



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

Loewenthal, L., Busby, J., Mc Dowell, R., Brown, T., Burhan, H., Chaudhuri, R., Dennison, P., Dodd, J., Doe, S., Faruqi, S., Gore, R., Idris, E., Jackson, D., Patel, M., Pantin, T., Pavord, I. D., Pfeffer, P., Price, D., Rupani, H., ... Menzies-gow, A. (2023). The impact of sex on severe asthma: a cross-sectional retrospective analysis of UK primary and specialist care: a cross-sectional retrospective analysis of UK primary and specialist care. *Thorax*, 1-9. Article thorax-2023-220512. Advance online publication. <https://doi.org/10.1136/thorax-2023-220512>

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**Published in:**  
Thorax

**Publication Status:**  
Published online: 16/12/2023

**DOI:**  
[10.1136/thorax-2023-220512](https://doi.org/10.1136/thorax-2023-220512)

**Document Version**  
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## SUPPLEMENT

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

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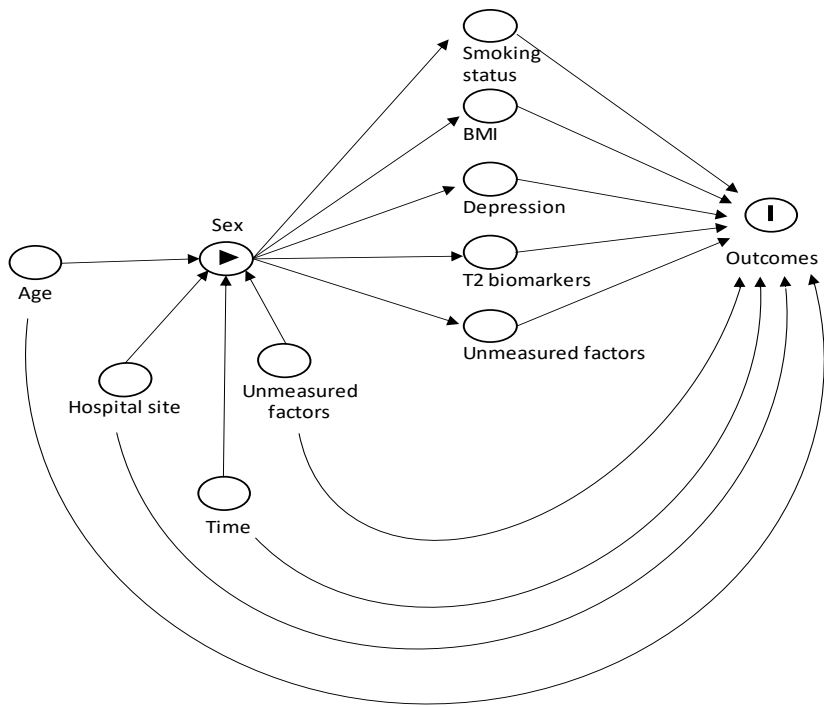
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**Supplement table 1. Definition of demographic and clinical outcomes in the OPCRD**

