Title

The impact of sex on severe asthma: a cross-sectional retrospective analysis of UK primary and specialist care

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ABSTRACT

Introduction: After puberty, females are more likely to develop asthma and in a more severe form than males. The associations between asthma and sex are complex with multiple intrinsic and external factors.

Aim: To evaluate the sex differences in the characteristics and treatment of patients with severe asthma (SA) in a real-world setting.

Methods: Demographic, clinical and treatment characteristics for patients with SA in the UK Severe Asthma Registry (UKSAR) and Optimum Patient Care Research Database (OPCRD) were retrospectively analysed by sex using univariable and multivariable logistic regression analyses adjusted for year, age, and hospital/practice.

Results: 3,679 (60.9% female) patients from UKSAR and 18,369 patients (67.9% female) from OPCRD with SA were included. Females were more likely to be symptomatic with increased Asthma Control Questionnaire-6 (UKSAR aOR: 1.14, 95% CI: 1.09, 1.18) and RCP-3 Question scores (OPCRD aOR: 1.29: 1.13, 1.47). However, they had a higher FEV_1% predicted (UKSAR 68.7% vs. 64.8%, p<0.001) with no significant difference in peak expiratory flow. Type-2 biomarkers IgE (UKSAR 129IU/ml vs. 208IU/ml, p<0.001) and FeNO (UKSAR 36ppb vs. 46ppb, p<0.001) were lower in females with no significant difference in blood eosinophils or biologic therapy. Females were less likely to be on maintenance OCS (UKSAR aOR 0.86: 0.75, 0.99) but more likely to be obese (UKSAR aOR 1.67: 145, 1.93; OPCRD SA aOR: 1.46: 1.34, 1.58).

Conclusions: Females had increased symptoms and were more likely to be obese despite higher FEV_1% predicted and lower type-2 biomarkers with consistent and clinically important differences across both datasets.

What is already known on this topic

Severe asthma is more common in females. It is associated with different disease characteristics between the sexes, including females having a higher symptom burden and lower expression of type-2 biomarkers.

What this study adds

Males and females with severe asthma have significant clinical differences in their asthma symptoms, healthcare utilisation, type-2 biomarkers, and associated comorbidities. These differences have been demonstrated in a large well characterised and robust real-world cohorts across both specialist and primary care adding understanding to the sex differences of specific clinical characteristics in severe asthma.

How this study might affect research, practice, or policy

Understanding the different characteristics associated with severe asthma between males and females is essential in establishing personalised care for patients and focusing future research on the mechanisms underlying the differences seen.

INTRODUCTION

Asthma has an estimated global prevalence of over 350 million[1] with 15.6% of the UK population being diagnosed in their lifetime[2]. This includes approximately 3-10% with severe asthma (SA)[3], many of whom are potentially hidden in primary care[4]. Despite its relatively small proportion, SA accounts for the majority of morbidity and economic costs associated with asthma[5, 6]. Severe asthma is defined by the European Respiratory Society/ American Thoracic Society (ERS/ATS) as asthma requiring treatment with high-dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy[3].

Asthma, which is characterised by chronic airway inflammation, remodelling and hyperresponsiveness with variable airflow obstruction and respiratory symptoms, is a heterogeneous disease in both pathogeneses and clinical characteristics. Whilst asthma prevalence of all severities is higher in males at prepuberty, the switch to a female predominance by adulthood is well established[7, 8]. Furthermore, females are more likely to develop asthma in their lifetime and in a more severe form than their male counterparts[1]. The associations between asthma and sex are, however, complex. Shifts in the sex prevalence of asthma coincide with changes in sex hormones suggesting a potential role in asthma pathogenesis[9, 10], however, epidemiological studies have been inconclusive[11]. Further factors, including sex and gender-associated exposures and behaviours such as occupation, smoking, healthcare utilisation and access, alongside genetic and epigenetic factors also influence the relationship between asthma and sex[8].

Despite a growing understanding of the complex and important relationship between the intrinsic and external factors associated with sex and asthma there is little understanding of the real-world differences seen in clinical practice. Previous studies have attempted to phenotype patients with SA through multivariate cluster analysis, identifying clusters supporting the complex and heterogenous relationship between asthma and sex[12]. Analysis from the UBIOPRED cohort identified a cluster of predominantly obese female patients with SA who had frequent exacerbations but near-normal lung function[13]. Type-2 (T2) asthma, which is driven by allergic and/ or eosinophilic pathways has been found to have a male predominance in further SA cohorts[14-16], and a male predominant cluster with SA, nasal polyps, eosinophilia, and high dose corticosteroid use was previously identified from the SARP programme[17]. These T2 pathways, which can be identified through biomarkers such as FeNO, IgE and blood eosinophils respond to corticosteroid therapy and can be targeted through

biological therapy in uncontrolled SA[18]. It is therefore important to understand the differences in disease characteristics and T2 markers between males and females for diagnostic and personalised treatment pathways to be developed in SA.

