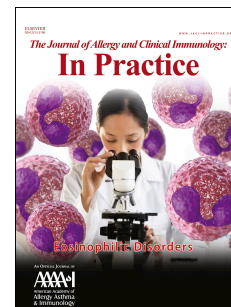


Journal Pre-proof

Potential severe asthma hidden in UK primary care

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Potential severe asthma hidden in UK primary care

Target Journal: JACI in Practice

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Highlights box

What is already known about this topic?

Primary care physicians (PCPs) are often reticent to refer asthma patients to specialist care, as 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 asthma patients in the UK 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 PCPs recognize those with hidden severe asthma in their care. These patients would benefit from a structured assessment by their PCP, with possible referral to specialist care.

55

Key words:

57 Optimum Patient Care Research Database; International Severe Asthma Registry; potential severe
58 asthma; referral; tertiary care

Abbreviations:

60 BEC: blood eosinophil count; FEV₁: forced expiratory volume in one second; FVC: forced vital
61 capacity; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; ISAR: international Severe
62 Asthma Registry; LABA: long-acting β_2 -agonist; LAMA: long-acting muscarinic receptor antagonist;
63 LTRA: leukotriene receptor antagonist; PEF: peak expiratory flow rate; PSA: potential severe asthma;
64 OCS: oral corticosteroid; OPCR: Optimum Patient Care Research Database; SABA: short acting β_2 -
65 agonist; UKSAR: UK Severe Asthma Registry

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Abstract [word count: 268]

Background: Severe asthma may be under-recognized 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 PSA patients with confirmed severe asthma patients from UK tertiary care.

Methods: Historical cohort study including patients from the Optimum Patient Care Research Database (OPCRD; 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 OPCR, PSA was defined as GINA 2018 Step 4 treatment and ≥ 2 exacerbations/year OR at GINA Step 5. The proportion of these patients and their referral status in the last year was quantified. Demographic and clinical characteristics of groups were compared.

Results: Of 207,557 OPCR patients with asthma, 16,409 (8%) had PSA. Of these, 72% had no referral/specialist review in the past year. Referred PSA patients tended to have greater prevalence of ICS/LABA-add-ons (54.1 vs 39.8%), and experienced significantly ($p < 0.001$) more exacerbations/year (median 3 vs 2/year), worse asthma control and worse lung function (% predicted post-bronchodilator FEV_1/FVC 0.69 vs 0.72) versus non-referred patients. Confirmed severe asthmatic patients (i.e. UK-ISAR) were younger (51 vs 65 years; $p < 0.001$), and significantly ($p < 0.001$) more likely to have uncontrolled asthma (91.4% vs 62.5%), a higher exacerbation rate (4/year [initial assessment] vs 3/year), use ICS/LABA add-ons (67.7% vs 54.1%), and have nasal polyposis (24.2% vs 6.8) than referred PSA patients.

Conclusion: Large numbers of patients with PSA in the UK are under-recognized in primary care. These patients would benefit from a more systematic assessment in primary care and possible specialist referral.

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 healthcare resources and advanced therapies.^{1,2} A specialist care review facilitates an accurate diagnosis, permits identification and control of co-morbidities, 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 UK 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 over-estimated — a reflection of incorrect inhaler use and poor medication adherence.¹⁰⁻¹² On the other hand, it may be under-estimated due to 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 (OCS) or at Global Initiative for Asthma (GINA) 2018⁴ Step 4 treatment with frequent exacerbations. There is a need to identify and understand this potential 'hidden' primary care severe asthma

population, as these patients may benefit from specialist review and specialist treatments (e.g. 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 UK, 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 over 700 general practices across the UK (approximately 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 multi-centre, multi-national, 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 (i) identify patients with PSA managed in UK primary care, (ii) estimate how many of these may be effectively 'hidden' (i.e. not reviewed or currently managed in specialist care) and (iii) compare the demographic and clinical characteristics of patients with PSA

216 with those of patients with a confirmed severe diagnosis managed in regional specialist centers in
217 the UK and included in ISAR.