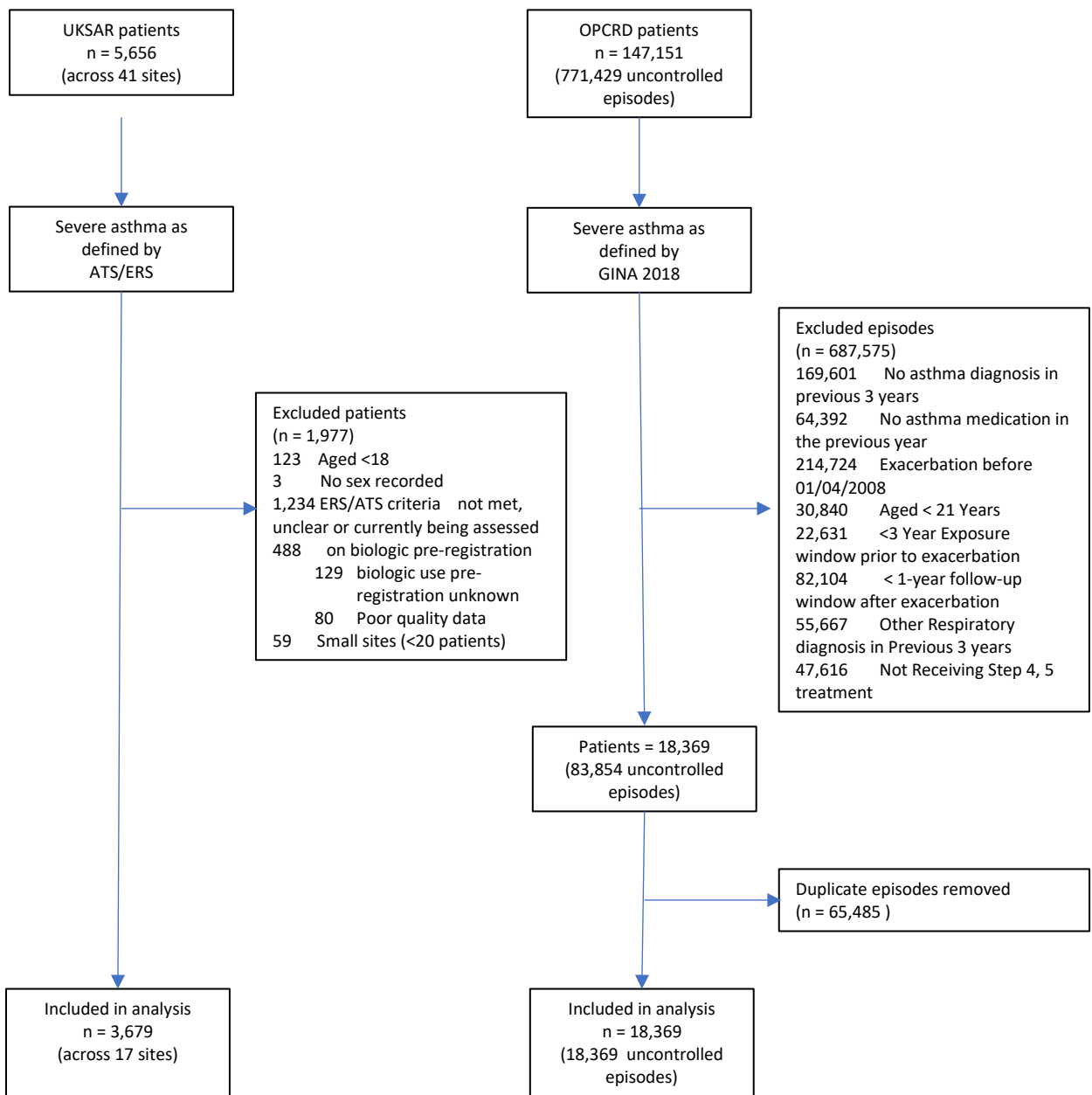
| Variable            | Description   | Ascertainment period           |
|---------------------|---|--------------------------------|
| Exposures           |   |                                |
| Sex                 | Reported by the general practice for all patients   | N/A                            |
| 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: Xaleq), Asthma follow-up (Xaler), Asthma monitoring by nurse (Xalu5), Asthma monitoring by doctor (Xalu6), Asthma medication review   | 1 year from start of follow up |

|                                |  |  |
|--------------------------------|--|--|
|                                | (XalfK) 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 <sup>1</sup> . 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 <sup>2</sup> . 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                               |

