SUPPLEMENT

The impact of sex on severe asthma: an analysis of UK primary and specialist care

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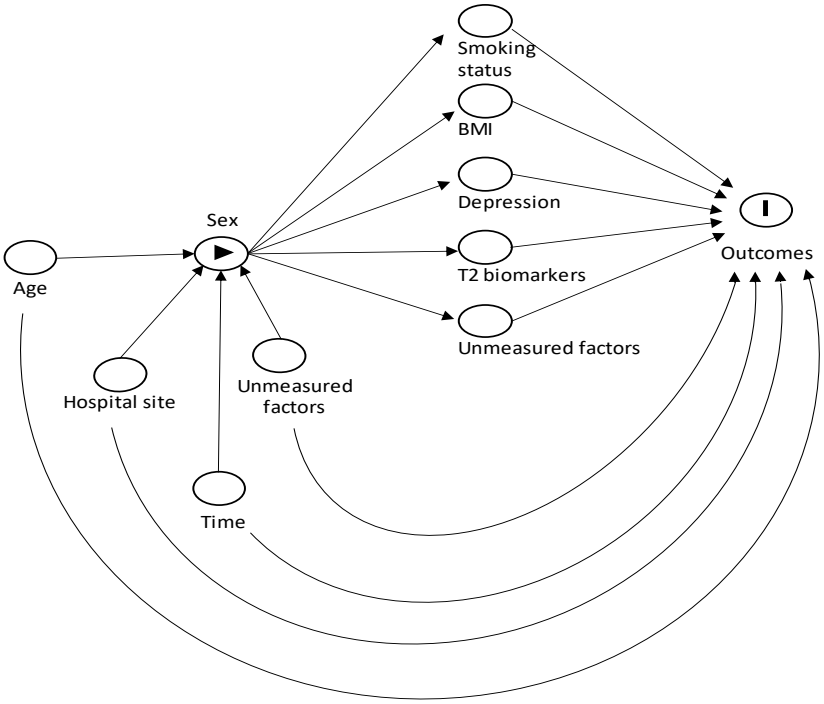
Supplement table 1. Definition of demographic and clinical outcomes in the OPCRD