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Methods

Study design

This was a historical cohort study, using data from the OPCR¹³ and from UK patients in ISAR¹⁴. Patients in primary care with PSA (see patient cohort definitions) were identified from the OPCR. Asthma-related outcome measures within the OPCR 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 ISAR (<http://isaregistries.org/>). UKSAR has received ethics approval to provide de-identified 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 ADEPT committee (ADEPT0319) and registered with the European Union electronic Register of Post-Authorization studies (EUPAS28611).²⁰

Inclusion criteria

Patients included from the OPCR (i.e. primary care) were required to be aged ≥ 16 years, have an active current diagnosis of asthma (prior to 2014 and no subsequent recorded asthma resolved Read Code after the latest asthma diagnosis), have received ≥ 1 asthma medication during the one year follow-up period and have ≥ 1 year of data from 2014 onwards (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 aged ≥ 18 years AND are receiving GINA (2018)⁴ Step 5 treatment OR have uncontrolled asthma at GINA 2018 Step 4 (e.g. ≥ 2 exacerbations/year). 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 co-morbidities).

Patient cohort definitions

The following patient cohorts were defined:

1. **PSA reviewed/referred from OPCRD cohort.** These were patients (aged ≥ 16 years) in primary care receiving GINA 2018⁴ Step 4 treatment AND experiencing ≥ 2 exacerbations/year 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 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 severe asthma patients from the ISAR cohort.** Patients (aged ≥ 18 years) managed in regional specialist centers, registered in the UKSAR and included in ISAR.

Study outcomes

OPCRD patients with active asthma (aged ≥ 16 years) with ≥ 1 asthma medication were categorized according to GINA 2018⁴ treatment step and number of exacerbations experienced/year. 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/year, asthma control, lung function, asthma treatments, adherence, co-morbidities (i.e. allergic rhinitis, eczema, nasal polyps) and blood eosinophil count (BEC). Definitions of outcomes assessed are presented in Table 1 (full details **Table E1**).

Statistics

Primary analyses

OPCRD data were assessed using Stata MP/6 version 15.1 (College Station, TX, US) and UK-ISAR data using Stata version 14 (College Station, TX, US) or SAS version 9.4/9.5 (Cary, NC, USA). Descriptive

statistics for demographic and clinical characteristics for each patient cohort from the OPCR and UK-ISAR were provided for continuous and categorical variables as either n (%) or mean (95% confidence interval) and median (25th, 75th percentile), as appropriate. Mean values were compared using a t-test, median values using Wilcoxon-Mann-Whitney and categorical values using chi squared or Fisher's Exact for variable with small (i.e. <5) values). A p-value ≤ 0.05 was considered statistically significant. The proportion of PSA patients (n, %) (i) referred/reviewed in the last year and (ii) NOT referred/reviewed in the last year was also calculated. Referral was defined as a referral code in OPCR to a respiratory specialist.

Sensitivity analyses

The proportion of patients with 0, 1, 2, 3, 4 and ≥ 5 exacerbations/year was calculated for the PSA referred patient cohort, for those aged ≥ 16 and ≥ 18 years, in the year before a referral to better understand referral drivers. Additionally, for those OPCR 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 OPCR look-back period (Mean: 19.2 years; 95% CI 19.1, 19.3). Finally, the demographic and clinical characteristics of patients in each OPCR cohort were described for patients aged ≥ 18 years and for those with a >5-year OPCR look-back period. The former analysis was conducted to align with UK-ISAR age inclusion criterion and to facilitate cross-comparison between OPCR 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 prior to 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 2018⁴ Step 3, 4, and 5, respectively. The number of exacerbations per year increased with treatment step (**Figure 2**). As expected, the majority of patients receiving GINA Step 5 treatment experienced 2 or more exacerbations/year, but many patients at lower GINA steps also experienced multiple exacerbations/year. A summary of asthma treatment by GINA 2018⁴ Step is provided in the online supplement (**Table E2**).

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

A total of 8% (n=16,409/207,557) of patients with active asthma in UK primary care (aged ≥ 16 years) were found to have PSA (**Figure 3**); or 4% of patients (n=16,409/416,125) 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 exacerbations and 5446 were at GINA 2018 Step 5. Of the 8% of patients with PSA, 72% (n=11,741/16,409) had not been reviewed by or referred to a specialist in the past year; 56% (n=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=2,628) had been referred or reviewed in specialist care, but >1 year ago (mean time since last review: 1.89 years) (**Figure 3; Figure E1**).

There were other patient cohorts within the OPCRd active asthma population that, despite not meeting the strict PSA criteria, nevertheless continued to experience ≥ 2 exacerbations/year at GINA 2018 Step 3 (1%; n=1889/207,557) or were at GINA 2018 Step 4 with 0 exacerbations/year (29%; n=60,425/207,557) or 1 exacerbation/year (7%; n=14,917/207,557).