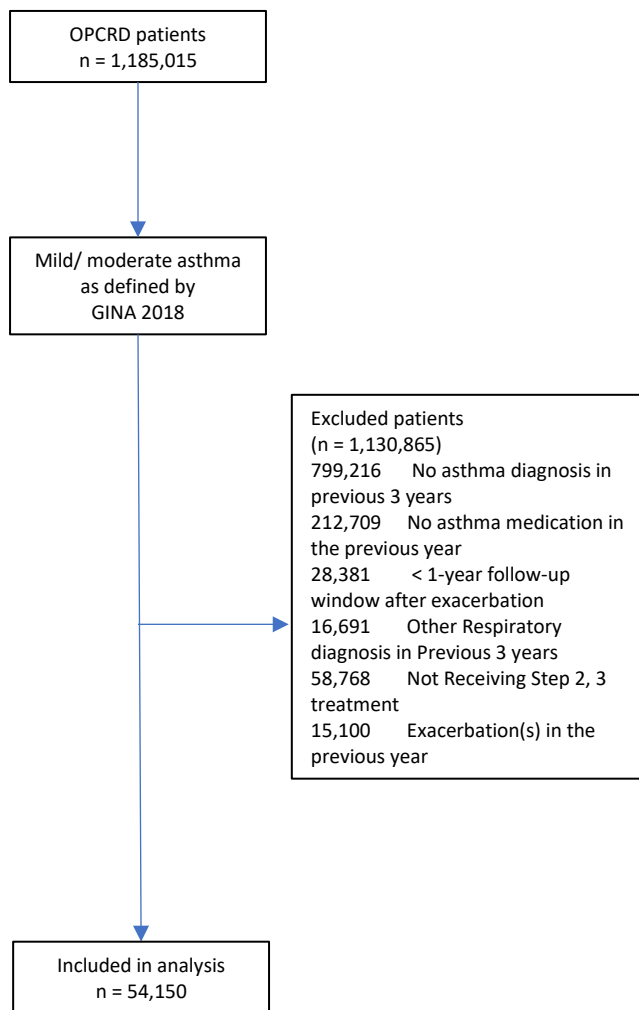
| Covariates      |  |   |
|-----------------|--|---|
| Atopic disease  | Record of hay fever or eczema <sup>3</sup> .   | Beginning of medical record to start of follow up |
| Body Mass Index | Using Read Codes and measured in kg/m <sup>2</sup> and categorised according to WHO criteria as <18.5 (underweight), 18.5 – 24.9 (normal weight), 25-29.9 (overweight) and ≥30 kg/m <sup>2</sup> (obese) <sup>4</sup> .  | Last record before start of follow up             |
| Comorbidities   | A large list of comorbidities were extracted including those comprising Charleston comorbidity score <sup>5</sup> , depression <sup>6</sup> , and those related to corticosteroid morbidity <sup>7</sup> . 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 <sup>8</sup> .  | 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 <sup>9</sup> . Combination therapies (e.g. ICS/LABA, ICS/LABA/LAMA) were broken into their constituent parts and ICS dose was converted to a BDP equivalent <sup>10</sup> . Step five was defined as more than 6 prescriptions of OCS in a year, spanning across at least two quarters <sup>11</sup> . | 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 |
| <b>Lung function</b>           |       |                  |                  |         |                  |         |
| FEV <sub>1</sub> (% 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   |
| <b>Asthma control</b>          |       |                  |                  |         |                  |         |
| 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 |
| <b>Healthcare utilisation</b>  |       |                  |                  |         |                  |         |
| 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 |
| <b>Comorbidities</b>           |       |                  |                  |         |                  |         |
| 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 |
| <b>Type-2 biomarkers</b>       |       |                  |                  |         |                  |         |
| 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 |
| <b>Medications</b>             |       |                  |                  |         |                  |         |
| 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<sub>1</sub> %, 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      |         | Multivariable    |         |
|-------------------------------|--------|------------------|------------------|---------|------------------|---------|
|                               |        |                  | Ratio (95% CI)   | P-value | Ratio (95% CI)   | P-value |
| <b>Lung function</b>          |        |                  |                  |         |                  |         |
| Peak flow (% predicted)       | 12,362 | Ratio            | 1.02 (1.00,1.03) | 0.006   | 1.01 (1.00,1.03) | 0.062   |
| <b>Asthma control</b>         |        |                  |                  |         |                  |         |
| Uncontrolled (RCP 3Q)         | 5,880  | OR               | 1.22 (1.09,1.36) | 0.001   | 1.29 (1.13,1.47) | <0.0001 |
| <b>Healthcare utilisation</b> |        |                  |                  |         |                  |         |
| 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   |
| <b>Comorbidities</b>          |        |                  |                  |         |                  |         |
| 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 |
| <b>Type-2 biomarkers</b>      |        |                  |                  |         |                  |         |
| Blood eosinophils             | 9,195  | Ratio            | 0.87 (0.84,0.90) | <0.0001 | 0.85 (0.82,0.89) | <0.0001 |
| <b>Medications</b>            |        |                  |                  |         |                  |         |
| 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<br>(N = 30,946) | Male<br>(N = 23,204) | P-value |
|---|------------------------|----------------------|---------|
| <b>Age (years)<sup>a</sup></b>                              | 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%)         |         |
| <b>Ethnicity<sup>b</sup></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%)            |         |
| <b>Index of multiple deprivation (quintile)<sup>b</sup></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%)        |         |
| <b>Peak flow (% predicted)<sup>c</sup></b>                  | 89.4 (77.7,100.3)      | 90.5 (78.0,102.4)    | <0.001  |
| <b>Uncontrolled (RCP 3 questions)<sup>b</sup></b>           | 3,875 (36.2%)          | 2,535 (32.9%)        | <0.001  |
| <b>Exacerbations<sup>c</sup></b>                            | 0.0 (0.0,0.0)          | 0.0 (0.0,0.0)        | <0.001  |
| <b>Any exacerbations<sup>b</sup></b>                        | 4,668 (15.1%)          | 2,638 (11.4%)        | <0.001  |
| <b>Prior exacerbations<sup>b</sup></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%)             |         |
| <b>ICS dose (BDP equivalent-ug)<sup>c</sup></b>             | 400 (400,500)          | 400 (400,500)        | <0.001  |
| <b>Treatment step (GINA 2018)<sup>b</sup></b>               |                        |                      | <0.001  |
| 2   | 18,701 (60.4%)         | 13,647 (58.8%)       |         |
| 3   | 12,245 (39.6%)         | 9,557 (41.2%)        |         |
| <b>Asthma review<sup>b</sup></b>                            | 14,529 (46.9%)         | 10,179 (43.9%)       | <0.001  |
| <b>Respiratory referral<sup>b</sup></b>                     | 905 (2.9%)             | 656 (2.8%)           | 0.503   |
| <b>Medication possession ratio fixed (%)<sup>c</sup></b>    | 41.0 (20.1,73.0)       | 41.0 (21.9,73.8)     | 0.001   |

