

1 **Title:** Ethnic differences in severe asthma clinical care and outcomes: an analysis of United Kingdom  
2 primary and specialist care

3

4 **Authorship:** Dr. John Busby<sup>1</sup>, Prof Liam Heaney<sup>1,2</sup>, Dr Thomas Brown<sup>3</sup>, Prof Rekha Chaudhuri<sup>4</sup>, Dr  
5 Paddy Dennison<sup>5</sup>, Dr Robin Gore<sup>6</sup>, Dr David J Jackson<sup>7,8</sup>, Prof Adel H Mansur<sup>9</sup>, Prof Andrew Menzies-  
6 Gow<sup>10</sup>, Dr Simon Message<sup>11</sup>, Dr Rob Niven<sup>12</sup>, Dr Mitesh Patel<sup>13</sup>, Prof David Price<sup>14,15</sup>, Prof Salman  
7 Siddiqui<sup>16</sup>, Dr. Robert Stone<sup>17</sup>, Dr Paul Pfeffer<sup>18</sup> on behalf of the UK Severe Asthma Registry

8

9 **Affiliations:**

10 <sup>1</sup> School of Medicine, Dentistry and Biomedical Sciences, Queen's University, Belfast, UK

11 <sup>2</sup> Belfast Health & Social Care NHS Trust, Belfast, UK

12 <sup>3</sup> Portsmouth Hospitals University NHS Trust, Portsmouth, UK

13 <sup>4</sup> Gartnavel General Hospital, Glasgow, UK.

14 <sup>5</sup> University Hospital Southampton NHS Foundation Trust, Southampton, UK

15 <sup>6</sup> Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

16 <sup>7</sup> Guy's Severe Asthma Centre, Guy's and St Thomas' Hospitals, London, United Kingdom

17 <sup>8</sup> Asthma UK Centre, King's College London, United Kingdom

18 <sup>9</sup> University of Birmingham and Heartlands Hospital, University Hospitals Birmingham, Birmingham,  
19 UK

20 <sup>10</sup> Royal Brompton and Harefield NHS Foundation Trust, London, UK

21 <sup>11</sup> Gloucester Royal Hospital, Gloucester, UK

22 <sup>12</sup> Wythenshawe Hospital, Manchester NHS Foundation Trust, Manchester, UK

23 <sup>13</sup> University Hospitals Plymouth NHS Trust, Plymouth, UK

24 <sup>14</sup> Observational and Pragmatic Research Institute, Singapore, Singapore

25 <sup>15</sup> Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen,  
26 Aberdeen, United Kingdom

27 <sup>16</sup> NIHR Leicester Biomedical Research Centre and College of Life Sciences, University of Leicester,  
28 Leicester, UK

29 <sup>17</sup> Somerset NHS Foundation Trust, Musgrove Park Hospital, Taunton, Somerset, UK

30 <sup>18</sup> Barts Health NHS Trust, London, UK

31

32 **Correspondence:** John Busby, Centre for Public Health, Queen's University Belfast, BT12 6BA.

33 +442890 976019, [john.busby@qub.ac.uk](mailto:john.busby@qub.ac.uk)

34

35 **Word Count; Abstract: 248, Manuscript: 3429**

36 **Abstract**

37 **Background:** Understanding the effects of ethnicity in severe asthma is important for optimal  
38 personalised patient care.

39

40 **Objective:** To assess ethnic differences in disease control, exacerbations, biological phenotype and  
41 treatment in UK severe asthma.

42

43 **Methods:** We compared demographics, type-2 biomarkers, lung function, asthma control,  
44 medications and healthcare utilisation between White and ethnic minority group [EMG] patients in  
45 the UK Severe Asthma Registry (UKSAR) and Optimum Patient Care Research Database (OPCRD).

46

47 **Results:** 3,637 patients (665 EMG) were included from UKSAR and 10,549 (577 EMG) from OPCRD.  
48 EMG patients had higher levels of uncontrolled disease when measured using the asthma control  
49 questionnaire in UKSAR (OR:1.47, 95%CI: 1.12-1.93) and the Royal College of Physicians 3 Questions  
50 in OPCRD (OR:1.82, 95%CI: 1.27-2.60). Although exacerbation rates were similar, EMG patients were  
51 more likely to have recently attended ED (OR:1.55, 95%CI: 1.26-1.92) or been hospitalised (OR:1.31,  
52 95% CI: 1.07-1.59) due to their asthma. Inflammatory biomarkers were consistently higher in EMG  
53 severe asthma including blood eosinophils in OPCRD (Ratio:1.12, 95%CI: 1.05-1.20) and in UKSAR  
54 blood eosinophils (Ratio:1.16, 95%CI: 1.06-1.27), FeNO (Ratio:1.14, 95%CI: 1.04-1.26) and IgE  
55 (Ratio:1.70, 95%CI: 1.47-1.97). EMG patients were more likely to be atopic in the UKSAR (OR:1.32;  
56 95%CI: 1.07-1.63) and OPCRD (OR:1.67; 95%CI: 1.26-2.21), and less likely to be using maintenance  
57 oral corticosteroids at referral (OR:0.75 [95%CI: 0.61-0.92]).

58

59 **Conclusions:** Severe asthma patients from EMGs presented with higher disease burden and were  
60 more likely to attend ED. They had a distinct phenotypic presentation, and differences in medicine  
61 utilisation, with higher levels of type-2 biomarkers.

62 **What is already known on this topic?**

63 In studies of mild-to-moderate asthma, poorer asthma outcomes have been reported among  
64 minority ethnic groups within Europe and the US. Mechanisms underlying this are debated however  
65 genetics, socioeconomic factors and health literacy have been proposed.

66

67 **What does this article add to our knowledge?**

68 Patients with severe asthma from minority ethnic groups had worse asthma control and higher rates  
69 of exacerbation requiring secondary healthcare utilisation. This may be driven by differential  
70 treatment patterns, medication adherence and unscheduled care use.

71

72 **How does this study impact current management guidelines?**

73 The distinct phenotypic presentation among EMG patients suggests ethnically tailored treatment  
74 strategies to address factors such as non-adherence and poor self-management may be appropriate.

75

76 **Keywords:** asthma, disparities, ethnicity

77

78 **Abbreviations:** ACQ : Asthma control questionnaire, BDP: Beclomethasone dipropionate, CI:  
79 Confidence Interval, ED: emergency department, EMG: Ethnic minority group, FeNO: Fractional  
80 exhaled nitric oxide, FEV1: Forced expiratory volume in the first second, FVC: forced vital capacity,  
81 GLI: Global Lung Initiative, ICS: Inhaled Corticosteroid, IgE: immunoglobulin E, IRR: Incidence Rate  
82 Ratio, MPR: medication possession ratio, OCS: oral corticosteroids, OPCR: Optimum Patient Care  
83 Research Database, OR: Odds Ratio, RCP 3Q: Royal College of Physicians 3 Questions, UKSAR: UK  
84 Severe Asthma Registry

85 **Introduction**

86 Substantial differences in severe asthma prevalence and disease characteristics have been reported  
87 worldwide, suggesting ethnicity may play an important role in the aetiology and severity of the  
88 disease.<sup>1</sup> In a recent international comparison, disparities were evident in lung function, blood  
89 eosinophil counts, comorbidities and medication usage across the US, Europe, South Korea and  
90 Australasia.<sup>2</sup> In the UK, South Asian and Black patients with asthma are at an increased risk of hospital  
91 admission when compared to White patients and large ethnic disparities have been reported in the  
92 rates of hospital readmission.<sup>3</sup> Evidence from the US similarly suggests higher mortality, rates of  
93 asthma exacerbation and hospitalisations among African-Americans.<sup>4, 5</sup> However, there is limited  
94 evidence exploring differences by ethnicity in those with severe asthma, despite these patients  
95 suffering poor healthcare-related quality of life and driving much of the healthcare cost of asthma.<sup>6</sup>

96

97 There are several mechanisms that could drive differences in asthma presentation. Evidence of ethnic  
98 differences in the biologic predictors in severe asthma from the US and an association between  
99 exacerbation frequency and African genetic ancestry support a genetic contribution.<sup>7, 8</sup> However,  
100 disentangling genetic effects from environmental factors amongst often more disadvantaged Black  
101 and Minority Ethnic populations remains difficult<sup>9</sup> and others have reported that substantial racial  
102 disparities in healthcare utilisation rates are largely or completely mediated by socioeconomic and  
103 environmental exposure variables such as income and housing conditions<sup>5, 10-12</sup> Cultural differences  
104 and disparities in asthma medication adherence and health literacy have also been identified.<sup>13</sup>  
105 Differences globally in environment, resources and healthcare system organisation may also underpin  
106 disparities and can confound inter-country comparisons. Leveraging the multi-ethnic makeup of the  
107 UK population facilitates a comparison within one country, which is less affected by largely  
108 unmodifiable healthcare organisation and environmental factors.

109

110 In this study we report differences in severe asthma presentation and treatment by ethnicity across  
111 two independent cohorts spanning UK primary and specialist care. By analysing phenotypic  
112 characteristics and healthcare utilisation we specifically aim to address possible mechanisms  
113 underlying these differences, necessary to help design interventions to narrow disparities and improve  
114 care for all patients. In particular we investigate disparities in type-2 biomarkers that have previously  
115 been prospectively linked with severe asthma outcomes.<sup>14, 15</sup>

116 **Methods**

117 **Study Population**

118 The UK Severe Asthma Registry (UKSAR) is a national database containing demographic, clinical and  
119 treatment characteristics on patients referred to specialist UK Severe Asthma centres with  
120 uncontrolled asthma.<sup>16</sup> All patients in the UKSAR have ethnicity recorded according to Global Lung  
121 Initiative (GLI) criteria although to increase our statistical power we made comparisons between  
122 White (Caucasian) and ethnic minority group (EMG: South East Asian, North East Asian, African, Mixed  
123 and Other) patients. As a primary aim of our study was to compare ethnic variation in presentation  
124 and treatment, we assessed eligibility for biologic monoclonal antibody therapies by ethnicity using  
125 the current NICE guidance from the UK (see Supplementary Methods).

126

127 The Optimum Patient Care Research Database (OPCRD) is a nationally-representative pseudonymised  
128 dataset of 9.7 million patients registered at 700 general practices within the UK (8% of the UK  
129 population).<sup>17</sup> It contains information on patient demographics, clinical diagnoses, medication  
130 prescriptions and referrals coded through the Read and SNOMED classification systems. Ethnicity is  
131 recorded in primary care records using UK census definitions, which were grouped as shown in Table  
132 E1 and categorised as White or EMG. From the OPCRD dataset we selected those patients with severe  
133 asthma to provide a comparison cohort to the UKSAR. Severe asthma was defined according to GINA  
134 2019 criteria as those who remained uncontrolled ( $\geq 2$  exacerbations within a year) on step 4  
135 treatment or who require maintenance oral corticosteroids (OCS) to achieve control.<sup>18</sup> Full details on  
136 the study population are provided in the Supplementary Methods.

137

138 **Exposures, Outcomes and Covariates**

139 The primary outcomes of interest were type-2 biomarkers (blood eosinophils, fractional exhaled nitric  
140 oxide [FeNO] and immunoglobulin E [IgE]), lung function (forced expiratory volume in the first second  
141 [FEV<sub>1</sub>], forced vital capacity [FVC] and peak flow), asthma control (measured by the asthma control  
142 questionnaire [ACQ] and Royal College of Physicians 3 Questions [RCP 3Q]), asthma phenotype  
143 (atopy), asthma medications (treatment adherence, maintenance oral corticosteroid [OCS] use,  
144 biologic therapy use) and healthcare utilisation (exacerbations, emergency department [ED]  
145 attendance, hospital admission, asthma review and respiratory referral). Full details of the variables  
146 used in the analysis, including the time-period in which they were assessed, are provided in Table E2.

147

148 **Statistical Analysis**

149 As this study was hypothesis generating we did not conduct a formal sample size calculation, and  
150 instead used all available data from the UKSAR and OPCR. We calculated descriptive statistics and  
151 compared the demographic and clinical characteristics of White and EMG patients. Multivariate  
152 analyses were conducted accounting for year, age (5-year categories) and gender. We choose this  
153 limited set of adjustment variables to prevent any overadjustment bias, whereby adjustment is made  
154 for variables which lie on the causal path between ethnicity and outcomes, to ensure that we captured  
155 the full magnitude of any ethnic disparities.<sup>19</sup> We conducted several supplementary analysis including  
156 additionally adjusting for deprivation, lifestyle factors (e.g. smoking status) and asthma treatment (e.g.  
157 oral corticosteroids). We reran our UKSAR analysis stratified by hospital site and repeated our OPCR  
158 analysis restricting to patients meeting the uncontrolled severe asthma definition after 1<sup>st</sup> January  
159 2014 (consistent with UKSAR time period). We conducted a further nested case-control study within  
160 the OPCR to assess the independent effect of ethnicity on respiratory referral and investigated the  
161 impact of missing data using multiple imputation with chained equations. Full details of the statistical  
162 methods and supplementary analysis are provided in the Supplementary Methods.

163 **Results**

164 **Cohort Demographics**

165 The UKSAR analysis contained 3,402 patients (638 [18.8%] from EMGs) from 18 specialist secondary-  
166 care clinical centres (Table 1), whilst the OPCR analysis contained 13,936 patients (680 [4.9%] from  
167 EMGs) within primary care (Table 2). Patient demographics were similar between UKSAR and OPCR  
168 in terms of mean age (50.0 years vs. 55.8 years) and female predominance (63.6% vs. 67.9%) although  
169 it is notable that the UKSAR patients were receiving greater doses of ICS (median: 2000 vs. 1000 BDP),  
170 and had higher rates of uncontrolled disease (81.7% vs. 51.3%) and exacerbations (median: 4 vs. 1)  
171 when compared to the OPCR. A smaller proportion of patients from the OPCR (5%) were from  
172 EMGs than in the UKSAR (19%), likely reflecting the location of the UKSAR severe asthma centres in  
173 multi-ethnic regions at the time of the analysis.

