Protocol to identify potential severe asthma in UK primary care

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Introduction

- Severe asthma affects 5-10% of the total asthma population[1] and should be managed in specialist care.[2,3]
- However, the true size of the severe asthma population may be considerably larger, due to mis-diagnosis in primary care resulting in under-referral and under-treatment.
- We hypothesise that many patients who could have severe asthma in primary care:
  - are not referred to specialist severe asthma care and so remain hidden and/or
  - were previously discharged from specialist care and are currently managed with long-term maintenance oral corticosteroids (OCS).
- There is a need to understand this primary care severe asthma population.

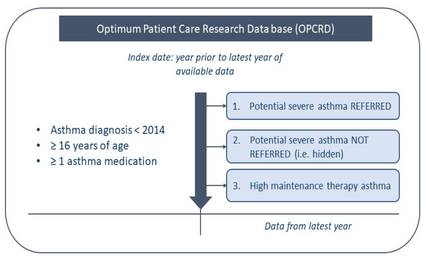
Aims

- To assess the prevalence of potential severe asthma in primary care.
- To describe and compare patient demographic, clinical outcomes and treatments for patients within four different cohorts:
  1. Potential severe asthma referred (Optimum Patient Care Research Database [OPCRD])
  2. Potential severe asthma not referred (i.e. hidden) (OPCRD)
  3. High maintenance therapy asthma (OPCRD) and
  4. Confirmed severe asthma (i.e. patients who are registered in the UK Severe Asthma Network and National Registry on Difficult Asthma and included in International Severe Asthma Registry [ISAR]).

Methods

- Patients with potential severe asthma and high maintenance therapy asthma in primary care were identified from the OPCRD:
  - This databased holds anonymous data from over 700 general practices in the UK, includes approximately 6.3 million patients, and accounts for approximately 8% of the UK population.[4]
  - Patients aged ≥16 years, with active current diagnosis of asthma, and receiving treatment were selected.
- Patients with confirmed severe asthma were those included in the UK Severe Asthma Network and National Registry on Difficult Asthma, included in ISAR (http://isaregistries.org/).
  - ISAR is a multi-country, multicentre, observational initiative, which collects data prospectively and retrospectively on patients with severe asthma from tertiary care.[5]
  - Patients have uncontrolled asthma on GINA (2018)[3] treatment Step 4 (e.g. ≥2 exacerbations/year) or are on GINA Step 5 treatment and have been assessed to ensure correct diagnosis and optimum management (including drug therapy, correct use of device(s), adherence & co-morbidities).
- The latest available year of data were used to analyse patients and categorise them according to GINA (2018)[3] treatment step and number of exacerbations per year requiring an OCS prescription (**Figure 1**).
- The following definitions were used for asthma seen in **primary care**:
  - **Potential severe asthma**: patients receiving treatment at GINA Step 4 AND experiencing ≥2 exacerbations/year OR receiving treatment at GINA Step 5. Frequent exacerbations at Step 4 may indicate severe asthma and align with the ISAR severe asthma definition.
    - **Referred**: had a referral to, or were managed, in a specialist severe asthma centre in the previous year
    - **Not referred (i.e. hidden)**: had no referral to, or were not managed in, a specialist asthma centre in the previous year
  - **High maintenance therapy asthma**: patients receiving treatment at GINA (2018)[3] Step 3 and experiencing ≥2 exacerbations/year, OR receiving treatment at GINA Step 4 and experiencing <2 exacerbations (i.e. 0 or 1 exacerbations).
- The demographic, treatments and clinical characteristics of the 4 patient cohorts detailed in the objectives above were compared.

Figure 1 – Study design



Results

- 207,557 patients, aged ≥ 16 years with a current asthma diagnosis and receiving ≥1 asthma treatment, were selected from the OPCRD database.
- **8%** of the OPCRD patients were found to have potential severe asthma (i.e. GINA 2018 Step 4 and ≥2 exacerbations OR at Step 5) (**Figure 2**).
  - Of these, **72%** were unreferred (hidden) and **28%** were referred to specialist care.
- **37%** of patients were classed as having high maintenance therapy asthma (**Figure 2**)
  - **1%**: GINA Step 3 (2018) and experiencing ≥2 exacerbations
  - **7%**: GINA Step 4 and 1 exacerbations
  - **29%**: GINA Step 4 and 0 exacerbations
- **Tables 1 and 2** compare demographic and clinical characteristics for those in primary care with potential severe asthma (referred and not referred) and with high maintenance therapy asthma, as well as those with confirmed severe asthma seen in tertiary care.