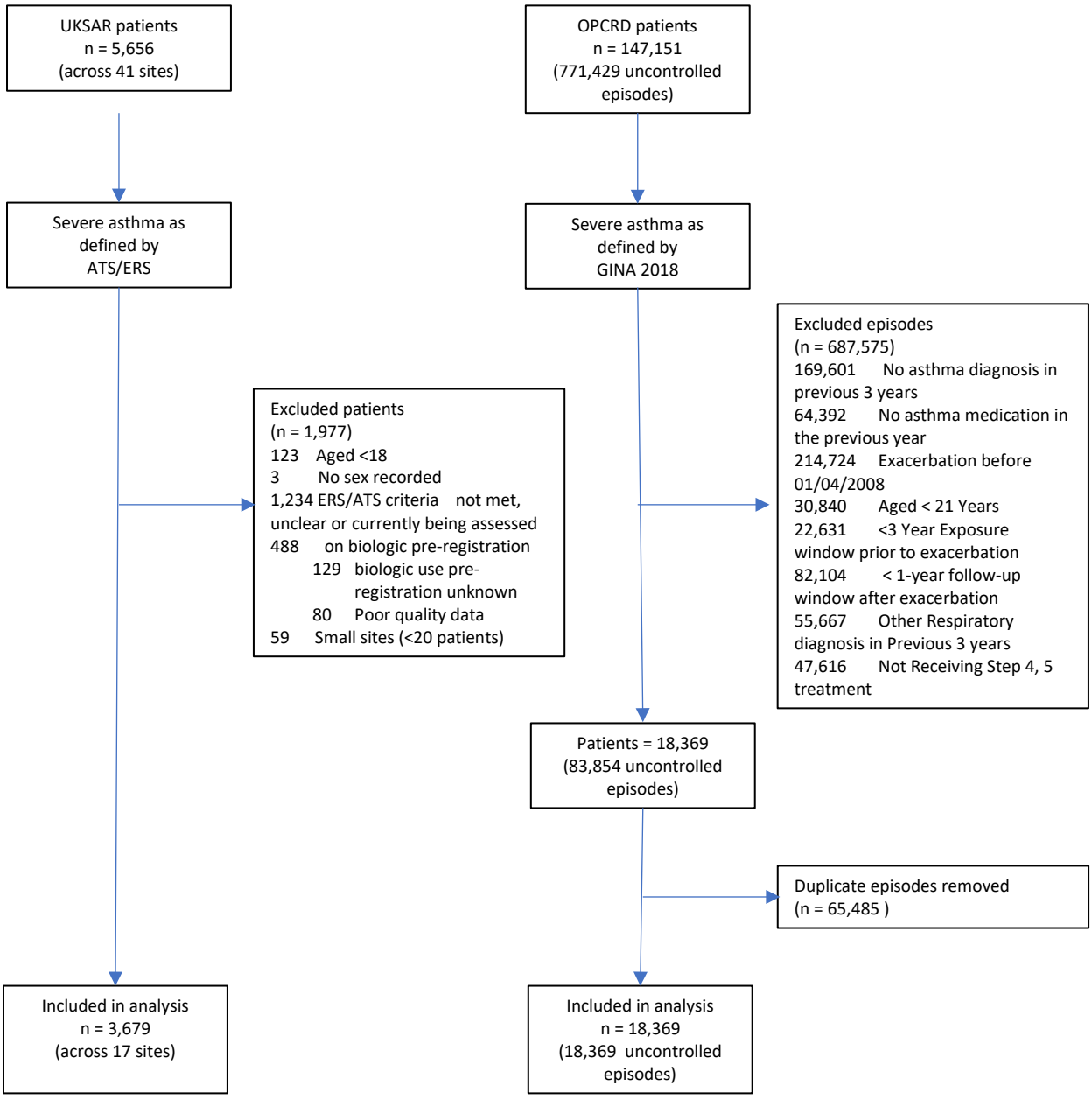
Variable	Description	Ascertainment period
Exposures		
Sex	Reported by the general practice for all patients	N/A
Outcomes		
Asthma exacerbation	Read code indicating an 'Asthma Exacerbation' or 'Asthma Attack, prescription of acute oral corticosteroids (OCS), or a lower respiratory infection requiring antibiotics. We applied an algorithm based on number of days medication given, strength of tablet, diagnosis codes recorded during the prescribing visit, dosing instruction and frequency of OCS prescription to differentiate maintenance and acute OCS use. OCS prescribed during annual asthma reviews were excluded.	1 year from start of follow-up
Asthma review	Read code list recognised within the NHS Quality and Outcomes Framework: Asthma annual review (Read code: XaIeq), Asthma follow-up (XaIer), Asthma monitoring by nurse (XaIu5), Asthma monitoring by doctor (XaIu6), Asthma medication review	1 year from start of follow up

	(XaIfK) or Asthma monitoring check done (XE2Nb).	
Blood Eosinophil count	Blood eosinophil count measured in cells per litre (109/L).	1 year from start of follow up, last measurement recorded
Highest blood eosinophil count	Blood eosinophil count measured in cells per litre (109/L).	1 year from start of follow up, highest measurement recorded
Peak Flow	Percent predicted values were calculated using raw measurements and the formula specified by Knudson et al[1]. We used a percent predicted peak flow value recorded directly in the medical records when no raw peak flow measure was available, or when the patient's height was unavailable.	1 year from start of follow up
Respiratory Referral	Read code for respiratory referral (Read Codes: XaAfm, XaAcS, XaAfl)	1 year from start of follow up
Treatment Adherence	Assessed using the fixed medications possession ratio of inhaled corticosteroids during the exposure period. Good adherence was defined as an MPR of greater than or equal to 70%. Medication quantity and dosing instructions were imputed using the most common for that medication (by Read Code) when insufficient information was recorded in the primary care record. When the patient received more than one type of ICS prescription, we averaged the MPR across all relevant medications.	1 year from start of follow up
Uncontrolled Disease	Measured using the Royal College of Physicians 3 questions[2]. Patients were classified as having poor control if 2 or 3 of the measures denote poor control or if patients experience difficulty sleeping because of their asthma symptoms.	1 year from start of follow up