174  
175 Patients from EMGs were more likely to reside in an area of lower socioeconomic status (OPCR:  
176 lowest decile: 11.9% vs. 6.4%;  $p < 0.001$ ) and to be never smokers (UKSAR: 77.4% vs. 64.1%,  $p < 0.001$ ;  
177 OPCR: 78.3% vs. 49.1%,  $p < 0.001$ ). Patients from EMGs had a higher prevalence of atopic co-  
178 morbidities: allergic rhinitis (OPCR: 19.3% vs. 10.8%;  $p < 0.001$ ), and eczema (OPCR: 17.4% vs. 12.8%;  
179  $p < 0.001$ ); and corticosteroid related co-morbidities: cataracts (OPCR: 4.4% vs. 2.3%;  $p = 0.005$ ),  
180 diabetes (OPCR: 18.7% vs. 9.3%;  $p < 0.001$ ) when compared to White patients. There was little  
181 difference in the prevalence of other comorbidities such as cerebrovascular disease, glaucoma,  
182 insomnia and renal disease.

183

184 **Asthma Outcomes and Corticosteroid Treatment**

185 In univariate analyses, there were substantial and consistent differences between EMG and White  
186 patients in asthma outcomes including worse asthma control, poorer lung function and increased  
187 rates of asthma ED attendance and hospitalisation (Table 1, Table 2). These differences remained in  
188 multivariate analyses adjusted for basic demographic factors (Figure 1, Table E4, Table E5) with a  
189 higher proportion of EMG patients having uncontrolled asthma when measured using both Asthma  
190 Control Questionnaire-6 (ACQ6) in UKSAR (OR: 1.47; 95% CI: 1.12, 1.93) and Royal College of Physicians  
191 3 Questions in OPCR (OR: 1.82; 95% CI: 1.27, 2.60). Model predictions suggest 63% of 50 year old  
192 EMG patients were symptomatically uncontrolled in the OPCR compared to 48% of White patients  
193 (Difference: 15%; 95% CI: 6, 23) after adjustment for demographics factors.

194

195 Exacerbation rates were similar between White and EMG patients in UKSAR (IRR: 1.00, 95% CI: 0.96,  
196 1.04) and OPCR (IRR: 0.86, 95% CI: 0.65, 1.14) after adjustment. However, EMG patients were much



197 more likely to report an ED attendance in the previous year (OR: 1.64; 95% CI: 1.33, 2.01), a finding  
198 that was consistent across the five individual UKSAR centres analysed with a sufficient number of EMG  
199 patients (Figure E1), and to report a hospital admission for asthma in the previous year (OR: 1.27; 95%  
200 CI: 1.05, 1.54). There was no evidence of fewer annual asthma reviews (OR: 1.04; 95% CI: 0.71, 1.53)  
201 or respiratory referrals (OR: 1.67; 95% CI: 0.93, 3.00) among EMG patients in the OPCRCD cohort.

202  
203 Percent predicted FEV<sub>1</sub> was 7% lower (Ratio: 0.93, 95% CI: 0.90, 0.96) in EMG UKSAR patients  
204 compared to White patients, while in the OPCRCD PEFr measurements were 12% lower (Ratio: 0.88,  
205 95% CI: 0.85, 0.91). Reduced lung function among EMG patients was largely consistent across  
206 individual UKSAR sites studied (Figure E1). The estimated peak flow for a 50 year old EMG patient was  
207 71% predicted compared to 81% for a White patient after accounting for demographic differences  
208 (Difference: 10%, 95% CI: 7, 12; Figure 2).

209  
210 Median ICS dose was similar across White and EMG groups (UKSAR: 2000 vs. 2000µg BDP equivalent,  
211 p=0.162; OPCRCD: 1000 vs. 1000µg BDP equivalent, p=0.282). EMG patients were less likely be receiving  
212 mOCS at referral to specialist care in UKSAR (OR: 0.75, 95% CI: 0.61, 0.92) and to be considered  
213 adherent with their maintenance medications after specialist assessment (OR: 0.65, 95% CI: 0.48,  
214 0.87). There was also evidence of lower maintenance medication adherence in UKSAR when using the  
215 medicine possession ratio (OR:0.73; 95%: 0.60, 0.88), and a similar trend when using general  
216 practitioner clinical impression (OR: 0.44; 95% CI: 0.16, 1.18). Model predictions suggested that 42%  
217 of 50 year old EMG patients were receiving mOCS at specialist referral compared to 49% of White  
218 patients (Difference: 7%; 95% CI: 2, 12; Figure 2).

219

## 220 **Biological Phenotypes and Treatment**

221 In univariate analyses, there were consistent differences between EMG and White patients in the  
222 biological phenotypes of severe asthma patients with higher rates of atopy and elevated type-2  
223 biomarkers in EMG patients (Table 1, Table 2) that persisted when adjusting for demographic factors  
224 (Figure 1, Table E4, Table E5). EMG patients had higher rates of atopy in both the UKSAR (OR: 1.32;  
225 95% CI: 1.07, 1.63) and OPCRCD (OR: 1.67; 95% CI: 1.26, 2.21). Whilst the proportion of patients with  
226 atopic sensitisation to a perennial aeroallergen was similar between White and EMG patients in the  
227 UKSAR (54.8% vs. 53.7%, p=0.679), the patterns of aeroallergen sensitisation were distinct. A  
228 significantly greater proportion of the perennial aeroallergen sensitised EMG patients had  
229 sensitisation to house-dust mite allergen (75.9% vs 67.0%, p=0.004) and lower proportion sensitised  
230 to dog allergen (28.5% vs. 38.6%, p=0.002).

231

232 Blood eosinophils were 16% (Ratio: 1.16, 95% CI: 1.06, 1.27) higher among EMG patients in the UKSAR  
233 and 12% (Ratio: 1.12, 95% CI: 1.05, 1.20) higher in the OPCR. IgE levels were 70% (Ratio: 1.70, 95%  
234 CI: 1.47, 1.97) and FeNO 14% (Ratio: 1.14, 95% CI: 1.04, 1.26) higher among EMG than White patients  
235 in the UKSAR. These findings were replicated across each of the five UKSAR centres investigated  
236 (Figure E1). Ethnic disparities in blood eosinophil counts in the UKSAR were unchanged when  
237 additionally adjusting for lifestyle factors including smoking history (OR: 1.15, 95% CI: 1.04, 1.26)  
238 although there was partial attenuation when additionally adjusting for asthma treatment (OR: 1.10,  
239 95% CI: 0.99, 1.22; Figure E2). A similar pattern of attenuation was seen for FeNO, although substantial  
240 differences remained for total IgE levels even when accounting for lifestyle factors or asthma  
241 treatment.

242

243 A slightly larger proportion of EMG patients were eligible for anti-IL5(R) therapies (50.8% vs. 46.0%,  
244  $p=0.032$ ) although a similar proportion were eligible for anti-IgE therapy therapies (32.9% vs. 30.7%,  
245  $p=0.328$ ) or both medications (14.8% vs. 13.1%,  $p=0.282$ ; Table 1). However, there was no evidence  
246 of any difference in the proportion of patients progressing to biologic therapy (OR: 0.96, 95% CI: 0.76,  
247 1.23) with the majority of both groups prescribed Anti-IL5(R) medications (78.7% vs. 79.7%,  $p=0.445$ ).

248

#### 249 **Supplementary Analysis**

250 Our findings were broadly unchanged when adjusting for socioeconomic deprivation in OPCR as  
251 measured by Index of Multiple Deprivation, or when using multiple imputation to account for missing  
252 data (Table E4, Table E5). Similarly, our findings were consistent when restricting the OPCR analysis  
253 to patients with uncontrolled severe asthma after 1st January 2014, albeit differences did not always  
254 reach statistical significance due to a smaller sample size (Table E8). Our conclusions were broadly  
255 consistent for individual ethnicities in both the UKSAR (Table E9) and OPCR (Table E10), although  
256 these results were often difficult to interpret due a small number of patients in each group. Of note,  
257 our findings of higher rates of uncontrolled disease and poorer treatment adherence were largely  
258 consistent across individual ethnicities when compared to White patients. There was some evidence  
259 from the UKSAR of higher exacerbation rates for Asian (RR: 1.51, 95% CI: 1.13, 2.03) and Black (RR:  
260 2.38, 95% CI: 1.53, 3.70) patients than those with Mixed ethnicity (RR: 1.02, 95% CI: 0.47, 2.23).

261

262 We identified 1,426 unique respiratory referrals in the OPCR dataset which were matched to 6,541  
263 controls (Table E6). Consistent with expectations from asthma guidelines, patients who received a  
264 respiratory referral were more likely to have had an exacerbation in the previous year (55.5% vs 30.1%;

265 p<0.001), have uncontrolled disease (66.6% vs. 39.4%; p<0.001) and had a lower peak flow (80.4% vs.  
266 87.9% predicted; p<0.001). There were a higher proportion of EMG patients in the referred group  
267 (7.7% vs. 5.5%; p=0.008), however, this was substantially attenuated after adjustment for differences  
268 in comorbidities, lung function, asthma control and prior healthcare utilisation (OR: 0.66; 95% CI: 0.36,  
269 1.20; Table E7).

270 **Discussion**

271 In an analysis of two independent cohorts spanning UK primary and specialist care, we found that  
272 severe asthma patients from ethnic minority groups had a higher disease burden with poorer lung  
273 function and worse asthma control than White patients. These differences persisted after adjustment  
274 for deprivation in the OPCR. There were consistent differences in asthma phenotypes, but no  
275 evidence that ethnicity affected referral patterns to secondary care. EMG patients were less likely to  
276 have smoked and more likely to report atopic disease, with distinct patterns of aeroallergen  
277 sensitisation. EMG patients had higher blood eosinophils and FeNO, even after adjustment for lifestyle  
278 factors (including smoking) and asthma treatment and were more likely to attend ED or be admitted  
279 to hospital for their asthma.

280

281 Poorer outcomes for severe asthma in EMG patients is consistent with previous research that has  
282 reported wide ethnic differences in asthma morbidity within the UK and elsewhere.<sup>4, 5, 20, 21</sup> Similarly  
283 poorer control has been noted among EMG patients in diabetes and cardiovascular disease within the  
284 UK<sup>22, 23</sup>, whilst worse outcomes have been reported across several disease areas<sup>24-26</sup>. The higher  
285 biomarkers of type-2 inflammation exhibited by EMG patients is concerning and reflects the increased  
286 asthma morbidity seen in these patients<sup>14, 15</sup>. Other studies have reported ethnic variation in blood  
287 eosinophils, FeNO and IgE in healthy adults and a milder asthma population.<sup>27-30</sup> Previous studies in  
288 asthma and other disease areas have found minority ethnicity to be associated with lower adherence  
289 to maintenance medications<sup>31-33</sup>. Whilst prescription charges are an important barrier to adherence,  
290 lower adherence as measured by MPR persisted after adjustment for deprivation. Lower adherence  
291 in patients of minority ethnicity may relate to treatments and how information on them are framed  
292 by healthcare providers to account for their cultural healthcare beliefs.<sup>34</sup> Given the evidence of distinct  
293 drivers of adherence by ethnicity, tailored and culturally-acceptable interventions are likely to be  
294 required to reduce disparities.<sup>35</sup>

295 Why EMG patients are less likely to be taking mOCS is also a pertinent question. It is notable that  
296 despite lower rates of mOCS, EMG patients had a higher prevalence of diabetes mellitus. In this  
297 context the lower rates of mOCS prescription may partly reflect a reasoned decision to avoid OCS side-  
298 effects in more susceptible EMG patients. Minority ethnicity is a known risk factor for diabetes,  
299 including medication induced diabetes.<sup>36</sup>

300 Factors such as education, household overcrowding and health literacy have been previously found to  
301 contribute to ethnic variation in several US studies.<sup>5, 10-12</sup> Socioeconomic and cultural mediating

302 factors are not directly coded in clinical records and so we were unable to explore this further in our  
303 dataset, or investigate how country of birth, English language proficiency or cultural healthcare beliefs  
304 influenced observed differences in this study. We have demonstrated a similar level of asthma reviews  
305 and referral patterns among EMG and White patients. However it remains unclear if ethnicity  
306 influences the benefit patients receive from standardised asthma education and self-management  
307 advice, and whether the quality of this advice varies.<sup>37, 38</sup> An inability to easily quantify and code in  
308 routine clinical records how well patients understand their disease, and quality of self-management,  
309 is a key barrier to further exploring this issue. Higher levels of allergic sensitisation among EMG have  
310 been described elsewhere and, again, could be related to environmental factors including early-life  
311 environmental factors and aeroallergen exposure.<sup>39-41</sup> Additionally we cannot rule out a genetic basis  
312 to our findings, and how ethnicity influences the impact of genes on asthma morbidity is largely  
313 unknown.<sup>9</sup>

314 The distinct phenotypic presentation among EMG patients might suggest different treatment  
315 strategies are appropriate. In our study the proportion of patients co-eligible for anti-IgE and anti-  
316 IL5(R) was not affected by ethnicity, nor progression to biologic therapy, however, insufficient follow-  
317 up data is available to investigate whether ethnicity may affect response to biologic therapy. We did  
318 find differences in specific aero-allergen sensitisation and whether different aeroallergens vary in their  
319 capacity to drive airways inflammation is an important question.<sup>42</sup> Potentially response to  
320 Omalizumab may be affected by which perennial aeroallergen a patient is sensitized to<sup>43</sup> and such  
321 considerations need further study. Pharmacogenetic differences in bronchodilator medication  
322 response by ethnicity has also been reported in asthma<sup>44</sup>. We are unaware of any evidence suggesting  
323 disparities in biologic therapy efficacy by ethnicity in other disease areas, although variation in adverse  
324 events incidence has been reported in breast cancer<sup>45</sup>.

