



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

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1 **Title**

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

4

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45

46 **ABSTRACT**

47

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

51

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

54

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

59

60 **Results:** 3,679 (60.9% female) patients from UKSAR and 18,369 patients (67.9% female) from OPCR  
61 with SA were included. Females were more likely to be symptomatic with increased Asthma Control  
62 Questionnaire-6 (UKSAR aOR: 1.14, 95% CI: 1.09, 1.18) and RCP-3 Question scores (OPCRD aOR: 1.29:  
63 1.13, 1.47). However, they had a higher FEV<sub>1</sub>% predicted (UKSAR 68.7% vs. 64.8%, p<0.001) with no  
64 significant difference in peak expiratory flow. Type-2 biomarkers IgE (UKSAR 129IU/ml vs. 208IU/ml,  
65 p<0.001) and FeNO (UKSAR 36ppb vs. 46ppb, p<0.001) were lower in females with no significant  
66 difference in blood eosinophils or biologic therapy. Females were less likely to be on maintenance OCS  
67 (UKSAR aOR 0.86: 0.75, 0.99) but more likely to be obese (UKSAR aOR 1.67: 1.45, 1.93; OPCR SA aOR:  
68 1.46: 1.34, 1.58).

69

70 **Conclusions:** Females had increased symptoms and were more likely to be obese despite higher FEV<sub>1</sub>%  
71 predicted and lower type-2 biomarkers with consistent and clinically important differences across  
72 both datasets.

73

74 **What is already known on this topic**

75 Severe asthma is more common in females. It is associated with different disease characteristics  
76 between the sexes, including females having a higher symptom burden and lower expression of type-  
77 2 biomarkers.

78

79 **What this study adds**

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

85

86 **How this study might affect research, practice, or policy**

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

90

91 **INTRODUCTION**

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

100

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

112

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

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

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

138

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

142

## 143 **METHODS**

### 144 **Study Population**

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

151

152 The Optimum Patient Care Research Database (OPCRD) is a UK nationally-representative  
153 pseudonymised dataset of 18 million patients registered at 1000 general practices within the UK (24%  
154 of the UK population)[22]. The OPCRD is approved by the UK National Health Service for clinical  
155 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.

162

163 SA in the OPCR cohort was defined according to GINA 2018[24] criteria as those who remained  
164 uncontrolled ( $\geq 2$  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<sub>1</sub>], 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.

175

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<sub>1</sub> 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 OPCR. 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<sup>2</sup> or greater. Comorbidities in the OPCR 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.



188

## 189 **Statistical Analysis**

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

208

## 209 **Sensitivity and supplementary analysis**

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

220

221 **RESULTS**

222 **Cohort Demographics**

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

229

230

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
<b>Age at baseline assessment<sup>a</sup></b>	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%)	
<b>Ethnicity<sup>b</sup></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%)	
<b>Age at onset of symptoms<sup>a</sup></b>	22.8 (18.4)	29.1 (21.5)	<0.001
<b>FEV<sub>1</sub> (% predicted)<sup>a</sup></b>	68.7 (21.1)	64.8 (21.0)	<0.001
<b>FVC (% predicted)<sup>a</sup></b>	83.6 (19.2)	84.4 (19.2)	0.248
<b>FEV<sub>1</sub> / FVC ratio<sup>b</sup></b>			<0.001
<70%	1,182 (56.6%)	988 (73.3%)	
>70%	907 (43.4%)	359 (26.7%)	
<b>KCO (% predicted)<sup>a</sup></b>	94.7 (32.9)	102.6 (20.4)	<0.001
<b>ACQ6 score<sup>a</sup></b>	3.1 (1.3)	2.6 (1.4)	<0.001
<b>Uncontrolled asthma (ACQ6 &gt;1.5)<sup>b</sup></b>	1,528 (85.6%)	850 (75.7%)	<0.001
<b>Courses of rescue steroids in last year<sup>b</sup></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%)	
<b>ED attendances for asthma (last year)<sup>c</sup></b>	0 (0,1)	0 (0,1)	<0.001
<b>Any ED Attendance (last year)<sup>b</sup></b>	808 (38.3%)	383 (28.7%)	<0.001
<b>Any hospital admissions (last year)<sup>b</sup></b>	884 (40.9%)	417 (30.5%)	<0.001
<b>On maintenance OCS<sup>b</sup></b>	1,045 (46.9%)	747 (52.3%)	0.001
<b>Maintenance OCS (mg)<sup>c</sup></b>	10 (8,20)	10 (8,15)	0.026
<b>ICS dose (BDP equivalent-ug)<sup>c</sup></b>	2000 (1600,2000)	2000 (1600,2000)	0.074
<b>Treatment adherent<sup>b</sup></b>	1,713 (81.5%)	1,081 (80.6%)	0.491
<b>On biologic therapy<sup>b</sup></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%)	
<b>FeNO (ppb)<sup>c</sup></b>	36 (18,66)	46 (26,81)	<0.001
<b>Blood eosinophil count (10<sup>9</sup>/L)<sup>c</sup></b>	0.37 (0.20,0.60)	0.40 (0.20,0.61)	0.1
<b>Highest blood eosinophil count (10<sup>9</sup>/L)<sup>b</sup></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%)	
<b>BMI (Kg/m<sup>2</sup>)<sup>a</sup></b>	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 <sup>2</sup> )	1,132 (52.8%)	548 (40.2%)	
<b>Smoking status<sup>b</sup></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%)	
<b>Comorbidities<sup>b</sup></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