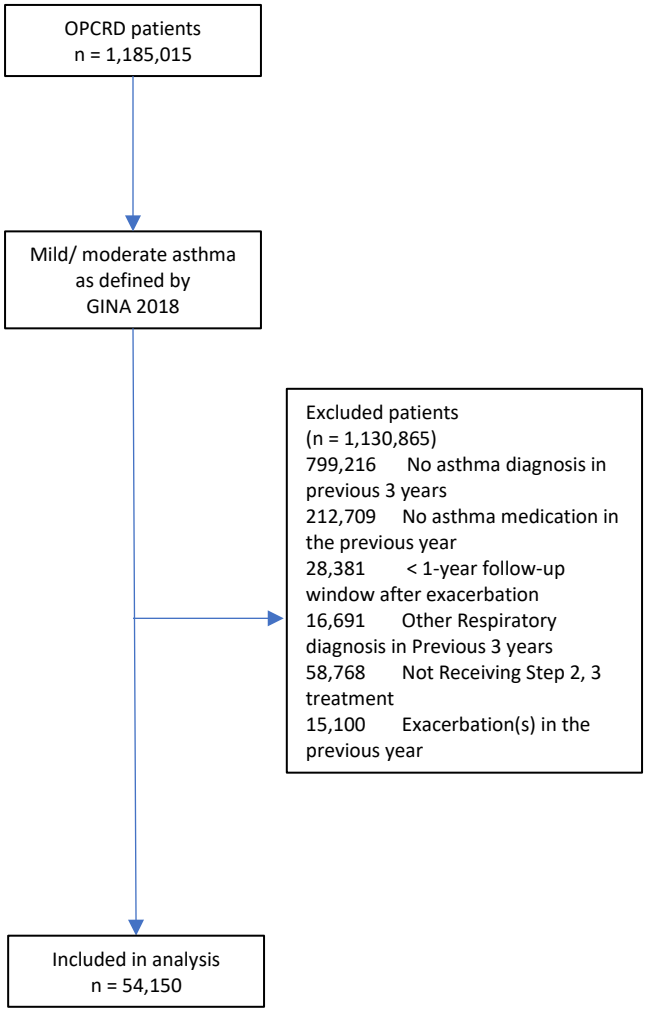
Covariates		
Atopic disease	Record of hay fever or eczema[3].	Beginning of medical record to start of follow up
Body Mass Index	Using Read Codes and measured in kg/m^2 and categorised according to WHO criteria as <18.5 (underweight), 18.5 – 24.9 (normal weight), 25-29.9 (overweight) and ≥30 kg/m2 (obese)[4].	Last record before start of follow up
Comorbidities	A large list of comorbidities were extracted including those comprising Charleston comorbidity score[5], depression[6], and those related to corticosteroid morbidity[7]. Comorbidities with low prevalence (e.g. AIDs) were excluded and some categories were combined (e.g. mild/moderate liver disease was combined with severe liver disease to form a single category).	3 years before start of follow up
Ethnicity	Read codes were grouped in five categories: White, Asian (including Asian British), Black (including Black British), Chinese and Mixed[8].	Entire Medical Record
Smoking Status	Using Read Codes and categorised as Non-smoker, Current smoker, Ex-smoker.	Last record before start of follow up
Treatment Step	Asthma medications were identified using Read/SNOMED hierarchies, and patients were categorised according to GINA 2018 treatment step[9]. Combination therapies (e.g. ICS/LABA, ICS/LABA/LAMA) where broken into their constituent parts and ICS dose was converted to a BDP equivalent[10]. Step five was defined as more than 6 prescriptions of OCS in a year, spanning across at least two quarters[11].	1 year before start of follow up
Year of birth	Reported by the general practice for all patients	N/A



Supplement figure 1. Directed acyclic graph on asthma outcomes showing confounders considered in the multivariable analysis and potential mediating variables.