325 The major strength of our study lies in the combination of two distinct cohorts spanning both primary  
326 and specialist care. UKSAR provides detailed information on biomarkers, asthma history, lung function  
327 and medications accurately measured within specialist centres. This is complemented by the OPCRD,  
328 which details consultations, comorbidities and asthma details in an asthma population of broader  
329 severity that is not subject to potential referral biases. Importantly our findings were broadly  
330 consistent across both cohorts and across the individual sites contributing to the UKSAR, which  
331 improves the robustness of our findings. Our study is novel, exploring ethnic differences in severe  
332 asthma and builds upon previous studies exploring disparities in those with mild-to-moderate disease.  
333 Furthermore, our exploration of differences in biomarkers adds new insight into the mechanisms

334 driving differences in outcomes in severe asthma. Our study has several potential weaknesses. It is  
335 observational and hence open to confounding due to unmeasured or poorly measured factors. With  
336 respect to lung function measurement in OPCRD, there are no ethnicity-adjusted peak flow reference  
337 values that can be appropriately applied to the UK population. However, we were able to adjust for  
338 height, which will mediate some of the ethnicity effect and evidence from a small UK-based study  
339 suggests relatively minor and inconsistent ethnic variation in PEFV<sup>46</sup>. Recent debate has  
340 fundamentally questioned the use of race correction in clinical algorithms and the role this plays in  
341 entrenching inequality.<sup>47</sup> Some sites prioritise enrolment of biologic patients to the UKSAR which may  
342 lead to a predominance of those with type-2 inflammation. However, we do not believe this will  
343 materially bias our conclusions as registry enrolment is unlikely to be related to patient ethnicity.  
344 Finally, there were a relatively low number of patients from ethnic minority groups in both the UKSAR  
345 and OPCRD cohorts, which hindered our ability to make robust comparisons of outcomes between  
346 specific ethnicities.

347

348 In conclusion, patients from ethnic minority groups had higher disease burden in both primary and  
349 specialist care. They had a distinct phenotypic presentation, with higher rates of atopy, worse asthma  
350 control and being more likely to attend ED. They were less likely to be taking maintenance oral  
351 corticosteroids but differences in type-2 biomarkers persisted after accounting for this. The reason for  
352 these disparities remains unclear and could have genetic, environmental or societal roots. Further  
353 epidemiological studies of high-quality linked datasets, with robust measures of medication  
354 adherence, are required to better understand the drivers of these differences and help design  
355 interventions to standardise care and outcomes. Although there was no effect of ethnicity on  
356 progression to biologic therapy, the impact of ethnicity on treatment response is an important  
357 question for future research.

358 **Declarations**

359 **Collaborators:** Dr Paul Dilworth, Dr Martin Doherty, Dr Deepak Subramanian, Dr Aashish Vyas

360

361 **Contributors:** JB performed statistical analyses, interpreted the data, and wrote the initial draft of the  
362 manuscript. LH curated the data for the study, supervised the research, interpreted the data and  
363 critically revised the manuscript. TB, RC, PD, RG, DJJ, AHM, AMG, SM, RN, MP, DP, SS and RS curated  
364 the data for the study, interpreted the data and critically revised the manuscript. PEP conceptualised  
365 the research question, curated the data for the study, supervised the research, interpreted the data  
366 and critically revised the manuscript. JB is guarantor of the study, accepts full responsibility for the  
367 research, had access to the data, and controlled the decision to publish. The corresponding author  
368 attests that all listed authors meet authorship criteria and that no others meeting the criteria have  
369 been omitted.

370

371 **Competing interests:** All authors have completed the ICMJE uniform disclosure form at  
372 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare to following: **JB, SM** and **MP** declare no competing  
373 interests. **LGH** is Academic Lead for the Medical Research Council Stratified Medicine UK  
374 Consortium in Severe Asthma which involves industrial partnerships with a number of pharmaceutical  
375 companies. **TB** reports grants from Asthma UK & Innovate UK, grants, personal fees and non-financial  
376 support from Astra Zeneca, grants, personal fees and non-financial support from Glaxo Smith Klein,  
377 personal fees and non-financial support from Teva, non-financial support from Napp Pharmaceuticals,  
378 personal fees and non-financial support from Novartis, outside the submitted work. **RG** declares  
379 speaking fees in past 12 months for Astra Zeneca and GSK. Speaking fees in past 24 months for  
380 Novartis UK. **RC** reports grants, personal fees and non-financial support from AstraZeneca, personal  
381 fees from GSK, personal fees and non-financial support from Teva, personal fees from Novartis,  
382 personal fees and non-financial support from Chiesi, non-financial support from Napp  
383 Pharmaceuticals, outside the submitted work. **PD** reports, personal fees for lecturing and non-financial  
384 support from Astra Zeneca, Glaxo Smith Klein, and Teva, consultancy fees from Teva and AstraZeneca,  
385 and grants from Novartis, Glaxo Smith Kline and Astrazeneca, all outside of/unrelated to the submitted  
386 work. **RG** reports personal fees from GSK UK, personal fees from Astra Zeneca UK, personal fees from  
387 Novartis UK, outside the submitted work. **DJJ** has received advisory board and speaker fees from  
388 AstraZeneca plc, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline plc, Napp  
389 Pharmaceuticals Limited, Novartis International. **AHM** received personal and department funds for  
390 talks and advisory board meetings and was sponsored to attend national and international  
391 conferences from pharmaceutical companies that include GlaxoSmithKline, Astra Zeneca, Novartis,  
392 NAPP, Boehringer Ingelheim, Roche, Chiesi. **AMG** has consultancy agreements with Astra Zeneca,  
393 Vectura and Sanofi, he is participating in research funded by Astra Zeneca, he has received lecture  
394 fees from Teva, Astra Zeneca, Novartis and Sanofi attended advisory boards for Novartis, Sanofi, Glaxo  
395 SmithKline, Astra Zeneca and Teva and attended international conferences with Teva. **RN** has received  
396 an unrestricted grant of £10,000 from Novartis in 2010 towards development of clinical services at the  
397 University Hospital of South Manchester. He has run preceptorship programmes in 2015 and 2016.  
398 These programmes have resulted in payment to the University Hospital of South Manchester  
399 for amounts not exceeding £10,000. He has also performed lecturing at Pharmaceutically

400 sponsored meetings for the following pharmaceutical companies in the last 3 years:- Astra Zeneca  
401 (<£1,000), Boehringer Ingelheim (<£2,000), Boston scientific (<£5,000), Chiesi (<£1,000), Novartis <  
402 £10,000, Napp (<£2,000), Teva (<£2,000). He has sat on advisory boards for the following companies  
403 in the last 3 years, (Astra Zeneca, Boehringer Ingelheim, Boston scientific, Chiesi, GSK, Novartis  
404 Vectura and Teva), receiving reimbursement not exceeding £5,000 per company. He has received  
405 sponsorship support to attend international academic meetings from Astra Zeneca, Boehringer  
406 ingelheim, Novartis, GSK, Chiesi and TEVA. Dr Niven, (or any members of his family) has no shares or  
407 any pecuniary interest in any pharmaceutical industry and has no shareholdings or dividends and is  
408 not a paid consultant for any company. **DP** has board membership with Amgen, AstraZeneca,  
409 Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals,  
410 Sanofi Genzyme, Teva Pharmaceuticals, Thermofisher; consultancy agreements with Amgen,  
411 AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mylan, Mundipharma, Novartis, Pfizer,  
412 Teva Pharmaceuticals, Theravance; grants and unrestricted funding for investigator-initiated studies  
413 (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca,  
414 Boehringer Ingelheim, Chiesi, Circassia, Mylan, Mundipharma, Novartis, Pfizer, Regeneron  
415 Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Teva Pharmaceuticals,  
416 Theravance, UK National Health Service; payment for lectures/speaking engagements from  
417 AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Mundipharma,  
418 Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals; payment for the  
419 development of educational materials from Mundipharma, Novartis; payment for  
420 travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma,  
421 Mylan, Novartis, Thermofisher; funding for patient enrolment or completion of research from  
422 Novartis; stock/stock options from AKL Research and Development Ltd which produces  
423 phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and  
424 UK) and 74% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding  
425 in Timestamp which develops adherence monitoring technology; is peer reviewer for grant  
426 committees of the Efficacy and Mechanism Evaluation programme, and Health Technology  
427 Assessment; and was an expert witness for GlaxoSmithKline. **SS** has received fees from consultancy  
428 agreements/other services from Astra Zeneca, GSK, Boehringer Ingelheim, Napp, Mundipharma,  
429 Chiesi, ERT Medical, Owlstone Medical. **RS** has received presentation fees from AZ. **PEP** has attended  
430 advisory board for Novartis; has given lectures at meetings with/without lecture honoraria supported  
431 by AstraZeneca and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca,  
432 GlaxoSmithKline and Novartis; and is conducting research funded by GlaxoSmithKline for which his  
433 institution receives remuneration.

434

435 **Funding:** The authors have not declared a specific grant for this research from any funding agency in  
436 the public, commercial or not-for-profit sectors. OPCRD dataset provided by Optimum Patient Care  
437 Limited.

438

439 **Patient consent for publication:** None required

440

441 **Ethical approval:** Approval for collection and analysis of pseudonymised UKSAR data was granted by  
442 ORECNI (15/NI/0196). The OPCRD has been reviewed and ethically approved by the NHS Health



443 Research Authority to hold and process anonymized data as part of service delivery (Research Ethics  
444 Committee reference: 15/EM/0150). Specific approval for this research study was granted by the  
445 Anonymised Data Ethics Protocols and Transparency committee (ADEPT approval reference:  
446 ADEPT0120).

447

448 **Data sharing:** No further data is available

449

450 **Transparency:** The lead author (JB) affirms that this manuscript is an honest, accurate, and  
451 transparent account of the study being reported; that no important aspects of the study have been  
452 omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been  
453 explained.

454

455 **Acknowledgements:** We thank the data input and medical staff in the UK Difficult Asthma Centres.

## References

1. Pearce N, Sunyer J, Cheng S, Chinn S, Bjorksten B, Burr M, et al. Comparison of asthma prevalence in the ISAAC and the ECRHS. *European Respiratory Journal* 2000; 16:420-6.
2. Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN, et al. Characterization of Severe Asthma Worldwide: Data From the International Severe Asthma Registry. *CHEST* 2020; 157:790-804.
3. Netuveli G, Hurwitz B, Levy M, Fletcher M, Barnes G, Durham SR, et al. Ethnic variations in UK asthma frequency, morbidity, and health-service use: a systematic review and meta-analysis. *Lancet* 2005; 365:312-7.
4. ZORATTI EM, HAVSTAD S, RODRIGUEZ J, ROBENS-PARADISE Y, LAFATA JE, MCCARTHY B. Health Service Use by African Americans and Caucasians with Asthma in a Managed Care Setting. *American Journal of Respiratory and Critical Care Medicine* 1998; 158:371-7.
5. Fitzpatrick AM, Gillespie SE, Mauger DT, Phillips BR, Bleecker ER, Israel E, et al. Racial disparities in asthma-related health care use in the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol* 2019; 143:2052-61.
6. O'Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. *Thorax* 2015; 70:376-8.
7. Gamble C, Talbott E, Youk A, Holguin F, Pitt B, Silveira L, et al. Racial differences in biologic predictors of severe asthma: Data from the Severe Asthma Research Program. *The Journal of allergy and clinical immunology* 2010; 126:1149-56.e1.
8. Grossman NL, Ortega VE, King TS, Bleecker ER, Ampleford EA, Bacharier LB, et al. Exacerbation-prone asthma in the context of race and ancestry in Asthma Clinical Research Network trials. *Journal of Allergy and Clinical Immunology* 2019; 144:1524-33.
9. Ober C, McKennan CG, Magnaye KM, Altman MC, Washington C, 3rd, Stanhope C, et al. Expression quantitative trait locus fine mapping of the 17q12-21 asthma locus in African American children: a genetic association and gene expression study. *Lancet Respir Med* 2020; 8:482-92.
10. Silber JH, Rosenbaum PR, Calhoun SR, Reiter JG, Hill AS, Guevara JP, et al. Racial Disparities in Medicaid Asthma Hospitalizations. *Pediatrics* 2017; 139.
11. Beck AF, Huang B, Auger KA, Ryan PH, Chen C, Kahn RS. Explaining Racial Disparities in Child Asthma Readmission Using a Causal Inference Approach. *JAMA Pediatr* 2016; 170:695-703.
12. Beck AF, Huang B, Simmons JM, Moncrief T, Sauers HS, Chen C, et al. Role of financial and social hardships in asthma racial disparities. *Pediatrics* 2014; 133:431-9.
13. Lakhanpaul M, Bird D, Manikam L, Culley L, Perkins G, Hudson N, et al. A systematic review of explanatory factors of barriers and facilitators to improving asthma management in South Asian children. *Bmc Public Health* 2014; 14.
14. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *The Lancet Respiratory Medicine* 2015; 3:849-58.
15. Malinovsky A, Fonseca JA, Jacinto T, Alving K, Janson C. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. *J Allergy Clin Immunol* 2013; 132:821-7.e1-5.
16. Jackson DJ, Busby J, Pfeffer PE, Menzies-Gow A, Brown T, Gore R, et al. Characterisation of patients with severe asthma in the UK Severe Asthma Registry in the biologic era. *Thorax* 2020:thoraxjnl-2020-215168.
17. OPCR: Our Databases. 2020. [Cited 2020 21/0520.] Available from <https://opcrd.co.uk/our-database/>.