The effect of T2 biomarker guided therapy can also be impacted by sex. A post-hoc analysis by sex of the Refractory Asthma Stratification Programme (RASP-UK) biomarker study found a greater proportion of females with SA were able to reduce their corticosteroid dose using a T2 biomarker algorithm when compared to standard care, a difference not seen in males [19]. This study found a dissociation between the sexes in symptoms and T2 biomarkers with a higher proportion of females to be symptom high/ T2 biomarker low whilst males were symptom low/T2 biomarker high. The differences in self-reported symptoms were also shown to be mediated by obesity or a history of depression/ anxiety. Such findings demonstrate the importance of understanding sex differences in the delivery of SA therapy. However, the current literature does not address the need to provide real-world comparison of the differences in the disease and treatment between males and females with SA.

This study aims to evaluate the sex differences in disease characteristics, symptom control, exacerbations, biological phenotypes, and treatment in patients with SA using a retrospective epidemiological approach.

METHODS

Study Population

This is a retrospective epidemiological study using cohorts from two datasets. The UK Severe Asthma Registry (UKSAR) is a national database containing demographic, clinical and treatment characteristics on patients referred to specialist UK SA centres with SA[20]. All patients provide written informed consent and the UKSAR has database ethical approval from the Office of Research Ethics Northern Ireland (15/NI/0196). Patients have undergone systematic assessment and those diagnosed with SA according to the ERS/ATS criteria[21] were included in this analysis.

The Optimum Patient Care Research Database (OPCRD) is a UK nationally-representative pseudonymised dataset of 18 million patients registered at 1000 general practices within the UK (24% of the UK population)[22]. The OPCRD is approved by the UK National Health Service for clinical research use (15/EM/0150). It contains information on patient demographics, clinical diagnoses,

156 medication prescriptions and referrals coded through the Read and SNOMED classification systems.
157 To prevent time-window bias[23], a standard one-year window was used to assess outcomes for all
158 patients. Those with less than one year of eligible follow-up time were excluded from the study. A
159 one-year ascertainment period was randomly chosen for patients with more than one year's eligible
160 follow-up time. To increase the comparability of our cohort, those with an alternative respiratory
161 diagnosis in the three years prior to inclusion were also excluded.

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163 SA in the OPCRD cohort was defined according to GINA 2018[24] criteria as those who remained
164 uncontrolled (≥2 exacerbations within a year) on step 4 treatment or who require maintenance oral
165 corticosteroids (OCS) to achieve control.

166

167 **Exposures, Outcomes and Covariates**

168 The primary outcomes of interest were T2 biomarkers (blood eosinophils, fractional exhaled nitric
169 oxide [FeNO] and immunoglobulin E [IgE]), lung function (forced expiratory volume in the first second
170 [FEV_1], forced vital capacity [FVC] and peak expiratory flow [PEF]), asthma control, asthma phenotype
171 (atopy), asthma medications (treatment adherence, maintenance oral corticosteroid [OCS] use,
172 biologic therapy use), healthcare utilisation (exacerbations, emergency department [ED] attendance,
173 hospital admission, asthma review and respiratory referral) and comorbidities. Outcome
174 measurements were all taken at baseline prior to the initiation of biologic therapy.

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176 Lung function recordings were taken as raw measurements and percent predicated calculated using
177 the formula by Knudson et al[25] for PEF and Global Lung Function Initiative[26] for FEV_1 and FVC.
178 Asthma control was measured by the Asthma Control Questionnaire-6 (ACQ6)[27] in the UKSAR and
179 Royal College of Physicians-3 Questions (RCP 3Q)[28] in the OPCRD. Treatment adherence was
180 assessed using the fixed medication possession ratio (MPR) of inhaled corticosteroids (ICS) during the
181 ascertainment period. Good adherence was defined as an MPR of greater than or equal to 70%.
182 Obesity was defined as a BMI of 30kg/m^2 or greater. Comorbidities in the OPCRD cohort were
183 identified through Read codes, which were used to identify a list based on the Charlson comorbidity
184 index[29], depression/ anxiety and those related to systemic corticosteroid exposure[30]. Full details
185 of the variables used in the analysis, including the time-period in which they were assessed, are
186 provided in Supplement table 1. UKSAR baseline data was collected at the time of registration, prior
187 to biologic therapy being started, and follow-up data collected annually.

Statistical Analysis

This was a complete case analysis using all available data from the UKSAR and OPCRD. We calculated descriptive statistics and compared the demographic and clinical characteristics of male and female patients. Various statistical models were used depending on the distribution of the outcome variable including logistic (e.g. atopy, maintenance OCS use, any ED attendance, uncontrolled asthma) and Poisson (e.g. number of exacerbations) models. To aid interpretation and comparability across outcomes, all results are shown as ratios (continuous variables), odds ratios (binary variables) or risk ratios (count variables). Consequently, we used gamma generalised linear models with a log link function to analyse continuous outcomes. Multivariable analyses adjusted for demographic factors were conducted accounting for age (5-year categories) and year. The UKSAR analysis additionally adjusted for hospital site, while the clustering of patients within GP practices in the OPCRD was accounted for using cluster robust standard errors. We chose this limited set of adjustment variables to prevent any overadjustment bias, whereby adjustment is made for variables which lie on the causal path between sex and outcomes, to ensure that we captured the full magnitude of any sex disparities[31]. For example, adjustment for socioeconomic status within our models could lead us to exclude gender disparities driven by socioeconomic disadvantage among females. We accounted for clustering within hospitals using fixed-effect in the UKSAR, and clustering within practices in the OCPRD using cluster robust standard errors, while fixed-effects were used to account for clustering within hospitals in the UKSAR due to a much smaller number of sites.'