Supplement figure 2. Flow chart of the UK Severe Asthma Registry (UKSAR) and Optimum Patient Care Research Database (OPCRD) severe asthma patients included in the analysis



Supplement figure 3. Flow chart of Optimum Patient Care Research Database (OPCRD) mild/ moderate asthma patients included in the sensitivity analysis.

Supplement table 2. Multivariable analysis comparing males and females with severe asthma in the UK Severe Asthma Registry

Variable	N	Relative measure	Univariable		Multivariable	
			Ratio (95% CI)	P-value	Ratio (95% CI)	P-value
Lung function						
FEV_1 (% predicted)	3,359	Ratio	1.06 (1.04,1.08)	<0.0001	1.05 (1.03,1.07)	<0.0001
FVC (% predicted)	3,191	Ratio	0.99 (0.98,1.01)	0.361	0.99 (0.97,1.00)	0.119
Asthma control						
ACQ6	2,909	Ratio	1.16 (1.12,1.21)	<0.0001	1.14 (1.09,1.18)	<0.0001
Uncontrolled (ACQ6)	2,909	OR	1.90 (1.57,2.31)	<0.0001	1.80 (1.47,2.19)	<0.0001
Healthcare utilisation						
Exacerbations		RR	1.16 (1.12,1.19)	<0.0001	1.13 (1.10,1.17)	<0.0001
ED Attendance	3,445	OR	1.53 (1.31,1.78)	<0.0001	1.37 (1.17,1.60)	<0.0001
Hospital Admission	3,529	OR	1.58 (1.36,1.83)	<0.0001	1.46 (1.26,1.70)	<0.0001
Comorbidities						
Ex/ current smoker	3,601	OR	0.76 (0.65,0.87)	<0.0001	0.78 (0.67,0.90)	0.001
Atopic disease	3,573	OR	1.10 (0.95,1.26)	0.193	0.96 (0.83,1.11)	0.569
Depression or anxiety	3,679	OR	1.67 (1.28,2.17)	<0.0001	1.55 (1.18,2.02)	0.001
Obese	3,517	OR	1.68 (1.46,1.93)	<0.0001	1.67 (1.45,1.93)	<0.0001
Type-2 biomarkers						
Blood eosinophils	3,562	Ratio	0.96 (0.89,1.03)	0.213	0.94 (0.88,1.01)	0.081
FeNO	2,761	Ratio	0.81 (0.75,0.86)	<0.0001	0.79 (0.74,0.85)	<0.0001
IgE	3,453	Ratio	0.67 (0.59,0.76)	<0.0001	0.63 (0.56,0.72)	<0.0001
Medications						
Treatment adherent	3,444	OR	1.07 (0.87,1.32)	0.523	1.20 (0.97,1.49)	0.090
On maintenance OCS	3,657	OR	0.81 (0.70,0.93)	0.004	0.86 (0.75,0.99)	0.040
On biologic therapy	3,647	OR	1.02 (0.85,1.23)	0.795	1.07 (0.89,1.29)	0.451

ACQ6, Asthma Control Questionnaire-6; ED, emergency department; FeNO, Fractional exhaled nitric oxide; FEV_1 %, forced expiratory volume in 1 second percentage predicted; FVC %, forced vital capacity percentage predicted; IgE: Immunoglobulin E; OCS, oral corticosteroids; OR, odds Ratio; RR, Rate Ratio.