233

234 Data is calculated as mean (SD) using t-test (<sup>a</sup>), count (%) with chi-square (<sup>b</sup>) and median (IQR) with  
235 Man-Whitney U (<sup>c</sup>) statistical tests.

236

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
<b>Age (years)<sup>a</sup></b>	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%)	
<b>Ethnicity<sup>b</sup></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%)	
<b>Index of multiple deprivation (quintile)<sup>b</sup></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%)	
<b>Peak flow (% predicted)<sup>c</sup></b>	77.2 (62.7,91.4)	76.4 (59.4,91.5)	0.007
<b>Uncontrolled (RCP 3 questions)<sup>b</sup></b>	2,255 (56.0%)	950 (51.2%)	<0.001
<b>Exacerbations<sup>c</sup></b>	1.0 (0.0,2.0)	1.0 (0.0,2.0)	<0.001
<b>Any exacerbations<sup>b</sup></b>	7,018 (56.3%)	3,109 (52.7%)	<0.001
<b>Prior exacerbations<sup>b</sup></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%)	
<b>ICS dose (BDP equivalent-ug)<sup>c</sup></b>	1000 (1000,2000)	1000 (1000,2000)	<0.001
<b>Treatment step (GINA 2018)<sup>b</sup></b>			0.055
4	10,343 (83.0%)	4,962 (84.1%)	
5	2,125 (17.0%)	939 (15.9%)	
<b>Asthma review<sup>b</sup></b>	5,695 (45.7%)	2,646 (44.8%)	0.287
<b>Respiratory referral<sup>b</sup></b>	936 (7.5%)	416 (7.0%)	0.267
<b>Medication possession ratio fixed (%)<sup>c</sup></b>	48.8 (24.6,82.0)	49.9 (27.3,82.0)	<0.001
<b>Treatment adherent (MPR ≥70%)<sup>b</sup></b>	3,841 (31.6%)	1,930 (33.5%)	0.014

<b>Blood Eosinophil Count (10<sup>9</sup>/L)<sup>c</sup></b>	0.20 (0.10,0.31)	0.23 (0.13,0.40)	<0.001
<b>Highest blood eosinophil count (10<sup>9</sup>/L)<sup>b</sup></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%)	
<b>BMI (Kg/m<sup>2</sup>)<sup>a</sup></b>	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%)	
<b>Smoking status<sup>b</sup></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%)	
<b>Comorbidities<sup>b</sup></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

239

240 Data is calculated as mean (SD) using t-test (<sup>a</sup>), count (%) with chi-square (<sup>b</sup>) and median (IQR) with  
241 Man-Whitney U (<sup>c</sup>) statistical tests.