Sensitivity and supplementary analysis

Sensitivity analysis was performed using patients with mild to moderate asthma from the OPCRD cohort to assess the potential impact of disease severity on our findings. Mild/ moderate asthma was defined as patients with a diagnosis of asthma on GINA step 2-3 therapy[24]. Those patients who had required OCS within the last 12 months were excluded from the mild/ moderate asthma group to provide a clear comparator, avoiding patients with underlying SA whose therapy had not been stepped up. All patients with alternative respiratory diagnoses were excluded. We investigated potential mediation due to BMI (categorised as <25, 25-30, ≥30 kg/m^2), depression/ anxiety and smoking status using the methods of Baron and Kenny[32] to understand the extent to which they may mediate gender disparities. A directed acyclic graph displaying the assumed relationships between the variables included within our mediation analysis is provided in Supplementary figure 1.

RESULTS

Cohort Demographics

The UKSAR analysis contained 3,679 patients (2,242 [60.9%] females) with SA from 17 specialist secondary-care clinical centres, whilst the OPCRD analysis contained 18,369 patients (12,468 [67.9%] females) with SA within primary care. Details of the study flow diagram can be seen in Supplement figure 2). Patients in the UKSAR cohort were on higher doses of ICS than SA patients from the OPCRD cohort (median 2000 vs. 1000 BDP). Patient demographics and clinical characteristics are shown in tables 1 and 2, whilst details of the multivariable analysis are in supplement table 2 and 3.

231 **Table 1.** Comparison of female and male patients with severe asthma in the UK Severe Asthma
232 Registry

Characteristic	Female (n =2,242)	Male (n = 1,437)	P-value
Age at baseline assessment[a]	48.9 (15.3)	54.0 (14.1)	<0.001
<35	464 (20.7%)	157 (10.9%)	
35-54	907 (40.5%)	535 (37.3%)	
55-74	792 (35.4%)	668 (46.5%)	
75+	77 (3.4%)	76 (5.3%)	
Ethnicity[b]			0.094
Caucasian	1,808 (81.8%)	1,189 (83.7%)	
Southeast Asian	83 (3.8%)	58 (4.1%)	
Northeast Asian	43 (1.9%)	30 (2.1%)	
African	73 (3.3%)	25 (1.8%)	
Mixed	15 (0.7%)	11 (0.8%)	
Other	187 (8.5%)	107 (7.5%)	
Age at onset of symptoms[a]	22.8 (18.4)	29.1 (21.5)	<0.001
FEV_1 (% predicted)[a]	68.7 (21.1)	64.8 (21.0)	<0.001
FVC (% predicted)[a]	83.6 (19.2)	84.4 (19.2)	0.248
FEV_1 / FVC ratio[b]			<0.001
<70%	1,182 (56.6%)	988 (73.3%)	
>70%	907 (43.4%)	359 (26.7%)	
KCO (% predicted)[a]	94.7 (32.9)	102.6 (20.4)	<0.001
ACQ6 score[a]	3.1 (1.3)	2.6 (1.4)	<0.001
Uncontrolled asthma (ACQ6 >1.5)[b]	1,528 (85.6%)	850 (75.7%)	<0.001
Courses of rescue steroids in last year[b]			<0.001
0	178 (8.2%)	185 (13.4%)	
1	142 (6.6%)	106 (7.7%)	
2	163 (7.5%)	107 (7.8%)	
3	205 (9.5%)	161 (11.7%)	
≥4	1,477 (68.2%)	820 (59.5%)	
ED attendances for asthma (last year)[c]	0 (0,1)	0 (0,1)	<0.001
Any ED Attendance (last year)[b]	808 (38.3%)	383 (28.7%)	<0.001
Any hospital admissions (last year)[b]	884 (40.9%)	417 (30.5%)	<0.001
On maintenance OCS[b]	1,045 (46.9%)	747 (52.3%)	0.001
Maintenance OCS (mg)[c]	10 (8,20)	10 (8,15)	0.026
ICS dose (BDP equivalent-ug)[c]	2000 (1600,2000)	2000 (1600,2000)	0.074
Treatment adherent[b]	1,713 (81.5%)	1,081 (80.6%)	0.491
On biologic therapy[b]	1,608 (72.4%)	1,044 (73.3%)	0.553