Supplement table 3. Multivariable regression comparing males and females with severe asthma in the Optimum Patient Care Research Database

Variable	N	Relative measure	Univariable Ratio (95% CI)	Univariable P-value	Multivariable Ratio (95% CI)	Multivariable P-value
Lung function						
Peak flow (% predicted)	12,362	Ratio	1.02 (1.00,1.03)	0.006	1.01 (1.00,1.03)	0.062
Asthma control						
Uncontrolled (RCP 3Q)	5,880	OR	1.22 (1.09,1.36)	0.001	1.29 (1.13,1.47)	<0.0001
Healthcare utilisation						
Exacerbations	18,369	RR	1.04 (0.99,1.09)	0.139	1.06 (1.00,1.12)	0.038
Asthma review	18,369	OR	1.03 (0.97,1.10)	0.303	1.07 (0.99,1.16)	0.096
Respiratory referral	18,369	OR	1.07 (0.94,1.21)	0.287	1.09 (0.94,1.27)	0.267
Comorbidities						
Ex/Current smoker	17,984	OR	0.73 (0.69,0.78)	<0.0001	0.71 (0.65,0.76)	<0.0001
Atopic disease	18,369	OR	1.00 (0.92,1.08)	0.971	1.04 (0.94,1.15)	0.425
Depression or anxiety	18,369	OR	2.00 (1.79,2.24)	<0.0001	1.88 (1.65,2.14)	<0.0001
Obese	15,433	OR	1.43 (1.33,1.53)	<0.0001	1.46 (1.34,1.58)	<0.0001
Type-2 biomarkers						
Blood eosinophils	9,195	Ratio	0.87 (0.84,0.90)	<0.0001	0.85 (0.82,0.89)	<0.0001
Medications						
Treatment adherent	17,909	OR	0.92 (0.86,0.99)	0.021	0.96 (0.88,1.04)	0.278

OR, odds Ratio; RR, Rate Ratio; RCP 3Q, Royal College of Physicians 3 Questions

Supplement table 4. Comparison of female and male patients with mild to moderate asthma in the Optimum Patient Care Research Database

Characteristic	Female (N = 30,946)	Male (N = 23,204)	P-value
Age (years)[a]	51.8 (17.2)	49.6 (16.5)	<0.001
<35	5,834 (18.9%)	4,956 (21.4%)	
35-54	11,939 (38.6%)	9,719 (41.9%)	
55-7	9,982 (32.3%)	6,776 (29.2%)	
75+	3,191 (10.3%)	1,753 (7.6%)	
Ethnicity[b]			0.173
White	19,986 (95.0%)	14,374 (94.7%)	
Mixed	72 (0.3%)	52 (0.3%)	
Asian	729 (3.5%)	594 (3.9%)	
Black	160 (0.8%)	100 (0.7%)	
Other	84 (0.4%)	65 (0.4%)	
Index of multiple deprivation (quintile) [b]			0.077
5 (Least deprived)	6,762 (22.0%)	5,310 (23.1%)	
4	6,503 (21.2%)	4,875 (21.2%)	
3	6,147 (20.0%)	4,552 (19.8%)	
2	7,296 (23.8%)	5,372 (23.3%)	
1 (Most deprived)	3,976 (13.0%)	2,923 (12.7%)	
Peak flow (% predicted)[c]	89.4 (77.7,100.3)	90.5 (78.0,102.4)	<0.001
Uncontrolled (RCP 3 questions) [b]	3,875 (36.2%)	2,535 (32.9%)	<0.001
Exacerbations[c]	0.0 (0.0,0.0)	0.0 (0.0,0.0)	<0.001
Any exacerbations[b]	4,668 (15.1%)	2,638 (11.4%)	<0.001
Prior exacerbations [b]			
0	30,946 (100.0%)	23,204 (100.0%)	
1	0 (0.0%)	0 (0.0%)	
2	0 (0.0%)	0 (0.0%)	
3	0 (0.0%)	0 (0.0%)	
4+	0 (0.0%)	0 (0.0%)	
ICS dose (BDP equivalent-ug)[c]	400 (400,500)	400 (400,500)	<0.001
Treatment step (GINA 2018) [b]			<0.001
2	18,701 (60.4%)	13,647 (58.8%)	
3	12,245 (39.6%)	9,557 (41.2%)	
Asthma review[b]	14,529 (46.9%)	10,179 (43.9%)	<0.001
Respiratory referral[b]	905 (2.9%)	656 (2.8%)	0.503
Medication possession ratio fixed (%)[c]	41.0 (20.1,73.0)	41.0 (21.9,73.8)	0.001

