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

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Abstract

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

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

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

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

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

What is already known on this topic?

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

What does this article add to our knowledge?

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

How does this study impact current management guidelines?

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

Keywords: asthma, disparities, ethnicity

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

Introduction

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

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

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

Methods

Study Population

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

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

Exposures, Outcomes and Covariates

The primary outcomes of interest were type-2 biomarkers (blood eosinophils, fractional exhaled nitric oxide [FeNO] and immunoglobulin E [IgE]), lung function (forced expiratory volume in the first second [FEV_1], forced vital capacity [FVC] and peak flow), asthma control (measured by the asthma control questionnaire [ACQ] and Royal College of Physicians 3 Questions [RCP 3Q]), asthma phenotype (atopy), asthma medications (treatment adherence, maintenance oral corticosteroid [OCS] use, biologic therapy use) and healthcare utilisation (exacerbations, emergency department [ED] attendance, hospital admission, asthma review and respiratory referral). Full details of the variables used in the analysis, including the time-period in which they were assessed, are provided in Table E2.

Statistical Analysis

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

Results

Cohort Demographics

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

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

Asthma Outcomes and Corticosteroid Treatment

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

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

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

Percent predicted FEV_1 was 7% lower (Ratio: 0.93, 95% CI: 0.90, 0.96) in EMG UKSAR patients compared to White patients, while in the OPCRD PEFR measurements were 12% lower (Ratio: 0.88, 95% CI: 0.85, 0.91). Reduced lung function among EMG patients was largely consistent across individual UKSAR sites studied (Figure E1). The estimated peak flow for a 50 year old EMG patient was 71% predicted compared to 81% for a White patient after accounting for demographic differences (Difference: 10%, 95% CI: 7, 12; Figure 2).

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

Biological Phenotypes and Treatment

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

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

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

Supplementary Analysis

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

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

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

Discussion

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

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

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

Factors such as education, household overcrowding and health literacy have been previously found to contribute to ethnic variation in several US studies. [5, 10-12] Socioeconomic and cultural mediating

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

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

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

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

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

Declarations

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

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

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

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Data sharing: No further data is available

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

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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
Age At First Assessment (Years, N=3400)	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%)	
Gender(N=3402)			0.316
Female	1,748 (63.2%)	417 (65.4%)	
Male	1,016 (36.8%)	221 (34.6%)	
Ethnicity (N=3402)			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%)	
BMI (kg/m², N=3285)	31.2 (7.5)	30.1 (6.4)	<0.001
Smoking Status (N=3322)			<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%)	
Age at Onset of Symptoms (Years, N=3008)	25 (20)	26 (18)	0.313
Atopic Disease (N=3314)	1,618 (60.2%)	436 (69.5%)	<0.001
Positive to Perennial Allergen (N=3089)	1,135 (53.7%)	276 (54.8%)	0.679
Specific Perennial Allergen (N=1399)			
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
Nasal Polyps (N=3402)	356 (12.9%)	96 (15.0%)	0.146
FEV1 (% Predicted, N=3143)	69.6 (22.6)	64.8 (21.2)	<0.001
FVC (% Predicted, N=3091)	85.1 (19.2)	80.2 (20.3)	<0.001
KCO (% Predicted, N=1372)	98.1 (29.5)	98.1 (17.6)	0.981
Blood Eosinophil Count (10^9/L, N=3295)	0.30 (0.13,0.56)	0.39 (0.20,0.60)	<0.001
Highest Ever Blood Eosinophil Count (10^9/L, N=3129)	0.60 (0.33,0.97)	0.60 (0.40,0.92)	0.443
FeNO (ppb, N=2864)	34.0 (17.0,66.0)	41.0 (21.0,76.0)	<0.001
IgE (IU/mL, N=3193)	129 (41,389)	265 (97,646)	<0.001
ACQ6 Score (N=2995)	2.9 (1.4)	3.1 (1.4)	0.001
Uncontrolled Asthma (ACQ6>1.5, N=2995)	1,936 (80.8%)	505 (85.2%)	0.015
Exacerbations in the Last Year (N=3226)			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%)	
Any ED Attendance (Last Year, N=3127)	1,065 (42.0%)	302 (51.0%)	<0.001
Any Hospital Admissions (Last Year, N=3274)	1,027 (38.6%)	268 (43.5%)	0.026
Maintenance OCS (N=3310)	1,292 (48.0%)	249 (40.2%)	<0.001
Maintenance OCS (mg), N=1518)	10 (5,15)	10 (5,13)	0.060
ICS Dose (BDP equivalent [µg], N=3066)	2000 (1600,2000)	2000 (1600,2000)	0.162
SABA (N=3290)	2,524 (94.4%)	577 (93.8%)	0.608
Leukotriene Receptor Antagonists (N=3232)	1,351 (51.5%)	301 (49.6%)	0.404
Treatment Adherent (N=2737)	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 OPCRD