Table 1: **Comparison of the characteristics of patients with potential severe and high maintenance therapy asthma in primary care (OPCRD database) to those with confirmed severe asthma registered in ISAR and managed in specialist care in the UK (ISAR) [see table 2 for more details]**

	High Maintenance therapy Asthma* (OPCRD)	Potential Severe Asthma NOT REFFERED to specialist asthma centre* (OPCRD)	Potential Severe Asthma REFFERED to specialist asthma centre* (OPCRD)	Potential Severe asthma (ISAR)*
Age	Most likely in their 50s	Older patients (most likely in their 60s)	Older patients (most likely in their 60s)	Youngest (most likely in their 40s)
Gender	Least likely to be female (41% male, 59% female)	Likely to be female (35% male, 65% female)	Likely to be female (35% male, 65% female)	Likely to be female (36% male, 64% female)
Obesity	Least likely to be obese (36%)	Less likely to be obese (39%)	Less likely to be obese (40%)	Most likely to be obese (47%)
Ethnicity	Likely to be Caucasian (89%)	Likely to be Caucasian (90%)	Likely to be Caucasian (89%)	Least likely to be Caucasian (68%)
Smoking	Likely an ex-smoker (48%) or current smoker (20%)	Likely an ex-smoker (54%) or current smoker (21%)	Likely an ex-smoker (58%) or current smoker (20%)	Most likely to have never smoked (69%)
Medication	Most likely on ICS/LABA (79%)	Just as likely on ICS/LABA (45%) or ICS/LABA plus other treatment (40%)	More likely on ICS/LABA plus other treatment (54%)	Most likely on monoclonal antibodies (55%)
Adherence <70% MPR[a]	Most likely to have poor adherence (60%)	Less likely to have poor adherence (41%)	Less likely to have poor adherence (41%)	Least likely to have poor adherence (27%)
Exacerbations[†]	Most likely to have ≤ 2 exac/year (99%)	Likely to have ≤2 exac/year (63%)	More likely to have ≥2 exac/ year (54%)	More likely to have ≥4 exac/ year (62%)
Control[b]	More likely to self-report as 'controlled' (61%)	More likely to self-report as 'not controlled' (54%)	More likely to self-report as 'not controlled' (66%)	Most likely to self-report as "not controlled" (85%)
Biomarkers	More likely to have BEC ≤0.3 (63%)	More likely to have BEC ≤0.3 (66%)	More likely to have BEC ≤ 0.3 (67%)	More likely to have BEC >0.3 (63%)
Spirometry measurements[c]	% predicted FEV_1 likely to be ≥80%	% predicted FEV_1 likely to be >70%	% predicted FEV_1 likely to be <70%	Most likely to have irreversible airway obstruction (58%)
Comorbidity[d‡]	Unlikely to have nasal polyps (4%)	Unlikely to have nasal polyps (7%)	Unlikely to have nasal polyps (7%)	More likely to have nasal polyps (24%)

BEC: blood eosinophil count; FEV_1: forced expiratory volume in one second; ICS: inhaled corticosteroid; ISAR: International Severe Asthma Registry; LABA: long-acting β_2-agonist; MPR: medication procession ratio; OPCRD: Optimum Patient Care Research Database;
* see methods section for full definitions
(a) OPCRD adherence measured by Medication Possession Ratio (MPR). Poor adherence indicated by <70% days prescribed. ISAR poor adherence indicated using prescription records and clinical impression
(b) OPCRD population control scores based upon RCP Questionnaire. ISAR population control scores based on ACQ
(c) Spirometry readings based on average maximum value over the preceding 5 years
(d) OPCRD co-morbidities based on ever having a diagnosis
† 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[6-8]
‡ different co-morbidity rates likely due to self-reporting data capture

Table 2: Comparison of the characteristics of patients with potential severe and high maintenance therapy asthma (in primary care (OPCRD database) to those with confirmed severe asthma managed in specialist care (ISAR) in the UK.

