >5-y look-back period	With > 5-y look-back period	Without >5-y look- back period	With >5-y look-back period
Characteristic	**(n = 11,701)**	**(n = 9,918)**	**(n = 4,634)**	**(n = 3,888)**
Age (y)				
Mean (95% CI)	62 (62.2-62.8)	63.9 (63.6-64.3)	63 (62.4-63.4)	64.3 (63.7-64.8)
Median (25th, 75th percentile)	65 (51, 76)	66 (53, 77)	65 (51, 76)	67 (53, 77)
Sex, n (%)				
Male	4,052 (34.6)	3,456 (35)	1,615 (35)	1,370 (35)
Female	7,640 (65)	6,454 (65)	3,019 (65)	2,526 (65)
Ethnicity				
White, n (% nonmissing)	3,137 (61.8)	2,595 (61.0)	1,814 (61.0)	1,488 (60.4)
Black, n (%)	46 (0.9)	35 (0.8)	46 (1.6)	33 (1.3)
Asian, n (%)	1 (0.0)	1 (0.0)	2 (0.1)	2 (0.1)
Mixed/other, n (%)	22 (0.4)	17 (0.4)	14 (0.5)	10 (0.4)
Unknown, n (%)	1,873 (36.9)	1,611 (37.8)	1,093 (37.0)	928 (37.8)
Missing, n (% all records)	6,613 (56.6)	5,651 (57.0)	1,674 (36.1)	1,434 (36.8)
BMI (kg/m^2)				
Mean (95% CI)	29.2 (29.1-29.4)	29.3 (29.1-29.4)	29.3 (29.1-29.4)	29.4 (29.1-29.6)
Median (25th, 75th percentile)	28.2 (24.3, 33.1)	28.2 (24.3, 33.1)	28.3 (24.2, 33.4)	28.2 (24.2, 33.2)
BMI categories				
Underweight (<18.5), n (% nonmissing)	315 (3.0)	272 (3.1)	130 (3.3)	107 (3.2)
Normal weight (≥18.5 & <25), n (% nonmissing)	2,723 (26.3)	2,302 (26.0)	1,028 (26.1)	873 (26.3)
Overweight (≥25 & <30), n (% nonmissing)	3,240 (31.2)	2,776 (31.4)	1,189 (30.1)	1,008 (30.3)
Obese (≥30), n (% nonmissing)	4,096 (39.5)	3,505 (39.6)	1,594 (40.5)	1,334 (40.2)
Missing, n (% all records)	1,318 (11.3)	1,055 (10.7)	702 (15.1)	574 (14.7)
Smoking status				
Never, n (% nonmissing)	2,908 (25.0)	2,311 (23.3)	1,003 (23.4.7)	803 (20.7)
Current, n (% nonmissing)	2,453 (21.1)	1,981 (20.0)	912 (19.8)	721 (18.6)
Ex-smoker, n (% nonmissing)	6,265 (53.9)	5,577 (56.3)	2,697 (58.5)	2,356 (60.7)
Missing, n (% all records)	66 (0.6)	41 (0.4)	31 (0.7)	16 (0.4)
Exacerbations (1 y after referral)				
Mean (95% CI)	2.36 (2.33-2.39)	2.35 (2.31-2.39)	3.22 (3.15-3.28)	3.2 (3.13-3.28)
Median (25th, 75th percentile)	2 (2, 3)	2 (2, 3)	3 (2, 4)	3 (2, 4)
Exacerbation per year, n (%)				
0	2,033 (17.4)	1,771 (17.9)	286 (6.0)	254 (6.4)
1	632 (5.4)	551 (5.6)	265 (5.7)	226 (5.8)
2	4,657 (39.8)	3,895 (39.3)	1,609 (34.8)	1,346 (34.6)
3	2,100 (17.9)	1,774 (17.9)	952 (20.5)	797 (20.5)
4	1,168 (10.0)	975 (9.8)	588 (12.6)	489 (12.6)
≥5	1,102 (9.4)	945 (9.5)	943 (20.3)	783 (20.1)
Asthma control,* RCP Questionnaire				
Controlled, n (% nonmissing)	2,303 (46.3)	2011 (46.8)	1,010 (34.5)	852 (35.0)
Partial control, n (% nonmissing)	—	—	—	—
Not controlled, n (% nonmissing)	2,673 (53.7)	2,282 (53.2)	1,916 (65.5)	1,586 (65.0)
Missing, n (% all records)	6,716 (57.4)	5617 (56.7)	1,717 (37.0)	1,458 (37.4)
Asthma control,† ACT				

(continued)