Treatment adherent (MPR ≥70%)[b]	7,728 (26.1%)	5,905 (26.6%)	0.192
Blood Eosinophil Count (10^9/L)[c]	0.20 (0.10,0.30)	0.21 (0.15,0.35)	<0.001
Highest blood eosinophil count (10^9/L) [b]			<0.001
<0.150	3,984 (33.8%)	1,472 (24.8%)	
0.150-0.300	5,168 (43.8%)	2,790 (47.0%)	
>0.300	2,650 (22.5%)	1,679 (28.3%)	
BMI (Kg/m^2) [a]	28.0 (6.3)	27.5 (4.9)	<0.001
Underweight (<18.5)	445 (1.7%)	257 (1.4%)	
Normal weight (18.5-24.9)	8,925 (35.1%)	5,485 (30.3%)	
Overweight (25-29.9)	7,948 (31.3%)	7,723 (42.7%)	
Obese (≥30)	8,112 (31.9%)	4,628 (25.6%)	
Smoking status[b]			<0.001
Never smoked	18,010 (61.0%)	11,785 (53.3%)	
Ex-smoker	7,373 (25.0%)	6,994 (31.6%)	
Current smoker	4,123 (14.0%)	3,327 (15.1%)	
Comorbidities[b]			
Atopic dermatitis	3,200 (10.3%)	2,116 (9.1%)	<0.001
Atopic disease	4,783 (15.5%)	3,145 (13.6%)	<0.001
Allergic rhinitis	3,146 (10.2%)	2,064 (8.9%)	<0.001
Cataract	454 (1.5%)	224 (1.0%)	<0.001
Depression/ anxiety	3,351 (10.8%)	1,301 (5.6%)	<0.001
Diabetes	1,854 (6.0%)	1,408 (6.1%)	0.71
Nasal polyps	168 (0.5%)	229 (1.0%)	<0.001
Osteoporosis	462 (1.5%)	53 (0.2%)	<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.

Supplement table 4: Multivariable regression comparing males and females with mild to moderate asthma in the Optimum Patient Care Research Database

Variable	N	Relative measure	Univariable Ratio (95% CI)	Univariable P-value	Multivariable Ratio (95% CI)	Multivariable P-value
Lung function						
Peak flow (% predicted)	30,053	Ratio	0.99 (0.98,0.99)	<0.0001	0.99 (0.98,0.99)	<0.0001
Asthma control						
Uncontrolled (RCP 3Q)	18,409	OR	1.16 (1.09,1.24)	<0.0001	1.13 (1.05,1.22)	0.001
Healthcare utilisation						
Exacerbations	54,150	RR	1.38 (1.31,1.46)	<0.0001	1.32 (1.25,1.41)	<0.0001
Asthma review	54,150	OR	1.13 (1.09,1.17)	<0.0001	1.10 (1.05,1.15)	<0.0001
Respiratory referral	54,150	OR	1.04 (0.94,1.15)	0.502	1.03 (0.91,1.17)	0.610
Comorbidities						
Ex/ current smoker	51,612	OR	0.73 (0.70,0.76)	<0.0001	0.72 (0.68,0.76)	<0.0001
Atopic disease	54,150	OR	1.17 (1.11,1.22)	<0.0001	1.19 (1.12,1.27)	<0.0001
Depression or anxiety	54,150	OR	2.04 (1.89,2.21)	<0.0001	2.12 (1.93,2.32)	<0.0001
Obese	43,523	OR	1.36 (1.31,1.42)	<0.0001	1.35 (1.29,1.43)	<0.0001
Type-2 biomarkers						
Blood eosinophils	17,743	Ratio	0.89 (0.87,0.91)	<0.0001	0.90 (0.87,0.92)	<0.0001
Medications						
Treatment adherent	51,782	OR	0.97 (0.93,1.02)	0.223	0.93 (0.89,0.98)	0.010