Anti-IL5/ 5RA	1,184 (80.9%)	804 (84.9%)	
Anti-IgE	274 (18.7%)	140 (14.8%)	
Anti-IL4/13	5 (0.3%)	3 (0.3%)	
Other	1 (0.1%)	0 (0.0%)	
FeNO (ppb)[c]	36 (18,66)	46 (26,81)	<0.001
Blood eosinophil count (10^9/L)[c]	0.37 (0.20,0.60)	0.40 (0.20,0.61)	0.1
Highest blood eosinophil count (10^9/L)[b]			0.394
<0.150	483 (22.3%)	295 (21.2%)	
0.150-0.300	328 (15.1%)	197 (14.2%)	
>0.300	1359 (62.5%)	900 (66.7%)	
BMI (Kg/m^2)[a]	31.5 (7.8)	29.5 (5.8)	<0.001
Normal/ underweight (<24.9)	453 (21.1%)	278 (20.4%)	
Overweight (25-29.9)	559 (26.1%)	538 (39.4%)	
Obese (≥30 Kg/m^2)	1,132 (52.8%)	548 (40.2%)	
Smoking status[b]			<0.001
Never smoked	1,483 (67.5%)	861 (61.3%)	
Ex-smoker	603 (27.5%)	500 (35.6%)	
Current smoker	110 (5.0%)	44 (3.1%)	
Comorbidities[b]			
Atopic disease	1,210 (55.6%)	739 (52.9%)	0.113
Depression/ anxiety	219 (9.8%)	90 (6.3%)	<0.001
Nasal polyps	249 (11.1%)	242 (16.8%)	<0.001

Data is calculated as mean (SD) using t-test ([a]), count (%) with chi-square ([b]) and median (IQR) with Man-Whitney U ([c]) statistical tests.

237 **Table 2**. Comparison of female and male patients with severe asthma in the Optimum Patient Care
238 Research Database

Characteristic	Female (N = 12,468)	Male (N = 5,901)	P-value
Age (years)[a]	56.1 (16.4)	57.2 (15.8)	<0.001
<35	1,393 (11.2%)	549 (9.3%)	
35-54	4,507 (36.1%)	2,049 (34.7%)	
55-74	4,779 (38.3%)	2,475 (41.9%)	
75+	1,789 (14.3%)	828 (14.0%)	
Ethnicity[b]			0.275
White	8,404 (95.4%)	3,920 (94.7%)	
Mixed	22 (0.2%)	12 (0.3%)	
Asian	309 (3.5%)	160 (3.9%)	
Black	43 (0.5%)	22 (0.5%)	
Other	32 (0.4%)	25 (0.6%)	
Index of multiple deprivation (quintile)[b]			0.072
5 (Least deprived)	2,563 (20.7%)	1,281 (21.9%)	
4	2,420 (19.5%)	1,200 (20.5%)	
3	2,275 (18.4%)	1,075 (18.4%)	
2	3,378 (27.3%)	1,513 (25.8%)	
1 (Most deprived)	1,743 (14.1%)	788 (13.5%)	
Peak flow (% predicted)[c]	77.2 (62.7,91.4)	76.4 (59.4,91.5)	0.007
Uncontrolled (RCP 3 questions)[b]	2,255 (56.0%)	950 (51.2%)	<0.001
Exacerbations[c]	1.0 (0.0,2.0)	1.0 (0.0,2.0)	<0.001
Any exacerbations[b]	7,018 (56.3%)	3,109 (52.7%)	<0.001
Prior exacerbations[b]			0.007
0	0 (0.0%)	0 (0.0%)	
1	0 (0.0%)	0 (0.0%)	
2	7,000 (56.1%)	3,458 (58.6%)	
3	2,545 (20.4%)	1,146 (19.4%)	
4+	2,923 (23.4%)	1,297 (22.0%)	
ICS dose (BDP equivalent-ug)[c]	1000 (1000,2000)	1000 (1000,2000)	<0.001
Treatment step (GINA 2018) [b]			0.055
4	10,343 (83.0%)	4,962 (84.1%)	
5	2,125 (17.0%)	939 (15.9%)	
Asthma review [b]	5,695 (45.7%)	2,646 (44.8%)	0.287
Respiratory referral [b]	936 (7.5%)	416 (7.0%)	0.267
Medication possession ratio fixed (%)[c]	48.8 (24.6,82.0)	49.9 (27.3,82.0)	<0.001
Treatment adherent (MPR ≥70%)[b]	3,841 (31.6%)	1,930 (33.5%)	0.014

Blood Eosinophil Count (10^9/L)[c]	0.20 (0.10,0.31)	0.23 (0.13,0.40)	<0.001
Highest blood eosinophil count (10^9/L)[b]			<0.001
<0.150	2,180 (32.8%)	686 (26.8%)	
0.150-0.300	2,778 (41.9%)	1,029 (40.2%)	
>0.300	1,679 (25.3%)	843 (33.0%)	
BMI (Kg/m^2)[a]	30.0 (7.0)	28.8 (5.5)	<0.001
Underweight (<18.5)	174 (1.7%)	47 (1.0%)	
Normal weight (18.5-24.9)	2,578 (24.5%)	1,182 (24.1%)	
Overweight (25-29.9)	3,143 (29.8%)	1,927 (39.3%)	
Obese (≥30)	4,640 (44.0%)	1,742 (35.6%)	
Smoking status[b]			<0.001
Never smoked	6,511 (53.4%)	2,639 (45.6%)	
Ex-smoker	3,415 (28.0%)	2,236 (38.7%)	
Current smoker	2,273 (18.6%)	910 (15.7%)	
Comorbidities[b]			
Atopic dermatitis	1,540 (12.4%)	777 (13.2%)	0.120
Atopic disease	2,217 (17.8%)	1,048 (17.8%)	0.971
Allergic rhinitis	1,439 (11.5%)	599 (10.2%)	0.005
Cataracts	314 (2.5%)	129 (2.2%)	0.170
Depression/ anxiety	1,990 (16.0%)	512 (8.7%)	<0.001
Diabetes	1,150 (9.2%)	591 (10.0%)	0.087
Nasal polyps	157 (1.3%)	189 (3.2%)	<0.001
Osteoporosis	373 (3.0%)	62 (1.1%)	<0.001