TABLE E3. *(Continued)*

	OPCRD potential severe asthma NOT REFERRED to specialist care		OPCRD potential severe asthma REFERRED to specialist care	
	Without >5-y look-back period	With > 5-y look-back period	Without >5-y look- back period	With >5-y look-back period
Characteristic	**(n = 11,701)**	**(n = 9,918)**	**(n = 4,634)**	**(n = 3,888)**
Well controlled, n (% nonmissing)	57 (8.7)	51 (9.1)	19 (4.3)	14 (3.9)
Reasonably controlled, n (% nonmissing)	260 (39.5)	219 (39.2)	148 (33.3)	122 (33.9)
Not controlled, n (% nonmissing)	341 (51.8)	289 (51.7)	278 (62.5)	224 (62.2)
Missing, n (% all records)	11,034 (94.3)	9,351 (94.4)	4,198 (90.4)	3,536 (90.7)
Control measured by SABA use, n (%)				
<4 inhalers—No evidence of lack of control	4,270 (36.2)	3,360 (36.9)	1,429 (30.7)	1,222 (31.3)
≥4 inhalers—Not controlled	7,422 (63.8)	6,250 (63.1)	3,214 (69.3)	2,674 (68.7)
Risk Domain Asthma Control, n (%)				
Controlled	1,586 (13.6)	1,378 (13.9)	333 (7.1)	285 (92.8)
Not controlled	10,106 (86.4)	8,532 (86.1)	4,310 (92.9)	3,611 (7.3)
BEC				
Mean (95% CI)	295 (289-301)	296 (289-304)	299 (285-312)	299 (284-314)
Median (25th, 75th percentile)	230 (152, 350)	232 (155, 350)	230 (153, 342)	230 (155, 343)
≤0.15, n (% nonmissing)	2,595 (23.3)	2,169 (22.7)	1,021 (23.0)	861 (22.8)
>0.15-≤0.3, n (% nonmissing)	4,659 (41.9)	4,078 (42.6)	1,930 (43.4)	1,644 (43.6)
>0.3-≤0.45, n (% nonmissing)	2,236 (20.1)	1,920 (20.1)	881 (19.8)	760 (20.1)
>0.45, n (% nonmissing)	1,624 (14.7)	1,359 (14.6)	619 (13.8)	513 (13.5)
Missing, n (% all records)	578 (4.9)	348 (3.5)	192 (4.1)	118 (3.0)
Postbronchodilator FEV_1				
Mean (95% CI)	1.85 (1.83-1.87)	1.83 (1.80-1.84)	1.77 (1.74-1.80)	1.75 (1.72-1.79)
Missing, n (% all records)	6,557 (56.1)	5,398 (54.5)	2,243 (48.3)	1,815 (46.5)
% Predicted postbronchodilator FEV_1‡				
Mean (95% CI)	0.72 (0.71-0.72)	0.75 (0.71-0.72)	0.69 (0.68-0.70)	0.68 (0.67-0.69)
Postbronchodilator FVC				
Mean (95% CI)	2.81 (2.78-2.84)	2.79 (2.76-2.82)	2.73 (2.69-2.78)	2.71 (2.66-2.75)
% Predicted postbronchodilator FVC‡				
Mean (95% CI)	0.85 (0.84-0.85)	0.85 (0.84-0.85)	0.82 (0.81-0.83)	0.82 (0.81-0.83)
Postbronchodilator FEV_1/FVC ratio				
Mean (95% CI)	0.67 (0.67-0.68)	0.67 (0.66-0.67)	0.66 (0.65-0.67)	0.66 (0.65-0.66)
% Patients FEV_1/FVC ratio <70%	52.5	53.3	53.4	54.7
Postbronchodilator (PEF)				
Mean (95% CI)	321 (318-325)	318 (314-322)	313 (308-318)	309 (304-314)
Postbronchodilator % PPEF				
<50%, n (% nonmissing)	261 (10.5)	233 (11.1)	228 (13.6)	195 (14.1)
≥50%-<80%, n (% nonmissing)	1,278 (51.3)	1,073 (51.1)	825 (48.9)	690 (49.6)
≥80%, n (% nonmissing)	954 (38.2)	797 (37.9)	630 (37.5)	505 (36.4)
Missing, n (% all records)	9,199 (78.7)	7,807 (78.8)	2,960 (63.8)	2,506 (64.4)
FENO				
Low (<25 ppb), n (% nonmissing)	1 (33.3)	1 (50.0)	1 (100)	1 (100)

(continued)