242

### 243 **Asthma clinical characteristics and outcomes**

244 Females from the UKSAR database had an earlier average age of onset of symptoms (22.8 years vs.  
245 29.5 years; p<0.001), and average age of first assessment at a UKSAR centre than males (48.9 years in  
246 vs. 54.0 years, p<0.001). In adjusted analyses, of uncontrolled asthma were higher among females  
247 than males (figure 1, tables 1 and 2) as measured using the ACQ6 in UKSAR (adjusted odds ratio [aOR]:  
248 1.8, 95% confidence interval [CI]: 1.47, 2.19) or the RCP 3Q in OPCRD SA (aOR: 1.29, 95% CI: 1.13,  
249 1.47). Females in the UKSAR cohort had higher ACQ6 scores 6 (UKSAR aOR: 1.14, 95% CI: 1.09, 1.18),  
250 demonstrating increased symptoms and lower asthma control, across all domains with a clinically  
251 significant, unadjusted difference of 0.5 (3.1 vs. 2.6, p<0.001).

252

253 Exacerbation rates were higher in females than males across all cohorts (UKSAR IRR: 1.13, 95% CI:  
254 1.10, 1.17; OPCRDR IRR: 1.06, 95% CI: 1.00, 1.12). Secondary healthcare utilisation was also increased  
255 with females in the UKSAR dataset more likely to report a hospital admission (aOR: 1.46 95% CI: 1.26,  
256 1.70) or ED attendance (aOR: 1.37, 95% CI: 1.17, 1.60) in the last year. In primary care there was no  
257 evidence of differences in asthma reviews (OPCRDR SA aOR: 1.07, 95% CI: 0.99, 1.16) or differences in  
258 asthma referrals (OPCRDR SA aOR: 1.09, 95% CI: 0.94, 1.2).

259

260 FEV<sub>1</sub> percent predicted was higher in females with SA (UKSAR adjusted ratio: 1.05, 95% CI: 1.03, 1.07)  
261 representing a difference of 3.9% in absolute terms (68.7% vs. 64.8%, p<0.001). In primary care there  
262 was no evidence of significant differences in PEF (adjusted ratio: 1.01, 95% CI: 1.00, 1.03).

263

#### 264 **Type-2 Biomarkers**

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

274

#### 275 **Corticosteroid and biological therapy**

276 In multivariable analysis, females in the UKSAR cohort were less likely to be on maintenance OCS (aOR:  
277 0.86, 95% CI: 0.75, 0.99). No evidence of a difference in treatment adherence was found (UKSAR aOR:  
278 1.20, 95% CI 0.97, 1.49; OPCRDR SA aOR: 0.96, 95% CI: 0.88, 1.04). Fixed medication possession ratio of  
279 inhaled corticosteroids between females and males was similar in the OPCRDR SA (48.8% vs 49.9%,  
280 p<0.001) group (figure 1, tables 1 and 2).

281

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

284

### 285 **Comorbidities and lifestyle**

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

291

292 Females were less likely to have nasal polyps compared to males in both datasets (UKSAR: 11.1% vs  
293 16.8%; OPCR: SA 1.3% vs 3.2%,  $p < 0.001$ ). There was no significant difference in atopic disease in the  
294 UKSAR (aOR: 0.96, 95% CI: 0.83, 1.11) or OPCR SA (aOR: 1.04, 95% CI: 0.94, 1.15) groups. Allergic  
295 rhinitis was, however, more common in females (OPCR SA 11.5% vs 10.2%,  $p = 0.005$ ).

296

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

301

### 302 **Sensitivity and supplementary analysis**

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

311



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

315

## 316 **DISCUSSION**

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

324

325 More patients with SA were females (UKSAR: 60.9%; OPCRCD SA 67.9%), consistent with findings from  
326 other SA cohorts and registries[14, 16]. Asthma control, as measured by self-reported symptoms  
327 scores on both ACQ6 and RCP 3Q questionnaires, was statistically and clinically worse in females.  
328 However, females were less likely to have indicators of T2 inflammation with reduced FeNO and IgE  
329 levels in the UKSAR and lower blood eosinophil counts in the OPCRCD cohort. Aligning with the findings  
330 of a recent RASP-UK biomarker study post hoc analysis by sex which found the majority of females to  
331 be T2 biomarker low but high in their ACQ6 symptom scores with the converse seen in males[19].  
332 Interestingly, females had a higher percent predicted FEV<sub>1</sub> than males despite their worse asthma  
333 control scores. In prior cluster analyses, a similar group of females with poor asthma control and near  
334 normal lung function has previously been identified[13].