Data is calculated as mean (SD) using t-test ([a]), count (%) with chi-square ([b]) and median (IQR) with Man-Whitney U ([c]) statistical tests.

Asthma clinical characteristics and outcomes

Females from the UKSAR database had an earlier average age of onset of symptoms (22.8 years vs. 29.5 years; p<0.001), and average age of first assessment at a UKSAR centre than males (48.9 years in vs. 54.0 years, p<0.001). In adjusted analyses, of uncontrolled asthma were higher among females than males (figure 1, tables 1 and 2) as measured using the ACQ6 in UKSAR (adjusted odds ratio [aOR]: 1.8, 95% confidence interval [CI]: 1.47, 2.19) or the RCP 3Q in OPCRD SA (aOR: 1.29, 95% CI: 1.13, 1.47). Females in the UKSAR cohort had higher ACQ6 scores 6 (UKSAR aOR: 1.14, 95% CI: 1.09, 1.18), demonstrating increased symptoms and lower asthma control, across all domains with a clinically significant, unadjusted difference of 0.5 (3.1 vs. 2.6, p<0.001).

Exacerbation rates were higher in females than males across all cohorts (UKSAR IRR: 1.13, 95% CI: 1.10, 1.17; OPCRD IRR: 1.06, 95% CI: 1.00, 1.12). Secondary healthcare utilisation was also increased with females in the UKSAR dataset more likely to report a hospital admission (aOR: 1.46 95% CI: 1.26, 1.70) or ED attendance (aOR: 1.37, 95% CI: 1.17, 1.60) in the last year. In primary care there was no evidence of differences in asthma reviews (OPCRD SA aOR: 1.07, 95% CI: 0.99, 1.16) or differences in asthma referrals (OPCRD SA aOR: 1.09, 95% CI: 0.94, 1.2).

FEV_1 percent predicted was higher in females with SA (UKSAR adjusted ratio: 1.05, 95% CI: 1.03, 1.07) representing a difference of 3.9% in absolute terms (68.7% vs. 64.8%, p<0.001). In primary care there was no evidence of significant differences in PEF (adjusted ratio: 1.01, 95% CI: 1.00, 1.03).

Type-2 Biomarkers

Multivariable analysis found no evidence of a difference between sexes in baseline blood eosinophil count in the UKSAR dataset (adjusted ratio: 0.94, 95% CI: 0.88, 1.01), however, eosinophil counts were lower in females for the OPCRD SA dataset (adjusted ratio: 0.85, 95% CI: 0.82, 0.89 (figure 1, tables 1 and 2,). Similarly, eosinophil counts were lower in females when looking specifically at prevalence of eosinophils greater than 0.3 $x10^9$/L in OPCRD SA (25.3% vs. 33%) cohort but did not differ significantly in the UKSAR dataset. Female UKSAR patients also had lower levels of the T2 biomarkers IgE (adjusted ratio: 0.63, 95% CI: 0.56,0.72) and FeNO (adjusted ratio: 0.79, 95% CI: 0.74, 0.85). In absolute terms, FeNO levels in females were on average 10ppb less than males (36ppb vs. 46ppb, p<0.001), whilst IgE was 79 IU/ml lower (129 IU/ml vs. 208 IU/ml, p<0.001).

Corticosteroid and biological therapy

In multivariable analysis, females in the UKSAR cohort were less likely to be on maintenance OCS (aOR: 0.86, 95% CI: 0.75, 0.99). No evidence of a difference in treatment adherence was found (UKSAR aOR: 1.20, 95% CI 0.97, 1.49; OPCRD SA aOR: 0.96, 95% CI: 0.88, 1.04). Fixed medication possession ratio of inhaled corticosteroids between females and males was similar in the OPCRD SA (48.8% vs 49.9%, p<0.001) group (figure 1, tables 1 and 2).

There was no evidence of a difference in the proportion of females and males on biological treatment (OR: 1.07, 95% CI: 0.89, 1.29).

Comorbidities and lifestyle

A higher proportion of female patients were found to be obese (figure 1, tables 1 and 2) in both the UKSAR (aOR: 1.67; 95% CI: 1.45, 1.93) and OPCRD SA (aOR: 1.46, 95% CI: 1.34, 1.58) cohorts. In terms of smoking, females were significantly less likely to have smoked (UKSAR aOR: 0.78, 95% CI: 0.67, 0.90; OPCRD SA aOR: 0.71. 95% CI: 0.65, 0.76). However, a higher proportion of females were current smokers in both the UKSAR (5% vs. 3.1%, p <0.001) and OPCRD SA (18.6% vs. 15.7%, p<0.001) groups.