Demographic and clinical characteristics

Characteristics of PSA patients in primary care

Patients with PSA managed in UK primary care tended to be female, in their 60s and overweight/obese (**Table 2**). More than 70% of them were current or ex-smokers. These patients exhibited significant morbidity. Lung function was poor. Over 50% of patients had evidence of irreversible obstruction (i.e. post-bronchodilator forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) <0.7) and $>60\%$ of patients had a post-bronchodilator peak expiratory flow rate (PEF) $<80\%$ predicted. Although, PSA patients experienced a median of 2-3 exacerbations/year (**Table 2**), not all PSA patients experienced multiple exacerbations/year pre-referral (**Figure 4**). The majority had poorly controlled disease ($>60\%$ of patients were prescribed ≥ 4 short-acting β_2 -agonist [SABA] inhalers in the past year), despite treatment with ICS/long-acting β_2 -agonist (ICS/LABA) ($>40\%$ patients) and add-on therapy (i.e. leukotriene receptor antagonist [LTRA]) and/or long-acting muscarinic receptor antagonist [LAMA]) for $>40\%$ of patients (**Table 2; Figure 5**). Multi-morbidity was also a feature of this population, most commonly allergic rhinitis and eczema (1/3 of patients for each) (**Table 2**).

Characteristics of patients with PSA in primary care NOT referred/reviewed in specialist care

Compared to 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/year; $p<0.001$) 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 PSA patients (45.3%) experienced 0 exacerbations/year prior to referral (**Figure 4**). There was no significant difference in post-bronchodilator FEV_1/FVC ratios between PSA patients with and without a referral/review. Although, PSA patients without a referral/review also experienced significantly ($p<0.001$) worse asthma control and lung function, were more likely ($p<0.001$) to suffer from AR and

342 anxiety/depression and less likely ($p<0.05$) to have chronic rhinitis, diabetes, osteoporosis and heart
343 failure compared to referred PSA patients, these differences were small (**Table 2; Figure E2**).

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PSA in primary care vs confirmed severe asthma in tertiary care

Compared to PSA patients (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 ($p < 0.001$) younger, significantly ($p < 0.001$) more likely to have never smoked and to be of wider race diversity (**Table 2**), reported more exacerbations and frequency (at first assessment) (**Table 2; Figure 4**), have uncontrolled asthma (**Table 2; 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 2**). Interestingly, those in tertiary care and referred PSA patients 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 severe asthma patients managed in tertiary care were treated with biologics (**Table 2**).

Sensitivity analyses

The results were similar for OPCRD cohorts aged ≥ 18 years (vs ≥ 16 years) and did not markedly differ from those with an OPCRD look-back period > 5 years (**Table E3**).

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 based on 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). Other primary care patient cohorts were also identified; active asthma patients at GINA 2018 Step 4 treatment but experienced zero exacerbations/year (29%). These patients may be over-treated 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 exacerbations/year or receiving GINA 2018 Step 4 treatment with 1 exacerbation/year. This group should be considered for careful assessment/re-assessment 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 SABA use, add-on medications to ICS/LABA therapy, poor lung function and asthma control, frequent exacerbations and high multi-morbidity rates (**Table 2; Table E4**). 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 PSA patients may have suggested that some of them had COPD or asthma COPD overlap, the mean FEV₁/FVC 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 PSA patients to confirm an asthma diagnosis, exclude COPD, manage co-morbidities 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,^{21,22,23} and in the UK Severe Asthma Registry,²⁴ providing confidence in the definition of PSA employed 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, e.g. LTRA and anti-cholinergics), a high OCS burden, and commonly presented with ear, nose, and throat co-morbidities and a high BEC.²¹ Similarly, in the UK patients with severe asthma had significantly higher co-morbidity rates than those with mild-to-moderate disease, for conditions associated with systemic corticosteroid exposure (e.g. type II diabetes mellitus, osteoporosis, dyspeptic disorders and cataracts).²⁴ 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 (i.e. UK-ISAR). This is most likely driven by the National Institute for Health and Care Excellence (NICE) requirement for ≥ 4 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 (e.g. % 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 PSA patients, as many of those referred had not experienced an exacerbation in the year prior to referral. Other studies conducted in the UK have shown a similar reticence to refer to specialist care.^{7,9} The UNTWIST study found that of 19,837