335

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

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

346

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

363

364 As previously reported in the UKSAR, males were more likely to have raised T2 biomarkers, such as  
365 FeNO and total IgE, suggestive of T2 asthma, which can in turn be targeted through biological  
366 therapies[20]. Whilst baseline blood eosinophils were not statistically different between sexes in the  
367 UKSAR, eosinophil counts greater than  $0.3 \times 10^9/L$  were significantly higher in males compared to  
368 females in OPCRCD cohorts. Blood eosinophilia in moderate to SA has previously been associated with  
369 male sex[15]. There was no significant difference between the proportion of males and females  
370 receiving biologic therapy. There was no clear differentiation between medication adherence in males  
371 and females, however, medicine possession ratio is notoriously difficult to interpret as it is subject to  
372 significant reporting bias and multiple other confounders. There are, however, numerous studies  
373 investigating the relationship between sex and adherence with most finding no association, in line  
374 with our results[40].

375

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

387

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

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

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

417 In conclusion, this real-world data shows consistent and clinically important differences in the  
418 characteristics of males and females with SA, with the use of two distinct data sets demonstrating the  
419 applicability of the UKSAR to the wider unselected SA population. Females had worse asthma control,  
420 increased exacerbations and were more likely to be obese despite higher FEV<sub>1</sub> percent predicted,  
421 similar baseline blood eosinophils, lower FeNO and reduced total IgE compared with their male  
422 counterparts. Although related to sex the reasons and mechanisms behind these disparities are likely  
423 to be related to multiple factors such as hormonal, immunological, comorbidity and behavioural (both  
424 patient and healthcare professional) influences which were not measured in our dataset.

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

429

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431

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464

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466 LL, JB, RMcD, TB, HB, RC, PD, JWD, SD, SF, RG, EI, DJJ, MP, TP, IDP, PEP, DP, HR, SS, LGH and AMG  
467 made substantial contributions to the study conception, design, data acquisition and interpretation.  
468 JB and RMcD led the statistical analysis. LL was primarily responsible for manuscript drafting and  
469 revisions and all authors commented on previous versions of the manuscript. The final manuscript  
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477 LL has no conflicts of interest.

478

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

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481 RMcD has no conflicts of interest.

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486

487 HB has attended advisory board for AstraZeneca, GlaxoSmithKline and Sanofi; has given lectures at  
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492 RC has received lecture fees from GSK, AZ, Teva, Chiesi, Sanofi and Novartis; honoraria for Advisory  
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540 DP has advisory board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia,  
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583 Approval for collection and analysis of pseudonymized UKSAR data was granted by ORECNI  
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585 Health Research Authority to hold and process anonymized data as part of service delivery (Research  
586 Ethics Committee reference: 15/EM/0150). Specific approval for this research study was granted by  
587 the Anonymized Data Ethics Protocols and Transparency committee (ADEPT approval reference:  
588 ADEPT0120). The Optimum Patient Care Research Database (OPCRDR) is established and maintained  
589 by Optimum Patient Care (OPC) Ltd. The OPCRDR is approved by the UK National Health Service for  
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591

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593 No data are available for the UKSAR. Researchers can request access for OPCRDR data through the  
594 OPCRDR website or by contacting [info@opcrd.co.uk](mailto:info@opcrd.co.uk), although public access to the dataset is not  
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596

- 598 1. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths,  
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734

- 735 **LIST OF ABBREVIATIONS**
- 736 ACQ: asthma control questionnaire
- 737 BDP: beclomethasone dipropionate
- 738 BMI: body mass index
- 739 ED: emergency department
- 740 FeNO: fractional exhaled nitric oxide
- 741 FEV<sub>1</sub>: forced expiratory volume in 1 second
- 742 FVC: forced vital capacity
- 743 ICS: inhaled corticosteroids
- 744 IgE: Immunoglobulin E
- 745 KCO: carbon monoxide transfer coefficient
- 746 MPR: medicine possession ratio
- 747 OCS: oral corticosteroid
- 748 OPCR: Optimum Patient Care Research Database
- 749 PEF: peak expiratory flow
- 750 RASP-UK: Refractory Asthma Stratification Programme
- 751 RCP 3Q: Royal College of Physicians 3 Questions
- 752 SA: severe asthma
- 753 SARP: Severe Asthma Research Program
- 754 T2: type-2
- 755 UKSAR: UK Severe Asthma Registry