OR, odds Ratio; RR, Rate Ratio; RCP 3Q, Royal College of Physicians 3 Questions

Supplement figure 4. Mediation analysis of affect of body mass index, depression/ anxiety and smoking on sex differences in severe asthma in the UKSAR cohort

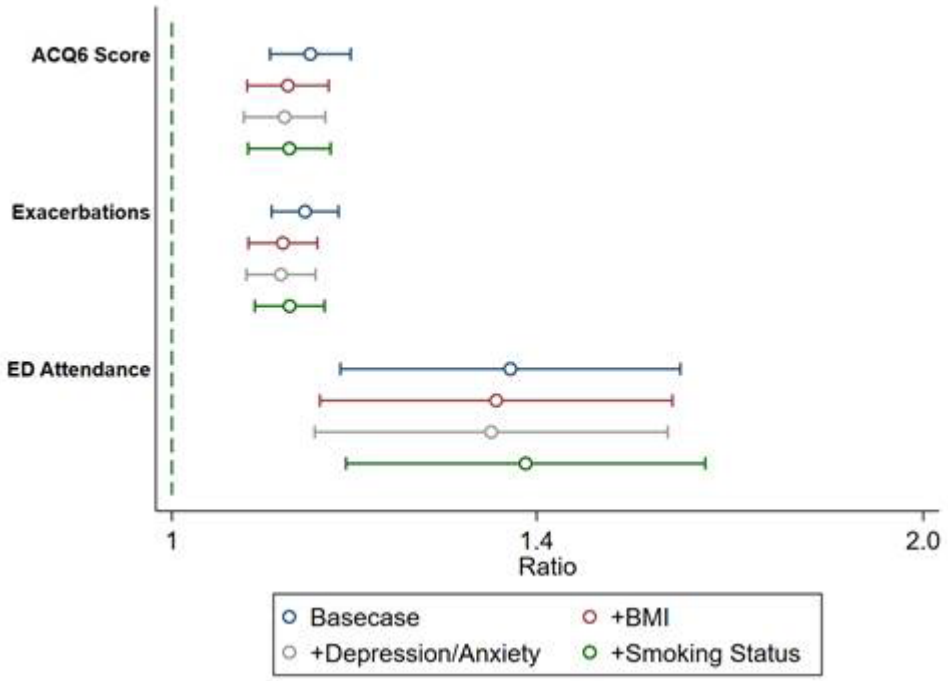


Figure legend

Supplement figure 4. Summary of mediation analysis results comparing males and females with severe asthma in the UK Severe Asthma Registry (UKSAR). Adjusting for body mass index, depression/anxiety and smoking status. ACQ6, Asthma Control Questionnaire-6; ED, emergency department; BMI, body mass index.