asthma patients (aged 18-65 years) eligible for referral in the UK according to British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) 2016 criteria,²⁴ 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 due to asthma in the UK, 47% had not been under specialist supervision during the 12 months prior to death.⁹ Similar findings have been reported in other countries.^{8,25-27} For example, the PACEHR study which 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 out of 5 patients had no contact with secondary care in the previous year.²⁶ Similarly, results from the Asthma Insight and Management Survey conducted in the U.S. in 2009 including 2,500 asthma patients 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; under-estimation of asthma severity and the long-term effects of OCS, high-dose ICS, and high use of SABA^{28,29}; 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 (e.g. biologics) and of asthma referral guidelines.⁶ Other barriers include high referral hurdles (i.e. only those with very severe disease qualify), lack of coordination between different parts of the health care system,³⁰ patient attitudes/expectations,³¹ financial pressures,³² and under-resourcing; currently there are 1.86 adult respiratory physicians/100,00 people in the UK compared to the European average of 4.4/100,000).³³

Numerous guidelines are available that provide guidance on when a patient with asthma should be referred to a specialist.^{4,24,34} According to the BTS guidelines (2016)²⁴ adults with asthma should be referred to specialist care in cases of diagnostic uncertainty, if they are high risk (e.g. 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 (e.g. on high-dose ICS or continuous/frequent use of OCS), and if biologics are considered. Over half of 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 UK. Unfortunately, in real life patients with severe asthma often experience several exacerbations and emergency department admissions prior to 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.^{35,36} Although both ICS and OCS have a positive impact on controlling symptoms and exacerbations,^{37,38} cumulative OCS use is associated with increased risk of acute and chronic adverse events (e.g. increased risk of diabetes and osteoporosis),³⁹ increased healthcare resource use, and increased costs.³⁵ Indeed, a recently published Swedish study found that the total health care cost was three-times greater for patients taking OCS regularly (€5,615) and twice as high for patients taking OCS intermittently (€2,948), compared with non-OCS users (€1,980).⁴⁰ Similarly, in UK general practice average annual costs for adverse outcomes and asthma were 42% greater for patients with active asthma exposed to systemic corticosteroids (versus those who were not).⁴¹

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 (e.g. inhaler technique). Specialist review of difficult-to-treat and severe asthma has not only been associated with an improvement in asthma control, quality of life, lung function, and exacerbation rate, but also

with reduced OCS burden.^{42,43} Higher costs associated with specialist review could, thus, be offset against these benefits. On the other hand, 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. Prior to referral, primary care physicians should play a key role in 'referral triage', assessing their asthma patients using a structured methodology (e.g. SIMPLES 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 co-morbidities.^{5,44} 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 (i) prescribed correctly in line with GINA 2018 recommendations and (ii) 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 OPCR. Additionally, although the presence of a referral code in the OPCR 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 (e.g. from primary care, A&E department) and/or whether the patient attended. Knowledge of referral reasons would allow cross reference with BTS/SIGN referral criteria²⁴ 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 OPCR. To counterbalance these limitations, it

should be noted that, due to 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 OPRCD comes from electronic medical records and has been used frequently for observational research.^{45–47} These data provide a snapshot of patients with asthma managed in real-life in practices all over the UK. 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.

In conclusion, there are large numbers of asthma patients in the UK 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 (SIMPLES),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, e.g. pharmacists, asthma nurses, etc.) 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 UK, 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 those 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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Table 1: Description of key outcome variables presented

Variable	Description
Co-morbidities	- For UK-ISAR co-morbidities are captured in free text so are likely under-reported (particularly when compared to the patients' long-term primary care record) - OPCRD: co-morbidities are coded
Exacerbation	Worsening of asthma requiring systemic corticosteroids
Asthma control	- OPCRD: assessed 5 ways - Royal College of Physicians questionnaire,⁴⁸ - Asthma Control Test,⁴⁹ - Risk Domain Asthma Control,¹⁹ - Overall Asthma Control¹⁹ and - short-acting β_2-agonist use. - UK-ISAR: assessed by the Asthma Control Questionnaire⁵⁰
Adherence	- OPCRD: assessed using the medication possession ratio, with good adherence to treatment defined as a ratio $\geq 70\%$ (based on inhaled corticosteroid prescription refills).⁵¹ - 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'.