Females were less likely to have nasal polyps compared to males in both datasets (UKSAR: 11.1% vs 16.8%; OPCRD: SA 1.3% vs 3.2%, p<0.001). There was no significant difference in atopic disease in the UKSAR (aOR: 0.96, 95% CI: 0.83, 1.11) or OPCRD SA (aOR: 1.04, 95% CI: 0.94, 1.15) groups. Allergic rhinitis was, however, more common in females (OPCRD SA 11.5% vs 10.2%, p=0.005).

Females were more likely than males to be suffering from depression and/ or anxiety in both datasets (UKSAR aOR: 1.55, 95% CI: 1.18, 2.02; OPCRD SA aOR: 1.88, 95% CI: 1.65, 2.14). Females in OPCRD SA had a higher prevalence of osteoporosis (3% vs 1%, p<0.001), however no significant sex difference was seen with other corticosteroid associated comorbidities, Including diabetes or cataracts.

Sensitivity and supplementary analysis

The OPCRD analysis included 54,150 (30,946 [57.1%] females) with mild/ moderate asthma (Supplement figure 3). Results from this mild/ moderate OPCRD cohort (Supplement table 4) were generally in line with the SA cohorts (Supplement table 2 and 3), revealing similar disparities. However, females were significantly more likely to have asthma reviews (aOR: 1.13, 95% CI: 1.09, 117) and atopic disease (aOR 1.17, 95% CI:1.11, 1.22) in the sensitivity analysis with no significant difference in the OPCRD SA cohort. Furthermore, females in the mild/ moderate group were also more likely to have exacerbations (IRR: 1.38, 95% CI: 1.31, 1.46), which was also seen with SA in the UKSAR but was not significant in the OPCRD SA group.

Mediation analysis found the disparities in asthma control, exacerbations, and ED attendance to persist even after adjustment for BMI, smoking status and co-existing depression/ anxiety (Supplement figure 4).

DISCUSSION

The analysis of these cohorts across two independent data sources and spanning UK primary and secondary care found females with asthma to have worse asthma symptoms of asthma control, increased exacerbation rates and obesity compared with their male counterparts. The inclusion of the OPCRD demonstrates the applicability of the UKSAR to a wider unselected population of patients with SA. Disparities were consistent across both SA cohorts and the sensitivity analysis in the mild/ moderate asthma cohort, suggesting that many of the sex differences seen in SA also exist in patients with mild/ moderate asthma.

More patients with SA were females (UKSAR: 60.9%; OPCRD SA 67.9%), consistent with findings from other SA cohorts and registries[14, 16]. Asthma control, as measured by self-reported symptoms scores on both ACQ6 and RCP 3Q questionnaires, was statistically and clinically worse in females. However, females were less likely to have indicators of T2 inflammation with reduced FeNO and IgE levels in the UKSAR and lower blood eosinophil counts in the OPCRD cohort. Aligning with the findings of a recent RASP-UK biomarker study post hoc analysis by sex which found the majority of females to be T2 biomarker low but high in their ACQ6 symptom scores with the converse seen in males[19]. Interestingly, females had a higher percent predicted FEV_1 than males despite their worse asthma control scores. In prior cluster analyses, a similar group of females with poor asthma control and near normal lung function has previously been identified[13].

Females from the UKSAR were also found to be significantly more likely to report hospital admissions and/or ED attendance within the last year. These findings were consistent with the SARP study where hospitalisations had a bimodal distribution, which mapped changes in asthma prevalence in the sexes, with males more likely to utilise healthcare for their asthma during childhood and females later in life[33]. Similarly, females in the RASP-UK biomarker study[19] were significantly more likely to have asthma exacerbations and attend primary care within the last year. Whilst, Trawick et al found females have also been found to be twice as likely as their male counterparts to have repeated asthma related hospital admissions[34]. More generally, sex has been found to affect healthcare utilisation with

females to be more likely to seek and utilise healthcare, even when female specific illnesses are accounted for[35, 36].

Variations in symptoms between the sexes are also likely to influence clinical presentation, interpretation, healthcare access and utilisation[37, 38]. Whilst caution should be applied when interpreting self-reported outcomes, a dissociation between T2 biomarkers and symptom reporting has been noted in both sexes [19]. The RASP-UK biomarker study post-hoc analysis, which was also based on UK SA centres, was able to eliminate sex differences in symptom reporting from the ACQ by adjusting for differences in obesity and depression/ anxiety[19]. However, we were unable to replicate this mediation affect in our cohorts perhaps in part due to the RASP-UK biomarker study selection criteria, including a baseline FeNO of less than 45 ppb to enrich for T2 biomarker low participants, compared with our real-world cohort. Other studies have suggested other contributory factors for the discrepancy. One study examining acute moderate and severe asthma exacerbations found males less likely to report symptoms or activity limitations despite clinically similar levels of PEF with inappropriately low healthcare utilisation by males [38]. Females are also recognised to have an enhanced somatosensory responses, including a heighted cough reflex sensitivity[39], which may play a role in SA. This raises the possibility of differential item functioning in the reporting and experience of asthma symptoms between males and females, and it is an area that is currently under active research.