18. GINA. Difficult-To-Treat And Severe Asthma In Adolescent And Adult Patients: Diagnosis And Management. 2019.
19. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology* 2009; 20:488-95.
20. Sheikh A, Steiner MFC, Cezard G, Bansal N, Fischbacher C, Simpson CR, et al. Ethnic variations in asthma hospital admission, readmission and death: a retrospective, national cohort study of 4.62 million people in Scotland. *Bmc Medicine* 2016; 14.
21. Hull SA, McKibben S, Homer K, Taylor SJC, Pike K, Griffiths C. Asthma prescribing, ethnicity and risk of hospital admission: an analysis of 35,864 linked primary and secondary care records in East London. *Npj Primary Care Respiratory Medicine* 2016; 26.
22. James GD, Baker P, Badrick E, Mathur R, Hull S, Robson J. Ethnic and social disparity in glycaemic control in type 2 diabetes; cohort study in general practice 2004-9. *Journal of the Royal Society of Medicine* 2012; 105:300-8.
23. Schofield P, Saka O, Ashworth M. Ethnic differences in blood pressure monitoring and control in south east London. *British Journal of General Practice* 2011; 61:2.
24. Ward E, Jemal A, Cokkinides V, Singh GK, Cardinez C, Ghafoor A, et al. Cancer disparities by race/ethnicity and socioeconomic status. *Ca-a Cancer Journal for Clinicians* 2004; 54:78-93.
25. Lanting LC, Joung IMA, Mackenbach JP, Lamberts SWJ, Bootsma AH. Ethnic differences in mortality, end-stage complications, and quality of care among diabetic patients - A review. *Diabetes Care* 2005; 28:2280-8.
26. Bryant AS, Worjolah A, Caughey AB, Washington AE. Racial/ethnic disparities in obstetric outcomes and care: prevalence and determinants. *American Journal of Obstetrics and Gynecology* 2010; 202:335-43.
27. Litonjua AA, Celedon JC, Hausmann J, Nikolov M, Sredl D, Ryan L, et al. Variation in total and specific IgE: Effects of ethnicity and socioeconomic status. *Journal of Allergy and Clinical Immunology* 2005; 115:751-7.
28. Nyenhuis SM, Krishnan JA, Berry A, Calhoun WJ, Chinchilli VM, Engle L, et al. Race is associated with differences in airway inflammation in patients with asthma. *Journal of Allergy and Clinical Immunology* 2017; 140:257-+.
29. Wang D, Wang YN, Liang H, David JE, Bray CL. Race and ethnicity have significant influence on fractional exhaled nitric oxide. *Annals of Allergy Asthma & Immunology* 2018; 120:272-+.
30. Bain BJ. Ethnic and sex differences in the total and differential white cell count and platelet count. *Journal of clinical pathology* 1996; 49:664-6.
31. Wells K, Pladevall M, Peterson EL, Campbell J, Wang M, Lanfear DE, et al. Race-Ethnic Differences in Factors Associated with Inhaled Steroid Adherence among Adults with Asthma. *American Journal of Respiratory and Critical Care Medicine* 2008; 178:1194-201.
32. Salt E, Frazier SK. Predictors of medication adherence in patients with rheumatoid arthritis. *Drug Development Research* 2011; 72:756-63.
33. Simoni JM, Huh D, Wilson IB, Shen J, Goggin K, Reynolds NR, et al. Racial/Ethnic disparities in ART adherence in the United States: findings from the MACH14 study. *J Acquir Immune Defic Syndr* 2012; 60:466-72.
34. Ahmed S, Steed L, Harris K, Taylor SJC, Pinnock H. Interventions to enhance the adoption of asthma self-management behaviour in the South Asian and African American population: a systematic review. *npj Primary Care Respiratory Medicine* 2018; 28:5.
35. McQuaid EL. Barriers to medication adherence in asthma: The importance of culture and context. *Ann Allergy Asthma Immunol* 2018; 121:37-42.
36. Goff LM. Ethnicity and Type 2 diabetes in the UK. *Diabet Med* 2019; 36:927-38.
37. Trent SA, Hasegawa K, Ramratnam SK, Bittner JC, Camargo CA, Jr. Variation in asthma care at hospital discharge by race/ethnicity groups. *J Asthma* 2018; 55:939-48.
38. Riera A, Navas-Nazario A, Shabanova V, Vaca FE. The impact of limited English proficiency on asthma action plan use. *J Asthma* 2014; 51:178-84.

39. Carey OJ, Cookson JB, Britton J, Tattersfield AE. The effect of lifestyle on wheeze, atopy, and bronchial hyperreactivity in Asian and white children. *Am J Respir Crit Care Med* 1996; 154:537-40.
40. Arbes SJ, Gergen PJ, Elliott L, Zeldin DC. Prevalences of positive skin test responses to 10 common allergens in the US population: Results from the Third National Health and Nutrition Examination Survey. *Journal of Allergy and Clinical Immunology* 2005; 116:377-83.
41. Stevenson LA, Gergen PJ, Hoover DR, Rosenstreich D, Mannino DM, Matte TD. Sociodemographic correlates of indoor allergen sensitivity among United States children. *Journal of Allergy and Clinical Immunology* 2001; 108:747-52.
42. Lombardi C, Savi E, Ridolo E, Passalacqua G, Canonica GW. Is allergic sensitization relevant in severe asthma? Which allergens may be culprit? *The World Allergy Organization journal* 2017; 10:2-
43. Wahn U, Martin C, Freeman P, Blogg M, Jimenez P. Relationship between pretreatment specific IgE and the response to omalizumab therapy. *Allergy* 2009; 64:1780-7.
44. Choudhry S, Ung N, Avila PC, Ziv E, Nazario S, Casal J, et al. Pharmacogenetic differences in response to albuterol between Puerto Ricans and Mexicans with asthma. *Am J Respir Crit Care Med* 2005; 171:563-70.
45. Litvak A, Batukbhai B, Russell SD, Tsai HL, Rosner GL, Jeter SC, et al. Racial disparities in the rate of cardiotoxicity of HER2-targeted therapies among women with early breast cancer. *Cancer* 2018; 124:1904-11.
46. Jackson SH, Beevers DG, Cruickshank JK, Bannan LT. Ethnic differences in peak expiratory flow rate in Birmingham factory workers. *Postgraduate medical journal* 1983; 59:671-3.
47. Vyas DA, Eisenstein LG, Jones DS. Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms. *New England Journal of Medicine* 2020; 383:874-82.
48. NICE. Mepolizumab for treating severe refractory eosinophilic asthma. 2017.
49. NICE. Omalizumab for treating severe persistent allergic asthma. 2013.
50. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *The European respiratory journal* 2012; 40:1324-43.
51. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983; 127:725-34.
52. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; 338:b2393.
53. Thomas M, Gruffydd-Jones K, Stonham C, Ward S, Macfarlane TV. Assessing asthma control in routine clinical practice: use of the Royal College of Physicians '3 questions'. *Prim Care Respir J* 2009; 18:83-8.
54. Pape K, Schlünssen V, Lodge CJ, Perret JL, Walters EH, Bui D, et al. Is self-reported history of eczema and hay fever a valid measure of atopy in those who report current asthma? *Allergy*; n/a.
55. Khan NF, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC Family Practice* 2010; 11:1.
56. Morgan C, Webb RT, Carr MJ, Kontopantelis E, Green J, Chew-Graham CA, et al. Incidence, clinical management, and mortality risk following self harm among children and adolescents: cohort study in primary care. *BMJ* 2017; 359:j4351.
57. Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, 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; 71:339-46.
58. Asthma Gf. Global Strategy for Asthma Management and Prevention, Updated. 2018.
59. NICE. Inhaled corticosteroid doses for NICE's asthma guideline. 2018.

60. Bloom CI, Nissen F, Douglas IJ, Smeeth L, Cullinan P, Quint JK. Exacerbation risk and characterisation of the UK's asthma population from infants to old age. *Thorax* 2018; 73:313-20.

## Tables and Figures

**Table 1: Comparison of White and ethnic minority group severe asthma patients in UK Severe Asthma Registry**

	White (n=2,764)	Ethnic Minority Group (n=638)	P-value
<b>Age At First Assessment (Years, N=3400)</b>	50.3 (14.7)	48.4 (13.4)	0.002
<35	473 (17.1%)	103 (16.1%)	
35-54	1,099 (39.8%)	323 (50.6%)	
55-74	1,100 (39.8%)	194 (30.4%)	
75+	90 (3.3%)	18 (2.8%)	
<b>Gender(N=3402)</b>			0.316
Female	1,748 (63.2%)	417 (65.4%)	
Male	1,016 (36.8%)	221 (34.6%)	
<b>Ethnicity (N=3402)</b>			N/A
Caucasian	2,764 (100.0%)	0 (0.0%)	
South East Asian	0 (0.0%)	211 (33.1%)	
North East Asian	0 (0.0%)	83 (13.0%)	
African	0 (0.0%)	101 (15.8%)	
Mixed	0 (0.0%)	31 (4.9%)	
Other	0 (0.0%)	212 (33.2%)	
<b>BMI (kg/m<sup>2</sup>, N=3285)</b>	31.2 (7.5)	30.1 (6.4)	<0.001
<b>Smoking Status (N=3322)</b>			<0.001
Never smoked	1,729 (64.1%)	482 (77.4%)	
Ex-smoker	832 (30.8%)	117 (18.8%)	
Current smoker	138 (5.1%)	24 (3.9%)	
<b>Age at Onset of Symptoms (Years, N=3008)</b>	25 (20)	26 (18)	0.313
<b>Atopic Disease (N=3314)</b>	1,618 (60.2%)	436 (69.5%)	<0.001
<b>Positive to Perennial Allergen (N=3089)</b>	1,135 (53.7%)	276 (54.8%)	0.679
<b>Specific Perennial Allergen (N=1399)</b>			
House Dust Mite	754 (67.0%)	208 (75.9%)	0.004
Cat dander	444 (39.5%)	94 (34.3%)	0.115
Dog dander	434 (38.6%)	78 (28.5%)	0.002
<b>Nasal Polyps (N=3402)</b>	356 (12.9%)	96 (15.0%)	0.146
<b>FEV1 (% Predicted, N=3143)</b>	69.6 (22.6)	64.8 (21.2)	<0.001
<b>FVC (% Predicted, N=3091)</b>	85.1 (19.2)	80.2 (20.3)	<0.001
<b>KCO (% Predicted, N=1372)</b>	98.1 (29.5)	98.1 (17.6)	0.981
<b>Blood Eosinophil Count (10<sup>9</sup>/L, N=3295)</b>	0.30 (0.13,0.56)	0.39 (0.20,0.60)	<0.001
<b>Highest Ever Blood Eosinophil Count (10<sup>9</sup>/L, N=3129)</b>	0.60 (0.33,0.97)	0.60 (0.40,0.92)	0.443
<b>FeNO (ppb, N=2864)</b>	34.0 (17.0,66.0)	41.0 (21.0,76.0)	<0.001
<b>IgE (IU/mL, N=3193)</b>	129 (41,389)	265 (97,646)	<0.001
<b>ACQ6 Score (N=2995)</b>	2.9 (1.4)	3.1 (1.4)	0.001
<b>Uncontrolled Asthma (ACQ6&gt;1.5, N=2995)</b>	1,936 (80.8%)	505 (85.2%)	0.015
<b>Exacerbations in the Last Year (N=3226)</b>			0.278
0	312 (11.9%)	60 (9.8%)	
1	206 (7.9%)	59 (9.7%)	
2	235 (9.0%)	47 (7.7%)	
3	280 (10.7%)	70 (11.5%)	
4+	1,582 (60.5%)	375 (61.4%)	
<b>Any ED Attendance (Last Year, N=3127)</b>	1,065 (42.0%)	302 (51.0%)	<0.001
<b>Any Hospital Admissions (Last Year, N=3274)</b>	1,027 (38.6%)	268 (43.5%)	0.026
<b>Maintenance OCS (N=3310)</b>	1,292 (48.0%)	249 (40.2%)	<0.001
<b>Maintenance OCS (mg), N=1518)</b>	10 (5,15)	10 (5,13)	0.060
<b>ICS Dose (BDP equivalent [µg], N=3066)</b>	2000 (1600,2000)	2000 (1600,2000)	0.162
<b>SABA (N=3290)</b>	2,524 (94.4%)	577 (93.8%)	0.608
<b>Leukotriene Receptor Antagonists (N=3232)</b>	1,351 (51.5%)	301 (49.6%)	0.404
<b>Treatment Adherent (N=2737)</b>	1,694 (76.8%)	403 (76.0%)	0.726

**Abbreviations:** BMI: body mass index, FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; KCO: carbon monoxide transfer coefficient; FeNO: fractional exhaled nitric oxide; IgE: Immunoglobulin E; ACQ:

asthma control questionnaire; OCS: oral corticosteroid; ICS: inhaled corticosteroid; BDP: beclometasone dipropionate; SABA: Short-acting beta-agonist

**Table 2: Comparison of White and ethnic minority group severe asthmatics in OPCR**

	<b>White (n=13,256)</b>	<b>Ethnic Minority Group (n=680)</b>	<b>P-value</b>
<b>Age (Years, N=13936)</b>	55.9 (16.6)	52.9 (16.6)	<0.001
<35	1,558 (11.8%)	105 (15.4%)	
35-54	4,608 (34.8%)	262 (38.5%)	
55-74	5,291 (39.9%)	234 (34.4%)	
75+	1,799 (13.6%)	79 (11.6%)	
<b>Gender (N=13936)</b>			0.028
Female	9,033 (68.1%)	436 (64.1%)	
Male	4,223 (31.9%)	244 (35.9%)	
<b>Ethnicity (N=13936)</b>			N/A
White	13,256 (100.0%)	0 (0.0%)	
Asian	0 (0.0%)	513 (75.4%)	
Black	0 (0.0%)	69 (10.1%)	
Mixed	0 (0.0%)	39 (5.7%)	
Other	0 (0.0%)	59 (8.7%)	
<b>BMI (Kg/M<sup>2</sup>, N=11939)</b>	29.6 (6.6)		<0.001
<b>Alcohol Consumption (Weekly Units, N=8695)</b>	2.0 (0.0,8.0)	0.0 (0.0,0.0)	<0.001
<b>Smoking Status (N=13601)</b>			<0.001
Never-Smoker	6,345 (49.1%)	527 (78.3%)	
Ex-Smoker	4,181 (32.3%)	70 (10.4%)	
Current Smoker	2,404 (18.6%)	76 (11.3%)	
<b>IMD Decile (N=13851)</b>			<0.001
1 (Least Deprived)	880 (6.7%)	17 (2.5%)	
2	2,045 (15.5%)	56 (8.3%)	
3	1,321 (10.0%)	64 (9.4%)	
4	1,285 (9.8%)	62 (9.1%)	
5	1,455 (11.0%)	35 (5.2%)	
6	877 (6.7%)	41 (6.0%)	
7	2,043 (15.5%)	28 (4.1%)	
8	1,523 (11.6%)	160 (23.6%)	
9	898 (6.8%)	134 (19.8%)	
10 (Most Deprived)	846 (6.4%)	81 (11.9%)	
<b>Comorbidities (N=13936)</b>			
Allergic rhinitis	1,432 (10.8%)	131 (19.3%)	<0.001
Cancer	1,625 (12.3%)	53 (7.8%)	<0.001
Cataract	305 (2.3%)	30 (4.4%)	<0.001
Cerebrovascular disease	308 (2.3%)	17 (2.5%)	0.766
Congestive heart disease	169 (1.3%)	13 (1.9%)	0.154
Depression/Anxiety	2,371 (17.9%)	70 (10.3%)	<0.001
Diabetes	1,228 (9.3%)	127 (18.7%)	<0.001
Eczema	1,695 (12.8%)	118 (17.4%)	<0.001
Glaucoma	193 (1.5%)	9 (1.3%)	0.778
Hypertension	2,126 (16.0%)	94 (13.8%)	0.124
Insomnia	458 (3.5%)	21 (3.1%)	0.609
Liver Disease	23 (0.2%)	1 (0.1%)	0.871
Myocardial infarction	98 (0.7%)	10 (1.5%)	0.034
Nasal polyps	248 (1.9%)	9 (1.3%)	0.301
Oral candidiasis	593 (4.5%)	28 (4.1%)	0.661
Osteoporosis	323 (2.4%)	20 (2.9%)	0.408
Renal disease	689 (5.2%)	30 (4.4%)	0.366
Rheumatological disease	581 (4.4%)	30 (4.4%)	0.971
<b>Atopic Disease (N=13936)</b>	2,342 (17.7%)	179 (26.3%)	<0.001
<b>Peak Flow (% Predicted, N=8116)</b>	81.6 (66.2,95.6)	72.9 (57.1,88.3)	<0.001
<b>Blood Eosinophils (10<sup>9</sup>/L, N=7087)</b>	0.20 (0.11,0.33)	0.24 (0.13,0.40)	0.019