Population characteristics	High Maintenance therapy asthma* (OPCRD)	Potential Severe asthma NOT REFERRED to specialist care* (OPCRD)	Potential Severe asthma REFERRED to specialist care* (OPCRD)	Potential Severe asthma (ISAR)*
	N=77,231	N=11,750	N=4,659	N=714
Age, mean (95% CI)	54 (53.9-54.2)	62 (62.0-62.7)	63 (62.1-63.2)	50 (48.8-50.8)
Male, n (%)	31,994 (41)	4,073 (35)	1,624 (35)	458 (36)
Weight category, n (%)				
Under/normal weight	21,254 (31)	3,066 (29)	1,170 (30)	149 (21)
Overweight	22,486 (33)	3,252 (31)	1,189 (30)	226 (32)
Obese	24,336 (36)	4,107 (39)	1,595 (40)	338 (47)
Ethnicity, n (%)				
Caucasian	20,980 (89)	2,903 (90)	1,671 (89)	488 (68)
Smoking status, n (%)				
Never	24,539 (32)	2,947 (25)	1,019 (22)	492 (69)
Ex or current	52,259 (68)	8,736 (75)	3,609 (78)	220 (31)
Medication, n (%)				
ICS/LABA	60,623 (79)	5,338 (45)	1,761 (38)	190 (27)
ICS/LABA + other	14,198 (18)	4,677 (40)	2,523 (54)	483 (68)
Biologics	0 (0)	9 (0.1)	10 (0.2)	393 (55)
Adherence (<70% MPR)[a]				
ICS/LABA, n (%)	46,314 (60)	4,861 (41)	1,888 (41)	530 (27)
Exacerbations, n (%)[†]				
≤2/year	76,538 (99)	7,366 (63)	2,167 (47)	196 (28)
3 /year	408 (0.5)	2,105 (18)	956 (21)	74 (10)
4/year	150 (0.2)	1,175 (10)	589 (13)	109 (15)
≥5/year	135 (0.2)	1,104 (9)	947 (20)	331 (47)
Asthma Control, n (%)[b]				
Controlled	24,201 (61)	2,314 (46)	1,013 (35)	33 (5)
Partially/ not controlled	15,457 (39)	2,692 (54)	1,922 (65)	657 (92)
BEC, n (%)				
≤0.3	42,163 (63)	7,344 (66)	2,981 (67)	262 (37)
>0.3	24,374 (37)	3,807 (34)	1,468 (33)	450 (63)
Spirometry[c]				0
Mean % $pFEV_1$ (95% CI)	0.79 (0.79-0.80)	0.72 (0.71-0.72)	0.68 (0.68-0.69)	.65 (0.64-0.67)
FEV_1/FVC <0.7, n (%)	7,016 (43)	1,677 (45)	760 (44)	403 (58)
Co-morbidity[d‡], n (%)				
Allergic rhinitis	25,374 (33)	3,660 (31)	1,245 (27)	33 (5)
Eczema	23,984 (31)	3,822 (33)	1,456 (31)	20 (3)
Nasal polyps	3,249 (4)	802 (7)	316 (7)	173 (24)

BEC: blood eosinophil count; CI: confidence interval; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; ICS: inhaled corticosteroid; ISAR: International Severe Asthma Registry; LABA: long-acting β_2-agonist; MPR: medication procession ratio; OPCRD: Optimum Patient Care Research Database
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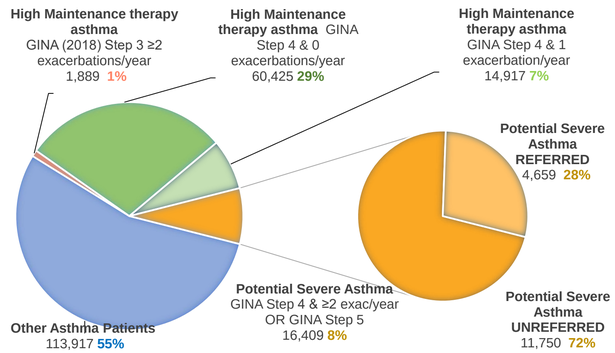
Figure 2 - 'Proportion of patients in primary care with (a) high maintenance therapy asthma and potential severe asthma and (b) for those with potential severe asthma, the proportion hidden who were not managed in specialist care



Conclusion

- **It has been possible to define potential severe asthma from primary care EMR using patients' diagnosis, treatments and measures of control.**
- **There are large numbers of patients in primary care with potential severe asthma who have not been referred to a specialist severe asthma centre despite guideline, NICE and GINA recommendations, and so do not benefit from a range of services which may ameliorate their asthma including access to biologics.**
  - **Those NOT referred are more likely to experience fewer exacerbations, report their asthma as controlled, have better lung function and are less likely to require add-on therapy to ICS/LABA compared to REFFERED patients.**
- **Patients with CONFIRMED severe asthma are younger, more likely to be obese and to have never smoked, better adherence, more exacerbations, worse control, irreversible airway obstruction and nasal polyps than potential severe asthmatics in primary care.**

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