|   |                  |                  |        |
|---|------------------|------------------|--------|
| <b>Treatment adherent (MPR <math>\geq</math>70%)<sup>b</sup></b>        | 7,728 (26.1%)    | 5,905 (26.6%)    | 0.192  |
| <b>Blood Eosinophil Count (<math>10^9/L</math>)<sup>c</sup></b>         | 0.20 (0.10,0.30) | 0.21 (0.15,0.35) | <0.001 |
| <b>Highest blood eosinophil count (<math>10^9/L</math>)<sup>b</sup></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%)    |        |
| <b>BMI (Kg/m<sup>2</sup>)<sup>a</sup></b>                               | 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 ( $\geq$ 30)  | 8,112 (31.9%)    | 4,628 (25.6%)    |        |
| <b>Smoking status<sup>b</sup></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%)    |        |
| <b>Comorbidities<sup>b</sup></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 |

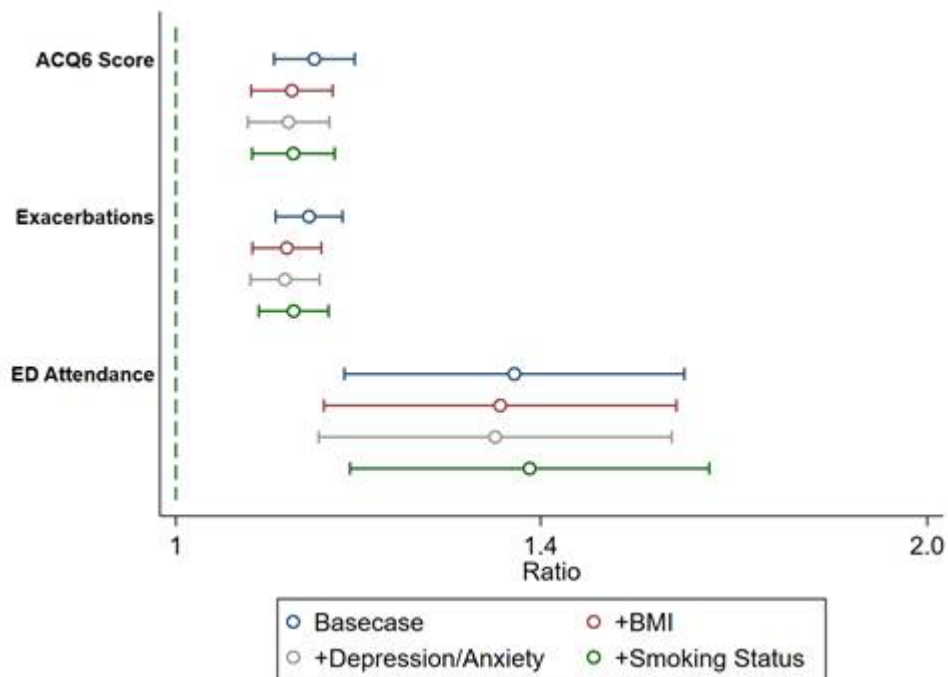
Data is calculated as mean (SD) using t-test (<sup>a</sup>), count (%) with chi-square (<sup>b</sup>) and median (IQR) with Man-Whitney U (<sup>c</sup>) statistical tests.