<b>Uncontrolled (RCP 3Q, N=4586)</b>	2,151 (50.0%)	142 (61.5%)	<0.001
<b>Exacerbations (N=13936)</b>	1.0 (0.0,2.0)	1.0 (0.0,2.0)	0.730
<b>Any Exacerbations (N=13936)</b>	7,264 (54.8%)	370 (54.4%)	0.844
<b>Asthma Review (N=13936)</b>	6,159 (46.5%)	336 (49.4%)	0.133
<b>Respiratory Referral (N=13936)</b>	118 (0.9%)	9 (1.3%)	0.246
<b>ICS Dose (BDP equivalent [<math>\mu</math>g], N=13591)</b>	1000 (1000,2000)	1000 (1000,1600)	0.068
<b>SABA (N=13936)</b>	11,996 (90.5%)	629 (92.5%)	0.081
<b>Leukotriene Receptor Antagonists (N=13936)</b>	2,669 (20.1%)	171 (25.1%)	0.002
<b>Treatment Adherent (Clinical Impression, N=1197)</b>	1,079 (94.3%)	65 (83.3%)	<0.001
<b>Treatment Adherent (MPR<math>\geq</math>70%, N=13534)</b>	4,094 (31.8%)	165 (25.1%)	<0.001

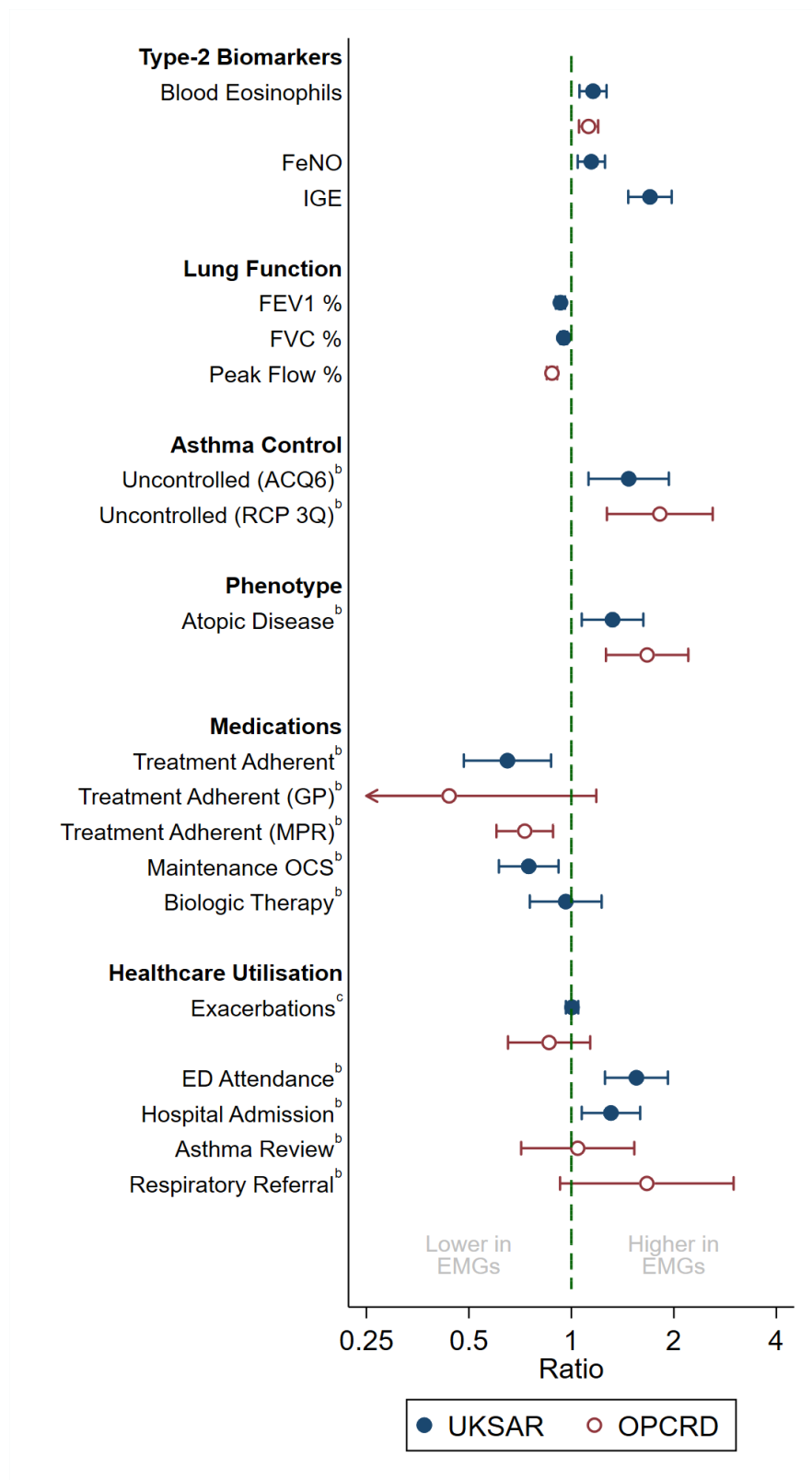
**Abbreviations:** BMI: body mass index, RCP 3Q: Royal College of Physicians 3 Questions; ICS: inhaled corticosteroid; BDP: beclometasone dipropionate; SABA: Short-acting beta-agonist; MPR: medicine possession ratio

## Figure Legends

**Figure 1:** Summary of multivariate regression results in the UKSAR and OPCRD comparing White and ethnic minority group severe asthmatics. Adjusting for hospital, year seen, age (5 year groups) and gender. <sup>b</sup> Odds Ratio, <sup>c</sup> Rate Ratio

**Figure 2:** Model-based predications of selected outcomes in the UKSAR and OPCRD analysis for White and ethnic minority group patients with severe asthma. Shaded area is 95% confidence interval.

**Figure 1: Summary of multivariate regression results in the UKSAR and OPCRD comparing White and ethnic minority group severe asthmatics<sup>a</sup>**

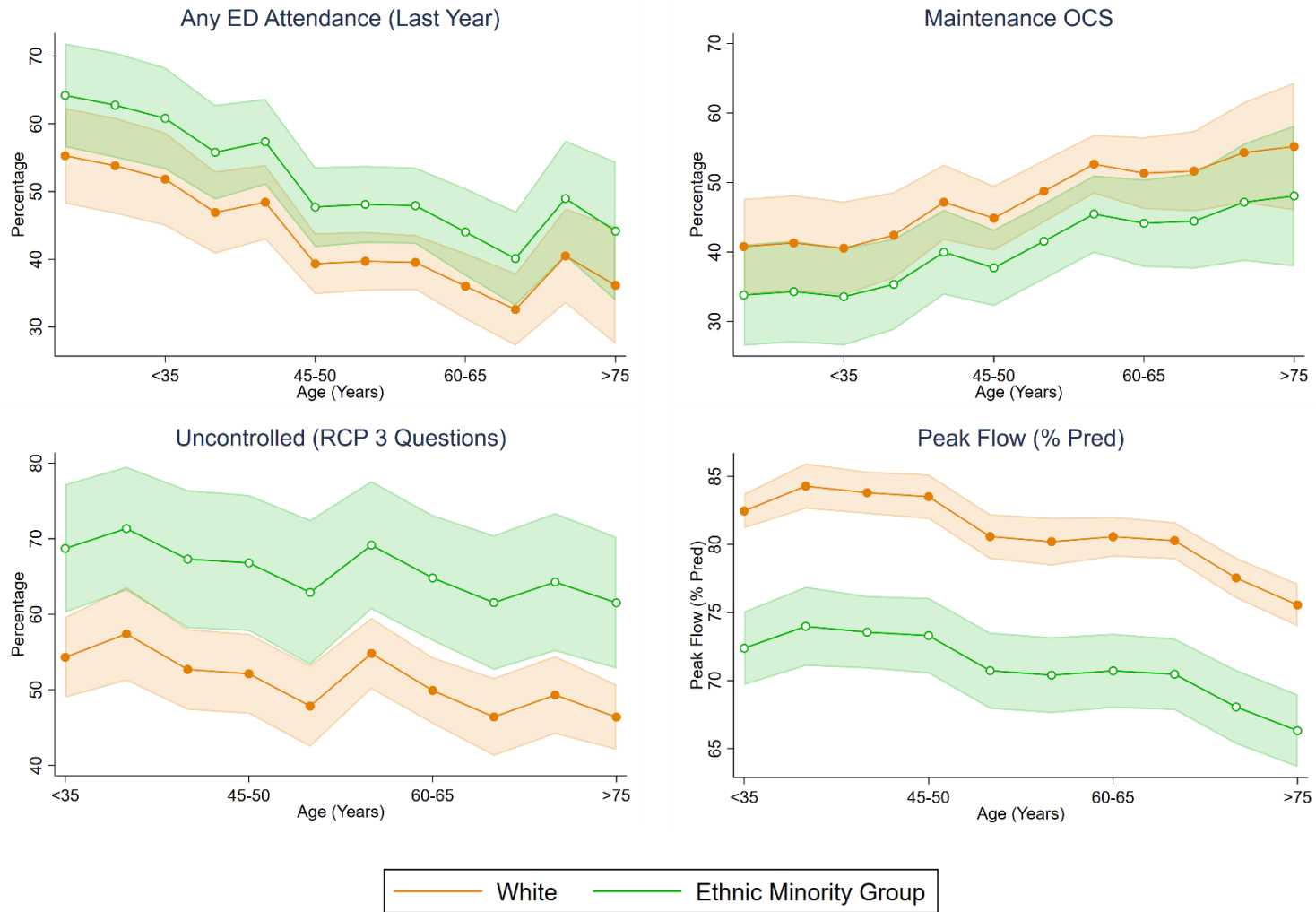


<sup>a</sup> Adjusting for hospital, year seen, age (5 year groups) and gender

<sup>b</sup> Odds Ratio

<sup>c</sup> Rate Ratio

**Figure 2: Model-based predications of selected outcomes in the UKSAR and OPCRD analysis for White and ethnic minority group patients with severe asthma**



## **Online Supplement**

### **Supplementary methods**

#### **UKSAR Biologic Therapy Eligibility**

As a primary aim of our study was to compare ethnic variation in presentation and treatment, we assessed eligibility for biologic monoclonal antibody therapies among White and EMG patients. Access criteria for biologic therapy differ between countries, therefore we used the current NICE guidance from the UK. For anti-interleukin-5 (anti-IL5) and anti-interleukin-5 receptor (anti-IL5R) therapies we used the criteria for mepolizumab: blood eosinophils  $>300/\mu\text{l}$  and recent systemic OCS exposure ( $\geq 4$  rescue steroids in the previous year or mOCS use)<sup>48</sup>. Similar access criteria are used for Benralizumab while Reslizumab is infrequently used in the UK due to intravenous administration. For anti-IgE therapy we used the criteria for omalizumab: a positive skin prick test for a perennial allergen,  $\text{FEV}_1 < 80\%$  and within the IgE/weight prescribing range.<sup>49</sup>

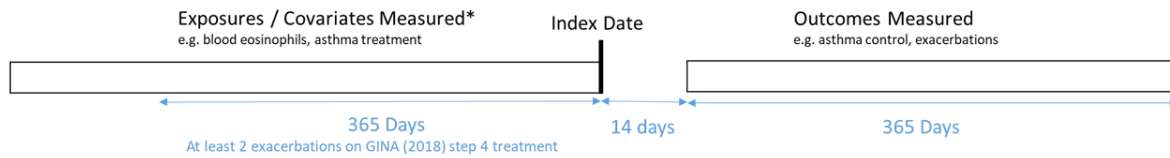
#### **OPCRD Study Population**

From the OPCR dataset we selected those patients with severe asthma to provide a comparison cohort to the UKSAR. Severe was defined according to GINA 2019 criteria as those who remained uncontrolled ( $\geq 2$  exacerbations within a year) on step 4 treatment or who require maintenance oral corticosteroids (OCS) to achieve control.<sup>18</sup> To increase the homogeneity of our cohort, patients with no asthma diagnosis and/or an alternative respiratory diagnosis (chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, pulmonary sarcoidosis or interstitial pneumonia) in the three years prior to meeting this definition were excluded. Our analysis was restricted to adult patients aged  $>18$  years and patients must have had three years prior data available to allow adequate time for potential confounder ascertainment. Patients who met the severe asthma definition before 1st April 2008 were excluded as electronic prescription recording was less common before this date.

Follow-up ended at the earliest date of when the patient left the practice, when data was last collected from the practice, or when the patient's asthma was recorded as resolved (Read Code: 21262). All patients were followed up for one year starting from 14 days after they became uncontrolled (as measurements during the initial acute exacerbation phase may not reflect the patient's asthma when stable). Patients with insufficient follow-up were excluded. Due to the stochastic nature of exacerbations, and the time-varying nature of asthma treatment intensity, patients could have multiple periods of severe disease, when this happened we randomly chose a single eligible one-year follow-up period for each patient. A schematic of the study design is given below.

In general, covariates were measured using the last record before the start of follow-up and outcomes were measured during the year-long follow-up period, full details are provided in the Table E2.