As previously reported in the UKSAR, males were more likely to have raised T2 biomarkers, such as FeNO and total IgE, suggestive of T2 asthma, which can in turn be targeted through biological therapies[20]. Whilst baseline blood eosinophils were not statistically different between sexes in the UKSAR, eosinophil counts greater than 0.3 $x10^9$/L were significantly higher in males compared to females in OPCRD cohorts. Blood eosinophilia in moderate to SA has previously been associated with male sex[15]. There was no significant difference between the proportion of males and females receiving biologic therapy. There was no clear differentiation between medication adherence in males and females, however, medicine possession ratio is notoriously difficult to interpret as it is subject to significant reporting bias and multiple other confounders. There are, however, numerous studies investigating the relationship between sex and adherence with most finding no association, in line with our results[40].

Females with SA were more likely to be obese across both independent cohorts. The association with obesity and asthma has multiple underlying mechanisms, including altered lung mechanics and airway inflammation[41, 42]. Obesity is associated with poor asthma control[43], hospitalisation[44] and asthma severity[45]. A number of studies have found the increased risk of asthma with obesity[46-48] and poor asthma control[19, 49] to be associated with females and not males. Furthermore, obesity may influence other parameters, for example, FeNO has been found to be lower in asthmatic patients who are obese, despite raised sputum eosinophils suggestive of T2 inflammation[50]. Depression/ anxiety, which was also more common in females, is associated with obesity and poor asthma control[51]. Despite the potential confounding influence of obesity, depression/ anxiety and smoking mediation analysis showed the disparities to persist even taking these factors into account, suggesting another mechanistic role for the sex differences seen in severe asthma.

The sensitivity analysis in the mild/ moderate OPCRD cohort aligned closely with the observations made in the SA cohorts. Although females exhibited a greater tendency to have atopic disease and undergo asthma reviews within the mild/ moderate group, the notable disparity in comparison to the SA groups could potentially stem from the larger sample sizes. The sensitivity analysis thus reinforces the strength of the findings derived from the SA cohorts, while also indicating that the disparities are unlikely to stem solely from variations in disease severity. Specialist care could inherently influence outcomes; however, referral rates from primary to specialist care did not exhibit any sex-based differences. Moreover, in the UKSAR group, who are receiving specialist care, females continued to have increased exacerbations, ED attendances and hospital admissions.

The UKSAR is a large well characterised cohort of patients with SA, as defined by ERS/ATS criteria[21]. It provides high quality and real-world data using robust standardised biomarker and spirometry measurements across multiple UK SA centres. It is important to note that the patients on the UKSAR have been referred to specialist care and may have more severe disease than the overall OPCRD population. Many patients are referred for biologic therapy, which focuses on T2 disease and may therefore bias the population towards those with T2 disease. Selection bias was minimised by examining two distinct data sources with the OPCRD providing an additional validatory data source to UKSAR in the wider unselected population and a sensitivity analysis comparator for mild to moderate asthma. This study, does however, have several potential limitations. Firstly, using retrospective datasets, it has been assumed that the diagnosis of SA is correct. Whilst patients in the UKSAR will have undergone specialist multi-disciplinary team assessment of their diagnosis, the OPCRD subjects were selected as those who remained uncontrolled (≥2 exacerbations within a year) on GINA 2018[24] step 4 treatment and not subject to the same diagnostic scrutiny. Secondly, as an observational study,

it is open to confounding influences such as unmeasured or poorly measured variables. Data used in the analysis, such as asthma control in the OPCRD dataset, was frequently missing and the timing of outcomes in relation to treatment can be difficult to account for. However, these factors are unlikely to have acted differentially based on sex. Further measures, such as health-seeking behaviour, which may mediate the effect seen between the sexes, and spirometry in primary care, which would provide a more robust comparison of lung function variables between datasets and is now recommended[3], were not measured and would benefit from further research.

In conclusion, this real-world data shows consistent and clinically important differences in the characteristics of males and females with SA, with the use of two distinct data sets demonstrating the applicability of the UKSAR to the wider unselected SA population. Females had worse asthma control, increased exacerbations and were more likely to be obese despite higher FEV_1 percent predicted, similar baseline blood eosinophils, lower FeNO and reduced total IgE compared with their male counterparts. Although related to sex the reasons and mechanisms behind these disparities are likely to be related to multiple factors such as hormonal, immunological, comorbidity and behavioural (both patient and healthcare professional) influences which were not measured in our dataset.

Further prospective epidemiologic studies with high-quality linked datasets and measure of other potential mediating factors such as symptom perception, alongside mechanistic studies are required to understand the drivers behind these sex differences and provide tailored and personalised care to people with SA.

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Contributorship statement:

LL, JB, RMcD, TB, HB, RC, PD, JWD, SD, SF, RG, EI, DJJ, MP, TP, IDP, PEP, DP, HR, SS, LGH and AMG made substantial contributions to the study conception, design, data acquisition and interpretation. JB and RMcD led the statistical analysis. LL was primarily responsible for manuscript drafting and revisions and all authors commented on previous versions of the manuscript. The final manuscript was approved by all the authors prior to submission.