TABLE E3. *(Continued)*

	OPCRD potential severe asthma NOT REFERRED to specialist care		OPCRD potential severe asthma REFERRED to specialist care	
	Without >5-y look-back period	With > 5-y look-back period	Without >5-y look- back period	With >5-y look-back period
Characteristic	**(n = 11,701)**	**(n = 9,918)**	**(n = 4,634)**	**(n = 3,888)**
Intermediate (25-50 ppb), n (% nonmissing)	2 (66.7)	1 (50.0)	0 (0.0)	0 (0.0)
High (>50 ppb), n (% nonmissing)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing, n (% all records)	11,699 (99.9)	9,908 (99.9)	4,624 (99.9)	3,895 (99.9)
Adherence measured using MPR of ICS,§ n (%)				
<70% MPR	4,836 (48.4)	4,053 (48.0)	1,878 (43.8)	1,576 (43.4)
≥70% MPR	5,152 (51.6)	4,390 (52.0)	2,407 (56.2)	2,008 (56.0)
Medication, n (%)				
ICS/LABA	5,312 (45.4)	4,479 (45.2)	1,753 (37.8)	1,461 (37.5)
ICS/LABA/LTRA	1,957 (16.8)	1,620 (16.3)	871 (18.9)	699 (17.9)
ICS/LABA/LAMA	1,982 (16.9)	1,717 (17.3)	1,117 (24.0)	971 (25.0)
ICS/LABA/LAMA/LTRA	714 (6.1)	612 (6.2)	525 (11.2)	440 (11.3)
SABA	10,149 (86.9)	8,596 (86.7)	4,187 (90.3)	3,502 (90.0)
Theophylline	930 (8.0)	804 (8.1)	638 (13.7)	540 (13.8)
Biologic treatments	0 (0.0)	0 (0.0)	19 (0.4)	15 (0.4)
Comorbidities,* n (%)				
Allergic rhinitis	3,638 (31.1)	3,202 (27.3)	1,240 (26.7)	1,109 (28.5)
Eczema	3,794 (32.4)	3,341 (28.6)	1,447 (31.2)	1,298 (33.3)
Nasal polyps	799 (6.9)	702 (6.0)	319 (6.8)	281 (7.2)
Anxiety/depression	97 (0.8)	79 (0.7)	39 (0.8)	31 (0.8)
Diabetes	1,058 (9.0)	948 (8.1)	585 (12.6)	530 (12.6)
Osteoporosis	928 (7.9)	833 (7.1)	431 (9.3)	390 (10.0)
Heart failure	424 (3.6)	383 (3.3)	212 (4.6)	196 (5.0)

ACT, Asthma Control Test; *FENO*, fractional exhaled nitric oxide; *FVC*, forced vital capacity; *LAMA*, long-acting muscarinic antagonist; *LTRA*, leukotriene receptor antagonist; *MPR*, medication possession ratio; *ppb*, parts per billion; *PEF*, peak expiratory flow; *PPEF*, percent predicted peak expiratory flow; *RCP*, Royal College of Physicians; *SABA*, short-acting β_2-agonist.

*Differences most likely due to the selection criteria for ISAR which requires patients receiving Reslizumab to have ≥3 exacerbations whilst Benralizumab and mepolizumab require ≥4 exacerbations before initiation.

†Different co-morbidity rates likely due to self-reporting data capture.

‡Post-referral.

§Before referral.

TABLE E4. Similarities and differences between patients with PSA (referred and nonreferred) and those with confirmed severe asthma

	Primary care (OPCRD)		Tertiary care (UK-ISAR)
Characteristic	PSA NOT reviewed or referred in specialist care (≥16 y)	PSA REVIEWED/REFERRED in specialist care (aged ≥16 y)	Confirmed severe asthma (aged ≥ 18 y)
Age (y)	Likely in 60s	Likely in 60s	Likely in 50s
Sex	Likely female: 65%	Likely female: 65%	Likely female: 64%
Obesity	Likely obese: 39%	Likely obese: 40%	More likely obese (48%)
Ethnicity	Predominantly white (62%) or unknown race (37%)	Predominantly white (61%) or unknown race (37%)	Predominantly white (68%) but greater race diversity
Smoking	Likely an ex-smoker (54%) or current smoker (21%)	Likely an ex-smoker (58%) or current smoker (20%)	Likely to have never smoked (69%)
Medication	Equal likelihood of ICS/LABA (45%) or ICS/LABA plus other treatment (40%)	More likely on ICS/LABA plus other treatment (54%)	Most likely on biologic (55%) and/or ICS/LABA plus other treatment (68%)
Adherence*	Many have poor adherence (48%)	Many have poor adherence (44%)	Most have good adherence (73%)
Exacerbations†	Likely to have 2 exacerbations/y ≥3 exacerbations/y (37%)	Likely to have 3‡ exacerbations/y ≥3 exacerbations/y (31%)§	Likely to have 4 exacerbations/y ≥3 exacerbations/y (72%)
Control‖	Not controlled: 52%	Not controlled: 62%	Most likely not controlled (91%)
Spirometry¶ (postbronchodilator)	FEV_1/FVC <0.7: 52%	FEV_1/FVC <0.7: 53%	FEV_1/FVC <0.7: 56%
Comorbidity#,**	Nasal polyps unlikely (7%)	Nasal polyps unlikely (7%)	Nasal polyps more likely (24%)