### OPCRD study schematic



\* Exposures / covariates measured over different timeframes, see online supplement 3 for full details



### Spirometry

In the UKSAR, spirometry was conducted according to ERS/ATS guidelines and percent predicted values corrected for ethnicity were calculated using the GLI 2012 multi-ethnic reference values.<sup>50</sup> In the OPCRD, raw peak flow measurements were extracted from the GP record alongside the patient's age, gender and height. We calculated percent predicted values using the equations specified by Knudson et al.<sup>51</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.

### Statistical Methods

Univariate analyses were conducted using t-tests, chi-square tests and Mann-Whitney U as appropriate. 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. Multivariate analyses adjusted for demographic factors were conducted accounting for year, age (5 year categories) and gender. 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. To improve the interpretability of our results we calculated the estimated marginal means of outcomes, adjusted for potential confounders, and plotted these separately for White and EMG patients.

### **Supplementary Analyses**

We re-ran our OPCR models additionally adjusting for the index of multiple deprivation (IMD) decile of the GP practice postcode to investigate the mediating effect of deprivation. We additionally investigated potential mediating role of lifestyle factors (smoking status, BMI) and asthma treatment (mOCS use, treatment adherence) for type-2 biomarkers in the UKSAR. We repeated our UKSAR analysis for individual hospitals to investigate the consistency of effects after adjusting for year, age (18-34, 35-54, 55-79, 80+) and gender. Our primary analysis was based on complete cases however we used multiple imputation with chained equations, which assumes that the data was missing at random, to assess the impact of missing data.<sup>52</sup> Ten imputation datasets were created, and imputation models included year, age, gender, ethnicity and hospital site (in the UKSAR only). Due to different time periods used in the UKSAR (post-2014) and OPCR (post-2008) we repeated our analysis of the OPCR restricting to patients meeting the uncontrolled severe asthma definition after 1<sup>st</sup> January 2014. Lastly, we repeated our analysis comparing outcomes between White patients and those from each individual ethnicity (Asian, Black, Mixed and Other) to explore if important differences existed.

We conducted a further analysis within the OPCR to assess the independent effect of ethnicity on respiratory referral (Read Codes: XaAfm, XaAcS, XaAfl). Referrals for children (aged<18) and those made before 1st April 2008 were excluded. To increase the likelihood that referrals were for asthma, we included only those made while the patient had an active asthma diagnosis, defined as having an asthma diagnosis code and a prescription of a GINA asthma medication (Table E3) in the year before referral. When a patient had multiple eligible respiratory referrals, we randomly selected a single referral meaning each patient could only act as a case once. Up to five controls with an active asthma diagnosis at the time of their case's referral were chosen matched on year of birth ( $\pm 3$  years), gender and treatment step. Full definitions of covariates and outcomes are given in Table E2. We used conditional logistic regression to estimate odds ratios for the association between ethnicity and respiratory referral. As our aim was to identify unwarranted ethnic variation we accounted for variables that could reasonably effect the decision to refer such as smoking status, comorbidities, lung function, asthma control and recent healthcare utilisation (alongside age, gender and treatment step which are accounted for due to matching).

**Table E1: Ethnicity Read Code group used in the OPCRD analysis**

<b>Ethnicity</b>	<b>Read Code Description</b>	<b>Read Code</b>
<b>White</b>	White - ethnic group	9S1..
	British or mixed British - ethnic category 2001 census	XaJQv
	Irish - ethnic category 2001 census	XaJQw
	Other White background - ethnic category 2001 census	XaJQx
	White: any other White ethnic group - Scotland ethnic category 2011 census	Xacuy
	White: Polish - Scotland ethnic category 2011 census	Xacux
	White: Gypsy or Irish Traveller - Scotland ethnic category 2011 census	Xacuv
	White: Irish - Scotland ethnic category 2011 census	Xacuu
	White: other British - Scotland ethnic category 2011 census	Xacut
	White: Scottish - Scotland ethnic category 2011 census	Xacus
	Irish Traveller - Northern Ireland ethnic category 2011 census	XacuR
	White - Northern Ireland ethnic category 2011 census	XacuQ
	White: any other White background - England and Wales ethnic category 2011 census	XactK
	White: Gypsy or Irish Traveller - England and Wales ethnic category 2011 census	XactJ
	White: Irish - England and Wales ethnic category 2011 census	XactI
White: English or Welsh or Scottish or Northern Irish or British - England and Wales ethnic category 2011 census	XactH	
<b>Mixed</b>	Mixed ethnic census group	XaFwG
	White and Black Caribbean - ethnic category 2001 census	XaJQy
	White and Black African - ethnic category 2001 census	XaJQz
	White and Asian - ethnic category 2001 census	XaJR0
	Other Mixed background - ethnic category 2001 census	XaJR1
	Mixed or multiple ethnic groups: any Mixed or multiple ethnic group - Scotland ethnic category 2011 census	Xacuz
	Mixed multiple ethnic groups: any other Mixed or multiple ethnic background - Northern Ireland ethnic category 2011 census	Xacua
	Mixed multiple ethnic groups: White and Asian - Northern Ireland ethnic category 2011 census	XacuU
	Mixed multiple ethnic groups: White and Black African - Northern Ireland ethnic category 2011 census	XacuT
	Mixed multiple ethnic groups: White and Black Caribbean - Northern Ireland ethnic category 2011 census	XacuS
	Mixed multiple ethnic groups: any other Mixed or multiple ethnic background - England and Wales ethnic category 2011 census	Xactf
	Mixed multiple ethnic groups: White and Asian - England and Wales ethnic category 2011 census	Xacte
	Mixed multiple ethnic groups: White and Black African - England and Wales ethnic category 2011 census	Xactd
	Mixed multiple ethnic groups: White and Black Caribbean - England and Wales ethnic category 2011 census	XactL
<b>Asian</b>	Asian - ethnic group	XaFwz
	Indian or British Indian - ethnic category 2001 census	XaJR2
	Pakistani or British Pakistani - ethnic category 2001 census	XaJR3



	Bangladeshi or British Bangladeshi - ethnic category 2001 census	XaJR4
	Other Asian background - ethnic category 2001 census	XaJR5
	Asian or Asian Scottish or Asian British: any other Asian group - Scotland ethnic category 2011 census	XacvG
	Asian or Asian Scottish or Asian British: Chinese - Scotland ethnic category 2011 census	XacvF
	Asian or Asian Scottish or Asian British: Indian, Indian Scottish or Indian British - Scotland ethnic category 2011 census	Xacv2
	Asian or Asian Scottish or Asian British: Bangladeshi, Bangladeshi Scottish or Bangladeshi British - Scotland ethnic category 2011 census	Xacv5
	Asian or Asian Scottish or Asian British: Pakistani, Pakistani Scottish or Pakistani British - Scotland ethnic category 2011 census	Xacv0
	Asian or Asian British: any other Asian background - Northern Ireland ethnic category 2011 census	Xacul
	Asian or Asian British: any other Asian background - Northern Ireland ethnic category 2011 census	Xacul
	Asian or Asian British: any other Asian background - Northern Ireland ethnic category 2011 census	Xacul
	Asian or Asian British: any other Asian background - Northern Ireland ethnic category 2011 census	Xacul
	Asian or Asian British: any other Asian background - Northern Ireland ethnic category 2011 census	Xacul
	Asian or Asian British: any other Asian background - England and Wales ethnic category 2011 census	Xactk
	Asian or Asian British: Chinese - England and Wales ethnic category 2011 census	Xactj
	Asian or Asian British: Bangladeshi - England and Wales ethnic category 2011 census	Xacti
	Asian or Asian British: Pakistani - England and Wales ethnic category 2011 census	Xacth
	Asian or Asian British: Indian - England and Wales ethnic category 2011 census	Xactg
<b>Black</b>	Black - ethnic group	XaFwH
	Caribbean - ethnic category 2001 census	XaJR6
	African - ethnic category 2001 census	XaJR7
	Other Black background - ethnic category 2001 census	XaJR8
	Caribbean or Black: any other Black or Caribbean group - Scotland ethnic category 2011 census	Xacva
	Caribbean or Black: Black, Black Scottish or Black British - Scotland ethnic category 2011 census	XacvZ
	Caribbean or Black: Caribbean, Caribbean Scottish or Caribbean British - Scotland ethnic category 2011 census	XacvJ
	African: any other African - Scotland ethnic category 2011 census	XacvI
	African: African, African Scottish or African British - Scotland ethnic category 2011 census	XacvH
	Black or African or Caribbean or Black British: other Black or African or Caribbean background - Northern Ireland ethnic category 2011 census	Xacuo
	Black or African or Caribbean or Black British: Caribbean - Northern Ireland ethnic category 2011 census	Xacun
	Black or African or Caribbean or Black British: African - Northern Ireland ethnic category 2011 census	Xacum
	Black or African or Caribbean or Black British: other Black or African or Caribbean background - England and Wales ethnic category 2011 census	Xactn
	Black or African or Caribbean or Black British: Caribbean - England and Wales ethnic category 2011 census	Xactm
	Black or African or Caribbean or Black British: African - England and Wales ethnic category 2011 census	Xactl

**Table E2: Definition of demographic and clinical outcomes in the OPCRD**

Variable	Description	Ascertainment Period	
		Severe Asthma Cohort	Referral Case-Control
<b>Exposures</b>			
<b>Ethnicity</b>	Read codes were grouped in five categories: White, Asian (including Asian British), Black (including Black British), Chinese and Mixed (see <b>Error! Not a valid result for table.</b> ). Our primary analysis compared White vs. ethnic minority group patients. Those with inconsistent ethnicity records (different categories at any time within the medical record) were excluded from the analysis	Entire Medical Record	Entire Medical Record
<b>Outcomes</b>			
<b>Asthma Control</b>	Measured using the Royal College of Physicians 3 questions <sup>53</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 FUP	1 year before referral
<b>Asthma Exacerbation</b>	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 between maintenance and acute OCS use. OCS prescribed on the date of an annual asthma review was excluded.	1 year from start of FUP	1 year before referral
<b>Asthma Review</b>	Read code list recognised within the 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 (Xalfk) or Asthma monitoring check done (XE2Nb).	1 year from start of FUP	1 year before referral
<b>Blood Eosinophil Count</b>	Blood eosinophil count measured in cells per litre ( $10^9/L$ ).	1 year from start of FUP	1 year before referral
<b>Peak Flow</b>	Percent predicted values were calculated using raw measurements and the formula specified by Knudson et al. <sup>51</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 FUP	1 year before referral
<b>Respiratory Referral</b>	Read code for respiratory referral (Read Codes: XaAfm, XaAcS, XaAfl)	1 year from start of FUP	N/A
<b>Treatment Adherence (GP)</b>	Using Read Codes and based on clinical impression	1 year from start of FUP	1 year before referral

<b>Treatment Adherence (MPR)</b>	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 FUP	1 year before referral
<b>Covariates</b>			
<b>Alcohol Consumption</b>	Using Read Codes and measured as units per week.	Last record before start of FUP	Last record before referral
<b>Atopic Asthma</b>	Record of hay fever or eczema. <sup>54</sup>	Beginning of medical record to start of FUP	Beginning of medical record to referral
<b>Body Mass Index (BMI)</b>	Using Read Codes and measured in kg/m <sup>2</sup> .	Last record before start of FUP	Last record before referral
<b>Comorbidities</b>	Several comorbidities were extracted using Read Code lists (comorbidity marked as present if the patient had any relevant code during the ascertainment period) including those comprising Charleston comorbidity score <sup>55</sup> , depression <sup>56</sup> , and those related to corticosteroid morbidity. <sup>57</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 FUP	3 years before referral
<b>Gender</b>	Reported by the general practice for all patients	N/A	N/A
<b>Smoking Status</b>	Using Read Codes and categorised as Non-smoker, Current smoker, Ex-smoker.	Last record before start of FUP	Last record before referral
<b>Socioeconomic Status</b>	Assessed using deciles of the 2011 Indices of Multiple Deprivation based on the practice postcode.	N/A	N/A
<b>Treatment Step</b>	Asthma medications were identified using Read/SNOMED hierarchies, and patients were categorised according to GINA 2018 treatment step. <sup>58</sup> Combination therapies (e.g. ICS/LABA, ICS/LABA/LAMA) where broken into their constituent parts and ICS dose was converted to a BDP equivalent. <sup>59</sup> Step five was defined as more than 6 prescriptions of OCS in a year, spanning across at least two quarters. <sup>60</sup>	1 year before start of FUP	1 year before referral
<b>Year of birth</b>	Reported by the general practice for all patients	N/A	N/A

**Table E3: Summary of asthma treatments by GINA (2018) Step<sup>a</sup>**

<b>GINA (2018) treatment step</b>	<b>Asthma treatment</b>
<b>Step 1</b>	only $\beta$ -agonist OR only muscarinic agonist
<b>Step 2</b>	low dose ICS without other controllers OR LTRA without other controllers OR low dose theophylline all without other controllers
<b>Step 3</b>	Medium or high dose ICS without other controllers OR Low dose ICS/LABA OR Low dose ICS/LAMA OR Low dose ICS (without LABA/LAMA) and/or theophylline OR LABA and/or LAMA (withouth ICS) OR LTRA plus theophylline (without ICS)
<b>Step 4</b>	Medium or high dose ICS/LABA OR Medium or high dose ICS/LAMA OR Medium or high dose ICS plus LTRA and/or theophylline OR $\geq 3$ controllers (without ICS)
<b>Step 5</b>	Maintenance OCS plus any other asthma treatment

<sup>a</sup>ICS: inhaled corticosteroid; LABA: long-acting  $\beta 2$ -agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroid

**Table E4: Multivariate analysis comparing ethnic minority group to White patients in the UKSAR<sup>a</sup>**

Variable	N	Univariate		Multivariate		Multiple Imputation	
		Ratio (95% CI)	P-value	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value
<b>Type-2 Biomarkers</b>							
Blood Eosinophil Count (10 <sup>9</sup> /L)	3,295	1.11 (1.02,1.21)	0.016	1.16 (1.06,1.27)	0.002	1.15 (1.05,1.27)	0.002
FeNO (ppb)	2,864	1.16 (1.07,1.26)	<0.001	1.14 (1.04,1.26)	0.004	1.15 (1.04,1.27)	0.007
IGE (IU/mL)	3,196	1.49 (1.29,1.73)	<0.001	1.70 (1.47,1.97)	<0.001	1.69 (1.45,1.96)	<0.001
<b>Lung Function</b>							
FEV1 (% Predicted)	3,143	0.93 (0.90,0.96)	<0.001	0.93 (0.90,0.96)	<0.001	0.93 (0.90,0.96)	<0.001
FVC (% Predicted)	3,091	0.94 (0.92,0.96)	<0.001	0.95 (0.93,0.97)	<0.001	0.95 (0.93,0.97)	<0.001
<b>Asthma Control</b>							
Uncontrolled Asthma (ACQ6>1.5) <sup>b</sup>	2,988	1.36 (1.06,1.74)	0.015	1.47 (1.12,1.93)	0.005	1.44 (1.11,1.88)	0.006
<b>Phenotype</b>							
Atopic Disease	3,314	1.51 (1.25,1.82)	<0.001	1.32 (1.07,1.63)	0.009	1.33 (1.08,1.64)	0.007
<b>Medications</b>							
Treatment Adherent	2,737	0.96 (0.77,1.20)	0.726	0.65 (0.48,0.87)	0.004	0.72 (0.53,0.98)	0.037
Maintenance OCS <sup>b</sup>	3,310	0.73 (0.61,0.87)	<0.001	0.75 (0.61,0.92)	0.005	0.75 (0.61,0.91)	0.005
Biologic Therapy	3,153	0.91 (0.76, 1.09)	0.325	0.96 (0.76, 1.23)	0.760		
<b>Healthcare Utilisation</b>							
Exacerbation <sup>c</sup>	3,229	1.02 (0.99,1.06)	0.219	1.00 (0.96,1.05)	0.826	1.01 (0.97,1.05)	0.744
ED Attendance (Last Year) <sup>b</sup>	3,135	1.44 (1.20,1.72)	<0.001	1.55 (1.26,1.92)	<0.001	1.49 (1.20,1.86)	<0.001
Hospital Admissions (Last Year) <sup>b</sup>	3,274	1.22 (1.02,1.46)	0.026	1.31 (1.07,1.59)	0.008	1.31 (1.08,1.60)	0.007

<sup>a</sup>Adjusting for hospital, year seen, age (5 year groups) and gender

<sup>b</sup>Odds Ratio

<sup>c</sup> Rate Ratio

**Table E5: Multivariate analysis comparing ethnic minority group to White patients in the OPCRDa**

Variable	N	Univariate		Multivariate		+Deprivation Adjustment		Multiple Imputation	
		Ratio (95% CI)	P-value	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value
<b>Type-2 Biomarkers</b>									
Blood Eosinophils (10 <sup>9</sup> /L)	7,087	1.13 (1.05,1.20)	<0.001	1.12 (1.05,1.20)	<0.001	1.12 (1.05,1.19)	0.001	1.11 (1.04,1.19)	0.002
<b>Lung Function</b>									
Peak Flow (L/Min)	8,116	0.88 (0.85,0.92)	<0.001	0.88 (0.85,0.91)	<0.001	0.89 (0.85,0.92)	<0.001	0.88 (0.85,0.90)	<0.001
<b>Asthma Control</b>									
Uncontrolled (RCP 3Q) <sup>b</sup>	4,586	1.89 (1.32,2.73)	0.001	1.82 (1.27,2.60)	0.001	1.64 (1.17,2.30)	0.004	1.84 (1.33,2.54)	<0.001
<b>Phenotype</b>									
Atopic Disease	13,936	1.71 (1.29,2.27)	<0.001	1.67 (1.26,2.21)	<0.001	1.67 (1.27,2.19)	<0.001	1.67 (1.26,2.21)	<0.001
<b>Medications</b>									
Treatment Adherent (GP)	1,197	0.44 (0.17,1.12)	0.086	0.44 (0.16,1.18)	0.104	0.50 (0.16,1.58)	0.238	0.50 (0.24,1.01)	0.053
Treatment Adherent (MPR)	13,534	0.68 (0.56,0.83)	<0.001	0.73 (0.60,0.88)	0.001	0.71 (0.59,0.87)	0.001	0.72 (0.60,0.87)	0.001
<b>Healthcare Utilisation</b>									
Exacerbations <sup>c</sup>	13,936	0.86 (0.68,1.09)	0.215	0.86 (0.65,1.14)	0.288	0.80 (0.60,1.07)	0.138	0.86 (0.65,1.14)	0.288
Asthma Review	13,936	1.06 (0.70,1.59)	0.796	1.04 (0.71,1.53)	0.825	1.19 (0.76,1.88)	0.450	1.04 (0.71,1.53)	0.825
Respiratory Referral	13,936	2.00 (1.09,3.68)	0.026	1.67 (0.93,3.00)	0.088	1.96 (0.95,4.06)	0.070	1.67 (0.93,3.00)	0.088

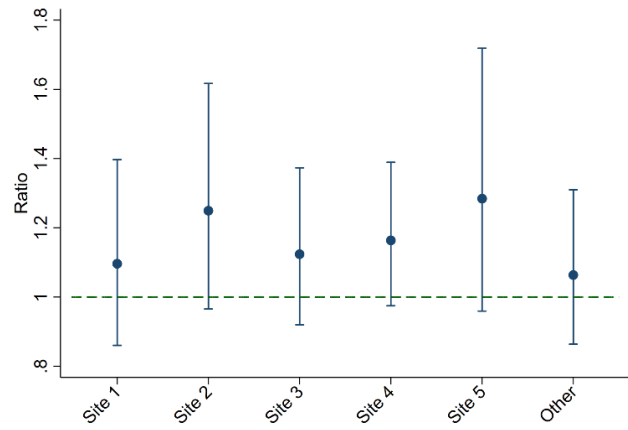
<sup>a</sup> Adjusted for year, age (5 year groups) and gender

<sup>b</sup> Odds Ratio

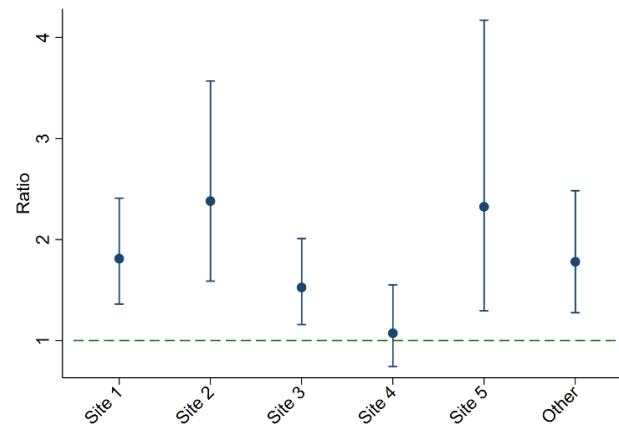
<sup>c</sup> Rate Ratio

Figure E1: Multivariate analysis comparing ethnic minority group to White patients within selected UKSAR centres

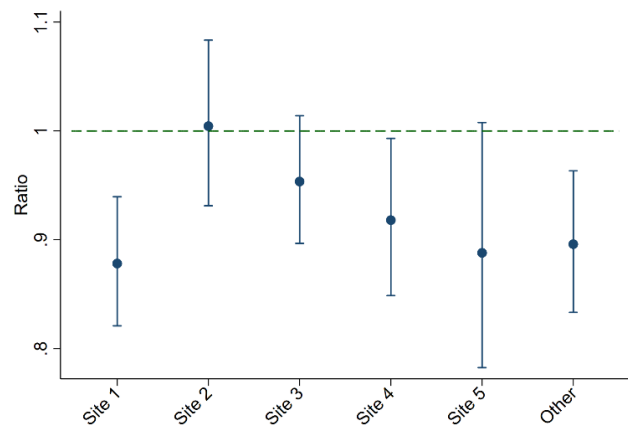
FeNO (ppb)



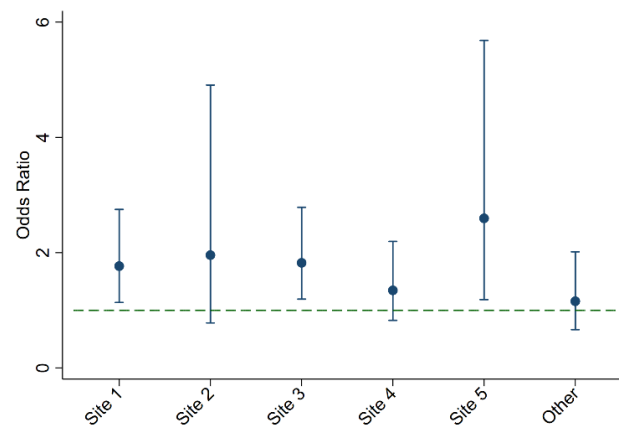
IgE (IU/mL)



FEV<sub>1</sub> (%)

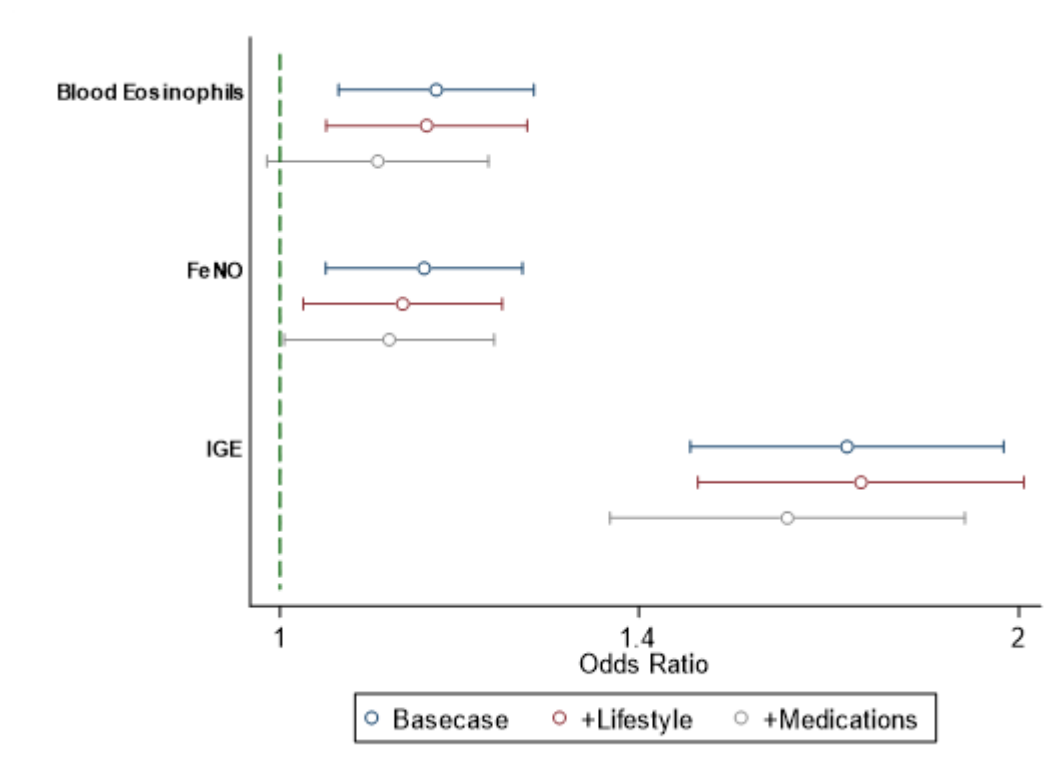


ED Attendance



—|— 95% CI

Figure E2: Multivariate analysis comparing biomarkers of ethnic minority group to White patients in the UKSAR with sequential adjustment





**Table E6: Comparison of patients with a respiratory referral (cases) to those with no respiratory referral (controls) in OPCRD**

	Controls (n=6,541)	Cases (n=1,426)	P-value
<b>Age (Years, N=7967)</b>	59.0 (14.4)	58.3 (15.1)	0.102
<35	362 (5.5%)	107 (7.5%)	
35-54	2,094 (32.0%)	455 (31.9%)	
55-74	3,126 (47.8%)	655 (45.9%)	
75+	959 (14.7%)	209 (14.7%)	
<b>Gender (N=7967)</b>			0.967
Female	4,129 (63.1%)	901 (63.2%)	
Male	2,412 (36.9%)	525 (36.8%)	
<b>Ethnic Minority Group (N=5593)</b>	255 (5.5%)	75 (7.7%)	0.008
<b>BMI (Kg/M<sup>2</sup>, N=7075)</b>	29.1 (6.2)	29.3 (6.5)	0.292
<b>Alcohol Consumption (Weekly Units, N=5192)</b>	2.0 (0.0,10.0)	1.0 (0.0,8.0)	<0.001
<b>Smoking Status (N=7875)</b>			0.055
Never-Smoker	3,596 (55.6%)	803 (56.9%)	
Ex-Smoker	2,099 (32.5%)	472 (33.5%)	
Current Smoker	769 (11.9%)	136 (9.6%)	
<b>IMD Decile (N=7947)</b>			<0.001
1 (Least Deprived)	465 (7.1%)	65 (4.6%)	
2	1,068 (16.4%)	289 (20.3%)	
3	552 (8.5%)	142 (10.0%)	
4	680 (10.4%)	161 (11.3%)	
5	692 (10.6%)	163 (11.5%)	
6	485 (7.4%)	125 (8.8%)	
7	897 (13.7%)	156 (11.0%)	
8	901 (13.8%)	151 (10.6%)	
9	462 (7.1%)	107 (7.5%)	
10 (Most Deprived)	322 (4.9%)	64 (4.5%)	
<b>Comorbidities (N=7967)</b>			
Allergic rhinitis	458 (7.0%)	120 (8.4%)	0.062
Cancer	796 (12.2%)	184 (12.9%)	0.445
Cataract	124 (1.9%)	46 (3.2%)	0.002
Cerebrovascular disease	156 (2.4%)	38 (2.7%)	0.534
Congestive heart disease	67 (1.0%)	22 (1.5%)	0.091
Depression/Anxiety	811 (12.4%)	241 (16.9%)	<0.001
Diabetes	647 (9.9%)	154 (10.8%)	0.302
Eczema	661 (10.1%)	148 (10.4%)	0.757
Glaucoma	113 (1.7%)	29 (2.0%)	0.429
Hypertension	983 (15.0%)	234 (16.4%)	0.189
Insomnia	136 (2.1%)	51 (3.6%)	<0.001
Liver Disease	13 (0.2%)	7 (0.5%)	0.046
Myocardial infarction	44 (0.7%)	11 (0.8%)	0.683
Nasal polyps	72 (1.1%)	23 (1.6%)	0.106
Oral candidiasis	173 (2.6%)	50 (3.5%)	0.074
Osteoporosis	113 (1.7%)	33 (2.3%)	0.135
Renal disease	226 (3.5%)	41 (2.9%)	0.270
Rheumatological disease	165 (2.5%)	39 (2.7%)	0.645
<b>Atopic Disease (N=7967)</b>	883 (13.5%)	192 (13.5%)	0.972
<b>Peak Flow (% Predicted, N=5803)</b>	87.9 (73.8,100.5)	80.4 (64.9,93.6)	<0.001
<b>Blood Eosinophils (10<sup>9</sup>/L, N=3742)</b>	0.20 (0.10,0.30)	0.20 (0.10,0.32)	0.459
<b>Uncontrolled (RCP 3Q, N=4717)</b>	1,486 (39.4%)	630 (66.6%)	<0.001
<b>Exacerbations (N=7967)</b>	0.0 (0.0,1.0)	1.0 (0.0,2.0)	<0.001
<b>Any Exacerbations (N=7967)</b>	1,967 (30.1%)	805 (56.5%)	<0.001
<b>Asthma Review (N=7967)</b>	4,925 (75.3%)	1,230 (86.3%)	<0.001
<b>Treatment Adherent (Clinical Impression, N=944)</b>	710 (91.3%)	154 (92.8%)	0.526
<b>Treatment Adherent (MPR≥70%, N=7272)</b>	1,924 (31.8%)	361 (29.3%)	0.082