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

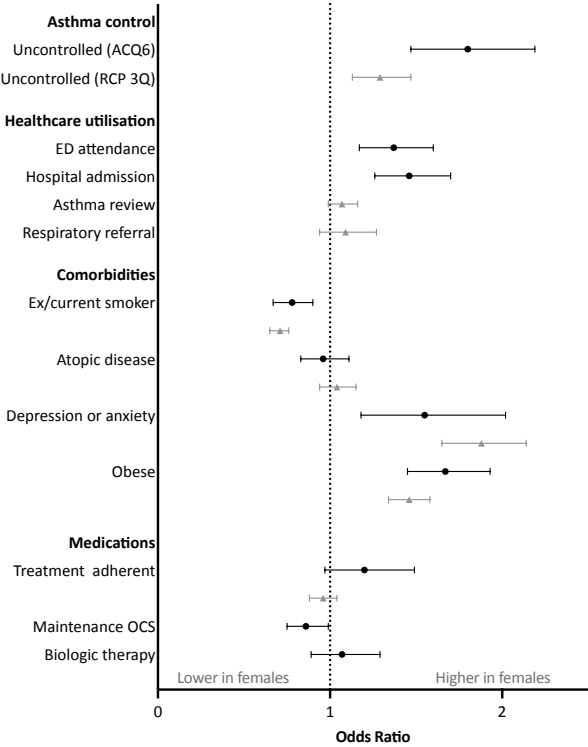
**Supplement figure 4.** Summary of mediation analysis results comparing males and females with severe asthma in the UK Severe Asthma Registry (UKSAR). Adjusting for body mass index, depression/anxiety and smoking status. ACQ6, Asthma Control Questionnaire-6; ED, emergency department; BMI, body mass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

### References

1. Knudson RJ, Lebowitz MD, Holberg CJ, et al. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;127(6):725-34.
2. Thomas M, Gruffydd-Jones K, Stonham C, et al. Assessing asthma control in routine clinical practice: use of the Royal College of Physicians '3 Questions'. *Primary Care Respiratory Journal* 2009;18(2):83-88.
3. Pape K, Schlünssen V, Lodge CJ, et al. Is self-reported history of eczema and hay fever a valid measure of atopy in those who report current asthma? *Allergy* 2020;75(11):2981-84.
4. World Health Organization (WHO). Obesity: preventing and managing the global epidemic: report of a WHO consultation 2000.
5. Khan NF, Perera R, Harper S, et al. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC Fam Pract* 2010;11(1):1-7.
6. Morgan C, Webb RT, Carr MJ, et al. Incidence, clinical management, and mortality risk following self harm among children and adolescents: cohort study in primary care. *BMJ* 2017;359

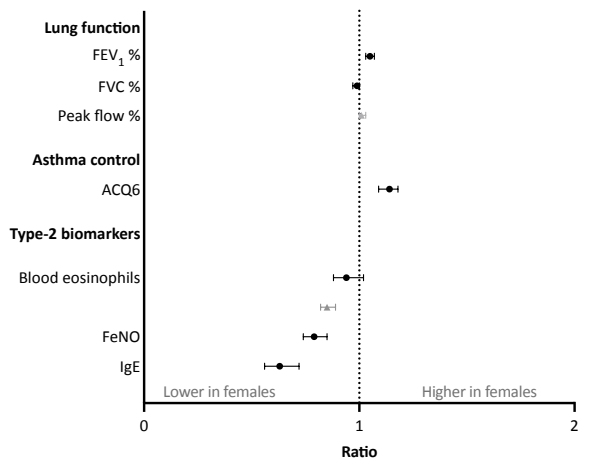
7. Sweeney J, Patterson CC, Menzies-Gow A, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax* 2016;71(4):339-46.
8. Busby J, Heaney LG, Brown T, et al. Ethnic differences in severe asthma clinical care and outcomes: an analysis of United Kingdom primary and specialist care. *The Journal of Allergy and Clinical Immunology: In Practice* 2022;10(2):495-505. e2.
9. Global Initiative for Asthma. Global strategy for asthma management and prevention: Global Initiative for Asthma; 2018 [Available from: <https://ginasthma.org/reports/>].
10. National Institute for Health Care Excellence (NICE). Inhaled corticosteroid doses for NICE's asthma guideline 2018.
11. Bloom CI, Nissen F, Douglas IJ, et al. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax* 2018;73(4):313-20.

A



● UKSAR    ▲ OPCRD (severe asthma)

B



C