FVC, Forced vital capacity; *PSA*, potential severe asthma.
*OPCRD adherence measured by medication possession ratio. Poor adherence indicated by <70% days prescribed. ISAR poor adherence indicated using prescription records and clinical impression.
†Differences most likely due to the selection criteria for ISAR, which requires patients receiving reslizumab to have ≥3 exacerbations, whereas benralizumab and mepolizumab require ≥4 exacerbations before initiation.
‡Postreferral.
§Before referral.
‖Control scores based on Asthma Control Test.
¶Spirometry readings based on average maximum value over the preceding 5 y.
#OPCRD comorbidities based on ever having a diagnosis.
**Different comorbidity rates likely due to self-reporting data capture.

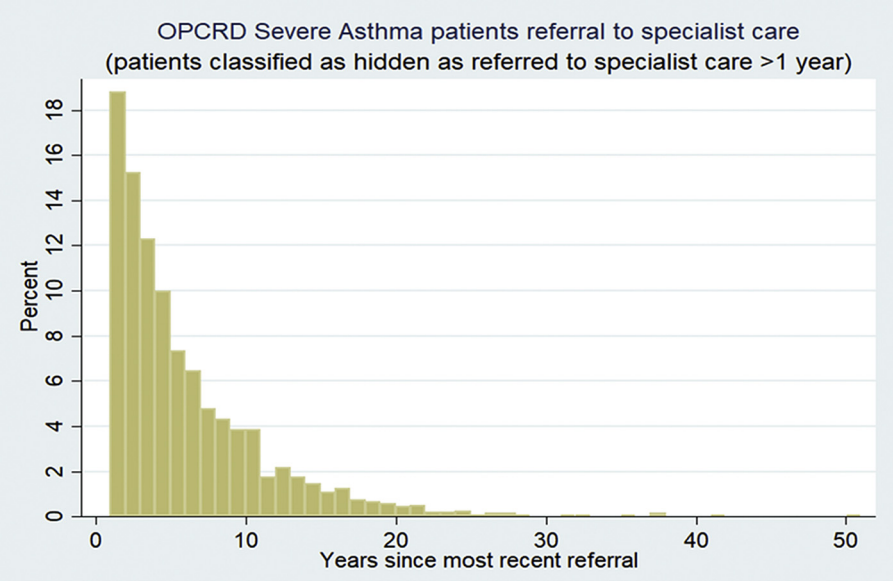

FIGURE E1. Time since last specialist consultation for patients with potentially severe asthma but no referral record in the last year (n = 2628).

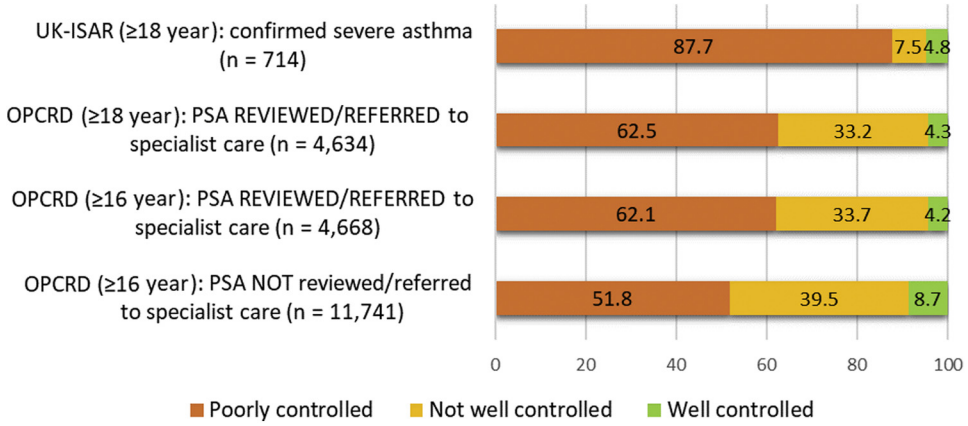

FIGURE E2. Asthma control status (assessed by Asthma Control Test) of patients in each cohort. *PSA*, Potential severe asthma; *UK-ISAR*, UK patients in the ISAR.

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