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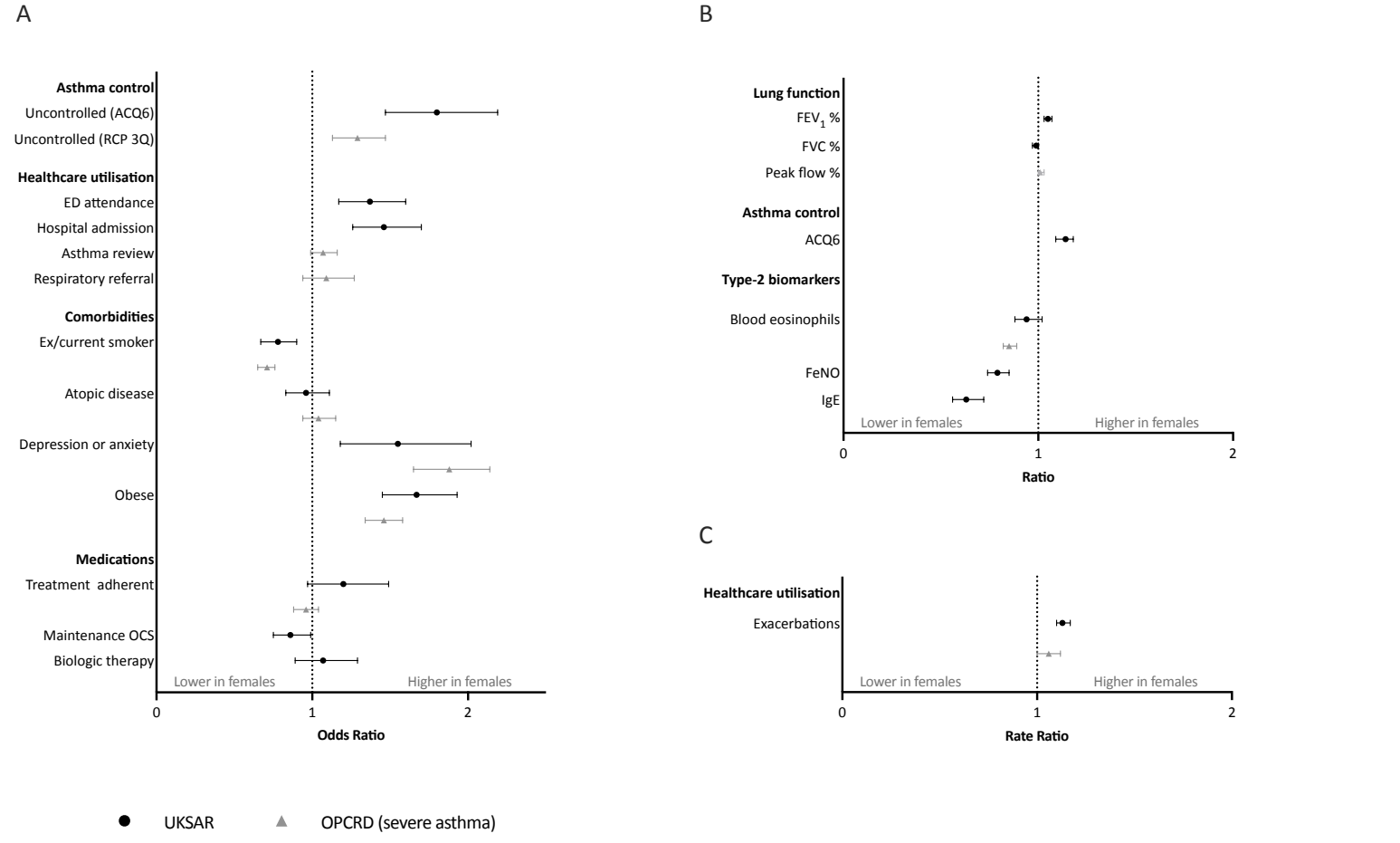
A
Asthma control
Uncontrolled (ACQ6)
Uncontrolled (RCP 3Q)
Healthcare utilisation
ED attendance
Hospital admission
Asthma review
Respiratory referral
Comorbidities
Ex/current smoker
Atopic disease
Depression or anxiety
Obese
Medications
Treatment adherent
Maintenance OCS
Biologic therapy
Lower in females
Higher in females
0
1
2
Odds Ratio
B
Lung function
FEV1 %
FVC %
Peak flow %
Asthma control
ACQ6
Type-2 biomarkers
Blood eosinophils
FeNO
IgE
Lower in females
Higher in females
0
1
2
Ratio
C
Healthcare utilisation
Exacerbations
Lower in females
Higher in females
0
1
2
Rate Ratio
UKSAR
OPCRD (severe asthma)