**Table E7: Analysis of factors associated with respiratory referral in OPCRD**

Variable	N	Univariate		Multivariate		+ Deprivation Adjustment	
		Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
<b>Ethnic Minority Group</b>	5,593	1.37 (1.02,1.84)	0.034	0.66 (0.36,1.20)	0.175	0.76 (0.40,1.42)	0.386
<b>Smoking Status</b>							
Never-Smoker	7,875	Ref		Ref		Ref	
Ex-Smoker	7,875	1.02 (0.90,1.16)	0.718	0.87 (0.65,1.17)	0.356	0.88 (0.65,1.18)	0.391
Current Smoker	7,875	0.76 (0.62,0.93)	0.008	0.57 (0.35,0.94)	0.027	0.57 (0.34,0.96)	0.033
<b>Comorbidities<sup>a</sup></b>							
Allergic rhinitis	7,967	1.20 (0.97,1.49)	0.089	1.79 (1.04,3.06)	0.035	1.80 (1.05,3.10)	0.032
Cancer	7,967	1.09 (0.91,1.29)	0.348	1.39 (0.96,2.03)	0.084	1.38 (0.94,2.03)	0.097
Cataract	7,967	1.74 (1.22,2.47)	0.002	1.89 (0.71,5.02)	0.203	1.74 (0.64,4.73)	0.274
Cerebrovascular disease	7,967	1.15 (0.80,1.66)	0.443	0.98 (0.43,2.23)	0.964	1.12 (0.49,2.59)	0.788
Congestive heart disease	7,967	1.42 (0.86,2.35)	0.173	1.28 (0.37,4.42)	0.701	1.32 (0.38,4.59)	0.660
Depression/Anxiety	7,967	1.41 (1.20,1.66)	<0.001	1.15 (0.75,1.74)	0.528	1.15 (0.75,1.77)	0.528
Diabetes	7,967	1.12 (0.93,1.36)	0.233	0.89 (0.57,1.37)	0.588	0.91 (0.58,1.41)	0.666
Eczema	7,967	1.02 (0.84,1.23)	0.872	0.98 (0.63,1.53)	0.929	0.95 (0.60,1.50)	0.817
Glaucoma	7,967	1.18 (0.77,1.79)	0.451	0.73 (0.25,2.16)	0.574	0.72 (0.24,2.16)	0.558
Hypertension	7,967	1.15 (0.98,1.35)	0.090	0.89 (0.61,1.29)	0.539	0.91 (0.62,1.33)	0.631
Insomnia	7,967	1.77 (1.27,2.47)	0.001	2.59 (1.05,6.36)	0.038	2.40 (0.95,6.03)	0.063
Liver Disease	7,967	2.55 (1.01,6.41)	0.046	5.82 (0.51,66.86)	0.157	7.01 (0.60,82.34)	0.121
Myocardial infarction	7,967	1.07 (0.55,2.09)	0.848	0.58 (0.11,3.04)	0.522	0.62 (0.12,3.26)	0.574
Nasal polyps	7,967	1.45 (0.90,2.34)	0.129	1.10 (0.27,4.47)	0.896	1.13 (0.28,4.62)	0.862
Oral candidiasis	7,967	1.23 (0.89,1.71)	0.212	1.02 (0.46,2.27)	0.956	0.97 (0.43,2.19)	0.942
Osteoporosis	7,967	1.34 (0.89,2.01)	0.158	0.77 (0.34,1.75)	0.526	0.74 (0.32,1.70)	0.481
Renal disease	7,967	0.82 (0.58,1.17)	0.275	0.55 (0.23,1.27)	0.161	0.56 (0.24,1.33)	0.191
Rheumatological disease	7,967	0.88 (0.60,1.29)	0.512	1.24 (0.54,2.84)	0.616	1.18 (0.51,2.73)	0.698
<b>Peak Flow (%)</b>							
<50%	5,803	Ref		Ref		Ref	
50-80%	5,803	0.65 (0.49,0.86)	0.003	0.57 (0.31,1.06)	0.077	0.54 (0.29,1.03)	0.062
>80%	5,803	0.38 (0.28,0.50)	<0.001	0.42 (0.22,0.78)	0.006	0.41 (0.21,0.77)	0.006
<b>Uncontrolled (RCP 3Q)</b>	4,717	3.27 (2.75,3.88)	<0.001	3.05 (2.27,4.09)	<0.001	3.11 (2.30,4.20)	<0.001
<b>Any Exacerbations</b>	7,967	3.09 (2.73,3.49)	<0.001	2.84 (2.13,3.80)	<0.001	2.87 (2.14,3.85)	<0.001

**Table E8: Multivariate analysis comparing ethnic minority group to White patients in the OPCRD restricted to those with uncontrolled asthma after 1st January 2014<sup>a</sup>**

Variable	N	Univariate		Multivariate		Primary Analysis (Multivariate)	
		Ratio (95% CI)	P-value	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value
<b>Type-2 Biomarkers</b>							
Blood Eosinophils (10 <sup>9</sup> /L)	1,696	1.20 (1.08,1.34)	0.001	1.18 (1.07,1.30)	0.001	1.12 (1.05,1.20)	<0.001
<b>Lung Function</b>							
Peak Flow (L/Min)	1,735	0.83 (0.78,0.88)	<0.001	0.83 (0.78,0.88)	<0.001	0.88 (0.85,0.91)	<0.001
<b>Asthma Control</b>							
Uncontrolled (RCP 3Q) <sup>b</sup>	1,426	1.96 (1.24,3.12)	0.004	1.91 (1.22,2.97)	0.004	1.82 (1.27,2.60)	0.001
<b>Phenotype</b>							
Atopic Disease	3,109	2.06 (1.05,4.07)	0.037	2.02 (1.01,4.01)	0.045	1.67 (1.26,2.21)	<0.001
<b>Medications</b>							
Treatment Adherent (GP)	244	0.29 (0.05,1.69)	0.168	0.29 (0.03,2.68)	0.275	0.44 (0.16,1.18)	0.104
Treatment Adherent (MPR)	3,036	0.84 (0.64,1.11)	0.231	0.94 (0.71,1.26)	0.690	0.73 (0.60,0.88)	0.001
<b>Healthcare Utilisation</b>							
Exacerbations <sup>c</sup>	3,109	0.71 (0.52,0.96)	0.026	0.74 (0.55,1.00)	0.048	0.86 (0.65,1.14)	0.288
Asthma Review	3,109	1.59 (1.15,2.19)	0.005	1.64 (1.19,2.26)	0.003	1.04 (0.71,1.53)	0.825
Respiratory Referral	3,109	1.63 (0.83,3.17)	0.154	1.47 (0.77,2.82)	0.247	1.67 (0.93,3.00)	0.088

<sup>a</sup> Adjusted for year, age (5 year groups) and gender

<sup>b</sup> Odds Ratio

<sup>c</sup> Rate Ratio

**Table E9: Multivariate analysis comparing individual ethnicities to White patients in the UKSAR<sup>a</sup>**

Variable	Asian		Black		Mixed		Other	
	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value
<b>Type-2 Biomarkers</b>								
Blood Eosinophil Count (10 <sup>9</sup> /L)	1.23 (1.09,1.39)	0.001	0.98 (0.82,1.17)	0.821	1.07 (0.81,1.41)	0.625	1.15 (1.00,1.31)	0.043
FeNO (ppb)	1.02 (0.90,1.16)	0.704	1.16 (0.98,1.39)	0.089	1.34 (0.90,1.98)	0.144	1.28 (1.12,1.47)	<0.001
IGE (IU/mL)	1.82 (1.51,2.20)	<0.001	1.22 (0.92,1.62)	0.173	2.24 (1.30,3.88)	0.004	1.67 (1.32,2.11)	<0.001
<b>Lung Function</b>								
FEV1 (% Predicted)	0.91 (0.87,0.95)	<0.001	0.89 (0.83,0.96)	0.003	0.92 (0.83,1.03)	0.141	0.98 (0.93,1.03)	0.395
FVC (% Predicted)	0.92 (0.89,0.95)	<0.001	0.96 (0.91,1.02)	0.173	0.99 (0.90,1.09)	0.837	0.99 (0.95,1.03)	0.510
<b>Asthma Control</b>								
Uncontrolled Asthma (ACQ6>1.5) <sup>b</sup>	1.73 (1.16,2.58)	0.007	1.64 (0.91,2.98)	0.102	1.80 (0.62,5.28)	0.281	1.13 (0.76,1.68)	0.546
<b>Phenotype</b>								
Atopic Disease	1.02 (0.77,1.35)	0.881	2.16 (1.33,3.50)	0.002	2.08 (0.88,4.92)	0.095	1.44 (1.03,2.00)	0.033
<b>Medications</b>								
Treatment Adherent	0.59 (0.40,0.88)	0.009	0.55 (0.30,0.98)	0.042	0.40 (0.15,1.05)	0.064	0.84 (0.55,1.29)	0.429
Maintenance OCS <sup>b</sup>	0.54 (0.41,0.72)	<0.001	0.53 (0.34,0.83)	0.006	0.82 (0.39,1.72)	0.603	1.41 (1.02,1.94)	0.037
Biologic Therapy	0.91 (0.65,1.27)	0.581	0.72 (0.45,1.15)	0.168	0.87 (0.36,2.15)	0.771	1.24 (0.86,1.79)	0.257
<b>Healthcare Utilisation</b>								
Exacerbation <sup>c</sup>	1.51 (1.13,2.03)	0.006	2.38 (1.53,3.70)	<0.001	1.02 (0.47,2.23)	0.956	1.39 (1.01,1.92)	0.044
ED Attendance (Last Year) <sup>b</sup>	1.20 (0.92,1.57)	0.171	1.82 (1.19,2.79)	0.006	1.29 (0.61,2.74)	0.502	1.27 (0.93,1.73)	0.135
Hospital Admissions (Last Year) <sup>b</sup>	0.59 (0.40,0.88)	0.009	0.55 (0.30,0.98)	0.042	0.40 (0.15,1.05)	0.064	0.84 (0.55,1.29)	0.429

<sup>a</sup> Adjusted for year, age (5 year groups) and gender

<sup>b</sup> Odds Ratio

<sup>c</sup> Rate Ratio

**Table E10: Multivariate analysis comparing individual ethnicities to White patients in the OPCRD<sup>a</sup>**

Variable	Asian		Black		Mixed		Other	
	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value
<b>Type-2 Biomarkers</b>								
Blood Eosinophils (10 <sup>9</sup> /L)	1.13 (1.05,1.22)	0.001	1.01 (0.72,1.40)	0.974	1.10 (0.76,1.59)	0.597	1.14 (0.92,1.41)	0.228
<b>Lung Function</b>								
Peak Flow (L/Min)	0.86 (0.82,0.90)	<0.001	0.97 (0.90,1.05)	0.448	0.96 (0.85,1.08)	0.476	0.84 (0.78,0.91)	<0.001
<b>Asthma Control</b>								
Uncontrolled (RCP 3Q) <sup>b</sup>	2.36 (1.65,3.39)	<0.001	0.62 (0.26,1.48)	0.280	1.91 (0.60,6.08)	0.273	0.90 (0.28,2.95)	0.863
<b>Phenotype</b>								
Atopic Disease	1.59 (1.18,2.14)	0.002	2.33 (1.23,4.44)	0.010	1.55 (0.71,3.35)	0.270	1.80 (0.96,3.39)	0.069
<b>Medications</b>								
Treatment Adherent (GP)	0.46 (0.15,1.46)	0.187			0.31 (0.04,2.57)	0.280	0.12 (0.01,0.96)	0.046
Treatment Adherent (MPR)	0.78 (0.64,0.94)	0.009	0.46 (0.24,0.89)	0.021	0.72 (0.31,1.64)	0.433	0.68 (0.37,1.24)	0.205
<b>Healthcare Utilisation</b>								
Exacerbations <sup>c</sup>	0.95 (0.70,1.29)	0.733	0.54 (0.32,0.93)	0.025	0.73 (0.47,1.15)	0.177	0.59 (0.39,0.90)	0.014
Asthma Review	1.07 (0.70,1.64)	0.745	1.24 (0.73,2.10)	0.435	1.11 (0.59,2.07)	0.743	0.65 (0.28,1.48)	0.306
Respiratory Referral	1.26 (0.85,1.87)	0.253	0.89 (0.40,1.97)	0.777	1.03 (0.36,2.99)	0.953	0.61 (0.27,1.42)	0.254

<sup>a</sup> Adjusted for year, age (5 year groups) and gender

<sup>b</sup> Odds Ratio

<sup>c</sup> Rate Ratio