ISAR: International Severe Asthma Registry; OPCR: Optimum Patient Care Research Database

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666 **Table 2: Demographic and clinical characteristics of potential severe asthma patients (aged ≥ 16 years) in UK primary care (OPCRD) versus those UK**
667 **patients with confirmed severe asthma in tertiary care (UK-ISAR)**

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	Primary Care (OPCRD)		P-value	Primary Care (OPCRD)	Tertiary Care (UK-ISAR)	P-value
Population	PSA NOT reviewed or referred in specialist care (aged ≥ 16 years)	PSA REVIEWED/REFERRED in specialist care in last year (aged ≥ 16 years)		PSA REVIEWED/REFERRED in specialist care in last year (aged ≥ 18 years)	Confirmed severe asthma (aged ≥ 18 years)	
Demographic characteristics						
	N=11,741	N=4,668		N=4,634	N=714	
Age			NS			p<0.001
Mean (95% CI)	62 (62.0, 62.7)	63 (62.1,63.2)		63 (62.4,63.4)	50 (48.8, 50.8)	
Median (25 th , 75 th 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		p<0.001
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 (25 th & 75 th 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 to <25), n (%)	2,743 (26.2%)	1,039 (26.2%)		1,026 (26.1%)	144 (20.2%)	
Overweight, (≥25 to <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%)	

	Primary Care (OPCRD)		P-value	Primary Care (OPCRD)	Tertiary Care (UK-ISAR)	P-value
Population	PSA NOT reviewed or referred in specialist care (aged ≥ 16 years)	PSA REVIEWED/REFERRED in specialist care in last year (aged ≥ 16 years)		PSA REVIEWED/REFERRED in specialist care in last year (aged ≥ 18 years)	Confirmed severe asthma (aged ≥ 18 years)	
Smoking status, n (%)	N=11,674	N=4,637	p<0.001	N=4,603	N=712	p<0.001
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/year (after referral)			p<0.001			p<0.001
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) ^a	
Median (25 th , 75 th 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	p<0.001	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	p<0.001	N=445	N=690 ^b	p<0.001
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 (%)			p<0.001			-
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 (%)			p<0.001			-
Controlled	928 (7.9%)	150 (3.2%)		144 (3.1%)	-	
Not controlled	10,813 (92.1%)	4,518 (96.8%)		4,490 (96.9%)	-	

	Primary Care (OPCRD)		P-value	Primary Care (OPCRD)	Tertiary Care (UK-ISAR)	P-value
Population	PSA NOT reviewed or referred in specialist care (aged ≥ 16 years)	PSA REVIEWED/REFERRED in specialist care in last year (aged ≥ 16 years)		PSA REVIEWED/REFERRED in specialist care in last year (aged ≥ 18 years)	Confirmed severe asthma (aged ≥ 18 years)	
SABA use, n (%)			p<0.001			
< 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						
% predicted post-bronchodilator FEV ₁	N=5,149	N=2,405	p<0.001	N=2,398	N=653	NS
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 post-bronchodilator FEV ₁ >80%, n (%)	6,599 (56.2%)	2,256 (48.4%)	NS	2,236 (48.3%)	-	-
% predicted post-bronchodilator FVC	N=4021	N=1931	p<0.001	N=1926	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)	
Post-bronchodilator FEV ₁ /FVC ^c	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, n (%)	52.4%	53.4%		53.4%	56.4%	
% predicted PEF	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%)		
Blood Eosinophil Count (BEC)						
Median BEC (25 th , 75 th percentile)	N=11,147	N=4,458	NS	N=4,442	N=712	-
Median Highest BEC (25 th , 75 th perc.)	230 (152, 350)	231 (154, 343)		231 (154, 343)	N/A	
	260 (160, 400)	270 (170, 400)		270 (170, 400)	278 (269, 287)	NS
Other treatments						
Theophylline, n (%)	935 (8.0%)	640 (13.7%)	NS	636 (13.7%)	173 (24.2%)	NS
Biologics, n (%)	0 (0.0%)	19 (0.2%)		10 (0.2%)	393 (55.0%)	
Adherence						