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LL has no conflicts of interest.

JB has attended advisory boards for NuvoAir, outside the submitted work.

RMcD has no conflicts of interest.

TB has received speaker fees from Astra Zeneca, Glaxo Smith Kline, Sanofi, Teva, Novartis and Chiesi; honoraria for advisory board attendance from Astra Zeneca, Sanofi and Teva; sponsorship to attend international scientific meetings from Sanofi, GSK, Teva, Chiesi and Napp Pharmaceuticals.

HB has attended advisory board for AstraZeneca, GlaxoSmithKline and Sanofi; has given lectures at meetings with/without lecture honoraria supported by AstraZeneca, GlaxoSmithKline and Chiesi; has attended international conferences with AstraZeneca and Chiesi; has taken part in clinical trials sponsored by AstraZeneca, Chiesi, GlaxoSmithKline, Teva and Sanofi.

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PD has received honoraria/consultancy fees/sponsorship from Teva, AZ, GSK, Novartis and Omron.

JWD declares he has received honoraria for participating in advisory boards and given lectures at meetings supported by GSK, Boerhinger Ingelheim, Chiesi, AstraZeneca, Fisher & Paykel, Aerogen; he has received sponsorship for attending international scientific meetings from Chiesi; he has also taken part in asthma clinical trials sponsored by Sanofi, AstraZeneca, Chiesi for which his institution received remuneration.

SD has received lecture fees from GSK, AZ, and Sanofi; honoraria for Advisory Board Meetings from GSK, AZ, and Novartis; sponsorship to attend international scientific meetings from AZ, Chiesi, Sanofi and GSK.

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MP has no conflicts of interest.

TP has received sponsorship for attending international scientific meetings from Chiesi, GlaxoSmithKline and Sanofi Genzyme; he is also taking part in asthma clinical trials sponsored by AstraZeneca and Sanofi Genzyme for which his institution receives remuneration.

IDP has received speaker's honoraria for speaking at sponsored meetings from Astra Zeneca, Boehringer Inglehiem, Aerocrine, Almirall, Novartis, Teva, Chiesi, Sanofi/Regeneron, Menarini and GSK and payments for organising educational events from AZ, GSK, Sanofi/Regeneron and Teva. He has received honoraria for attending advisory panels with Genentech, Sanofi/Regeneron, Astra Zeneca, Boehringer Ingelheim, GSK, Novartis, Teva, Merck, Circassia, Chiesi and Knopp and payments to support FDA approval meetings from GSK. He has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GSK, Astra Zeneca, Teva and Chiesi. He has received a grant from Chiesi to support a phase 2 clinical trial in Oxford.

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DP has advisory board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Viatris, Mundipharma, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals and Thermofisher; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Viatris, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals and Theravance; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Viatris, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals, Theravance and UK National Health Service; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Viatris, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Sanofi Genzyme and Teva Pharmaceuticals; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Circassia, Mundipharma, Novartis, Teva Pharmaceuticals and Thermofisher;

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556 monitoring technology; is peer reviewer for grant committees of the UK Efficacy and Mechanism
557 Evaluation programme, and Health Technology Assessment; and was an expert witness for
558 GlaxoSmithKline.

559

560 HR has received lecture fees from GSK, AZ, Chiesi, and Sanofi; honoraria for Advisory Board Meetings
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580 AMG is an employee of Astra Zeneca.

581

582 **Ethics approval:**

Approval for collection and analysis of pseudonymized UKSAR data was granted by ORECNI (15/NI/0196). The OPCRD has been reviewed and ethically approved by the National Health Service Health Research Authority to hold and process anonymized data as part of service delivery (Research Ethics Committee reference: 15/EM/0150). Specific approval for this research study was granted by the Anonymized Data Ethics Protocols and Transparency committee (ADEPT approval reference: ADEPT0120). The Optimum Patient Care Research Database (OPCRD) is established and maintained by Optimum Patient Care (OPC) Ltd. The OPCRD is approved by the UK National Health Service for clinical research use (Research Ethics Committee reference 15/EM/0150).

Data sharing:

No data are available for the UKSAR. Researchers can request access for OPCRD data through the OPCRD website or by contacting info@opcrd.co.uk, although public access to the dataset is not granted.

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LIST OF ABBREVIATIONS

ACQ: asthma control questionnaire

BDP: beclomethasone dipropionate

BMI: body mass index

ED: emergency department

FeNO: fractional exhaled nitric oxide

FEV_1: forced expiratory volume in 1 second

FVC: forced vital capacity

ICS: inhaled corticosteroids

IgE: Immunoglobulin E

KCO: carbon monoxide transfer coefficient

MPR: medicine possession ratio

OCS: oral corticosteroid

OPCRD: Optimum Patient Care Research Database

PEF: peak expiratory flow

RASP-UK: Refractory Asthma Stratification Programme

RCP 3Q: Royal College of Physicians 3 Questions

SA: severe asthma

SARP: Severe Asthma Research Program

T2: type-2

UKSAR: UK Severe Asthma Registry