Population	Primary Care (OPCRD)		P-value	Primary Care (OPCRD)	Tertiary Care (UK-ISAR)	P-value
	PSA NOT reviewed or referred in specialist care (aged ≥ 16 years)	PSA REVIEWED/REFERRED in specialist care in last year (aged ≥ 16 years)		PSA REVIEWED/REFERRED in specialist care in last year (aged ≥ 18 years)	Confirmed severe asthma (aged ≥ 18 years)	
$\geq 70\%$ MPR of ICS, n (%)	N=10,038 5,176 (51.6%)	N=4,303 2,416 (56.1%)	p<0.001	N=4,279 2,403 (56.2%)	N=708 ^d 520 (73.4%)	p<0.001
Co-morbidities^e						
Allergic rhinitis, n (%)	3,660 (31.2%)	1,245 (26.7%)	p<0.001	1,238 (26.7%)	33 (4.6%)	p<0.001
Chronic rhinosinusitis, n (%)	495 (4.2%)	241 (5.2%)	p<0.05	239 (5.1%)	N/A	-
Eczema, n (%)	3,822 (32.5%)	1,456 (31.3%)	NS	1,445 (31.2%)	20 (2.8%)	p<0.001
Nasal polyps, n (%)	801 (6.8%)	317 (6.8%)	NS	316 (6.8%)	173 (24.2%)	p<0.001
Anxiety/depression, n (%)	191 (1.6%)	39 (0.8%)	p<0.001	39 (0.8%)	20 (2.8%)	p<0.001
Diabetes, n (%)	1,058 (9.0%)	585 (12.6%)	p<0.001	585 (12.6%)	2 (0.3%)	p<0.001
GERD, n (%)	2,324 (19.7%)	970 (20.7%)	NS	968 (20.8%)	N/A	NS
Osteoporosis, n (%)	928 (7.9%)	431 (9.3%)	p<0.05	431 (9.3%)	2 (0.3%)	p<0.001
Heart failure, n (%)	424 (3.6%)	212 (4.6%)	p<0.05	212 (4.6%)	1 (0.1%)	p<0.001

669 ACT: Asthma Control Test; CI: confidence interval; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; ISAR: International Severe

670 Asthma Registry; MPR: medication possession ratio; OAC: Overall Asthma Control; OPCR: Optimum Patient Care Research Database; PEF: peak expiratory

671 flow rate; PSA: potential severe asthma; RCP: Royal College of Physicians; RDAC: Risk Domain Asthma Control; SABA: short-acting β_2 -agonist

672 a: at first assessment

673 b: assessed by the Asthma Control Questionnaire

674 c: age standardised FEV₁/FVC ratios

675 d: adherence assessed via the probe question, 'is there evidence of poor adherence'

676 e: OPCR: based on having a diagnosis at any point in time; ISAR: patient self-reported

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Legend to Figures

Figure 1: Optimum Patient Care Research Database Subject disposition

Figure 2: Number of exacerbations experienced by OPCRD patients (n=207,557) by GINA 2018 treatment step. OPCRD: Optimum Patient Care Research Database; GINA: Global Initiative for Asthma 2018

Figure 3: Proportion of active asthma patients (aged ≥ 16 years) managed in UK primary care with potential severe disease and their referral status. OPCRD: Optimum Patient Care Research Database; potential severe asthma: receiving treatment at GINA 2018 Step 4 AND experiencing ≥ 2 exacerbations/year OR receiving treatment at GINA 2018 Step 5; *: during the OPCRD look back period (mean: 19.2 years; 95% CI: 19.1, 19.3)

Figure 4: Proportion of patients in each cohort according to number of exacerbations experienced per year. * For those patients referred to specialist care, the exacerbation rate is the rate in the year prior to referral. OPCRD: Optimum Patient Care Research Database; PSA: potential severe asthma (patients (aged ≥ 16 years) in primary care receiving treatment at GINA 2018 Step 4 AND experiencing ≥ 2 exacerbations/year OR receiving treatment at GINA 2018 Step 5; UK-ISAR: UK patients in the International Severe Asthma Registry

Figure 5: Proportion of patients in each cohort on a multiple asthma treatment regimen. ICS: inhaled corticosteroid; LABA: long-acting β_2 -agonist; LAMA: long-acting muscarinic receptor antagonist; LTRA: leukotriene receptor antagonist; PSA: potential severe asthma (patients (aged ≥ 16 years) in primary care receiving treatment at GINA 2018 Step 4 AND experiencing ≥ 2 exacerbations/year OR receiving treatment at GINA 2018 Step 5; OPCRD: Optimum Patient Care Research Database; UK-ISAR: UK patients in the International Severe Asthma Registry