	White (n=13,256)	Ethnic Minority Group (n=680)	P-value
Age (Years, N=13936)	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%)	
Gender (N=13936)			0.028
Female	9,033 (68.1%)	436 (64.1%)	
Male	4,223 (31.9%)	244 (35.9%)	
Ethnicity (N=13936)			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%)	
BMI (Kg/M^2, N=11939)	29.6 (6.6)		<0.001
Alcohol Consumption (Weekly Units, N=8695)	2.0 (0.0,8.0)	0.0 (0.0,0.0)	<0.001
Smoking Status (N=13601)			<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%)	
IMD Decile (N=13851)			<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%)	
Comorbidities (N=13936)			
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
Atopic Disease (N=13936)	2,342 (17.7%)	179 (26.3%)	<0.001
Peak Flow (% Predicted, N=8116)	81.6 (66.2,95.6)	72.9 (57.1,88.3)	<0.001
Blood Eosinophils (10^9/L, N=7087)	0.20 (0.11,0.33)	0.24 (0.13,0.40)	0.019

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

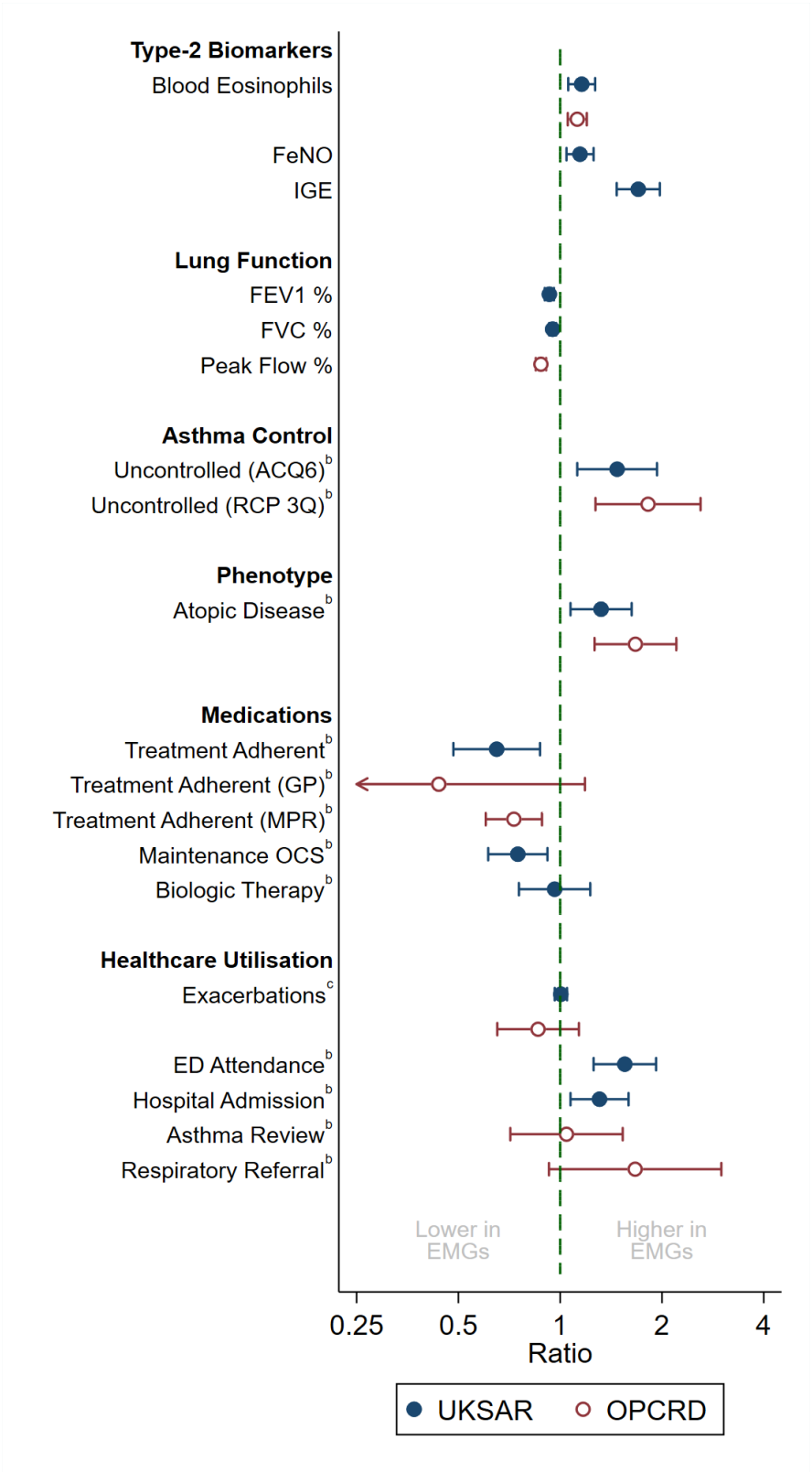
Abbreviations: BMI: body mass index, RCP 3Q: Royal College of Physicians 3 Questions; ICS: inhaled corticosteroid; BDP: beclometasone dipropionate; SABA: Short-acting beta-agonist; MPR: medicine possession ratio

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. [b] Odds Ratio, [c] Rate Ratio

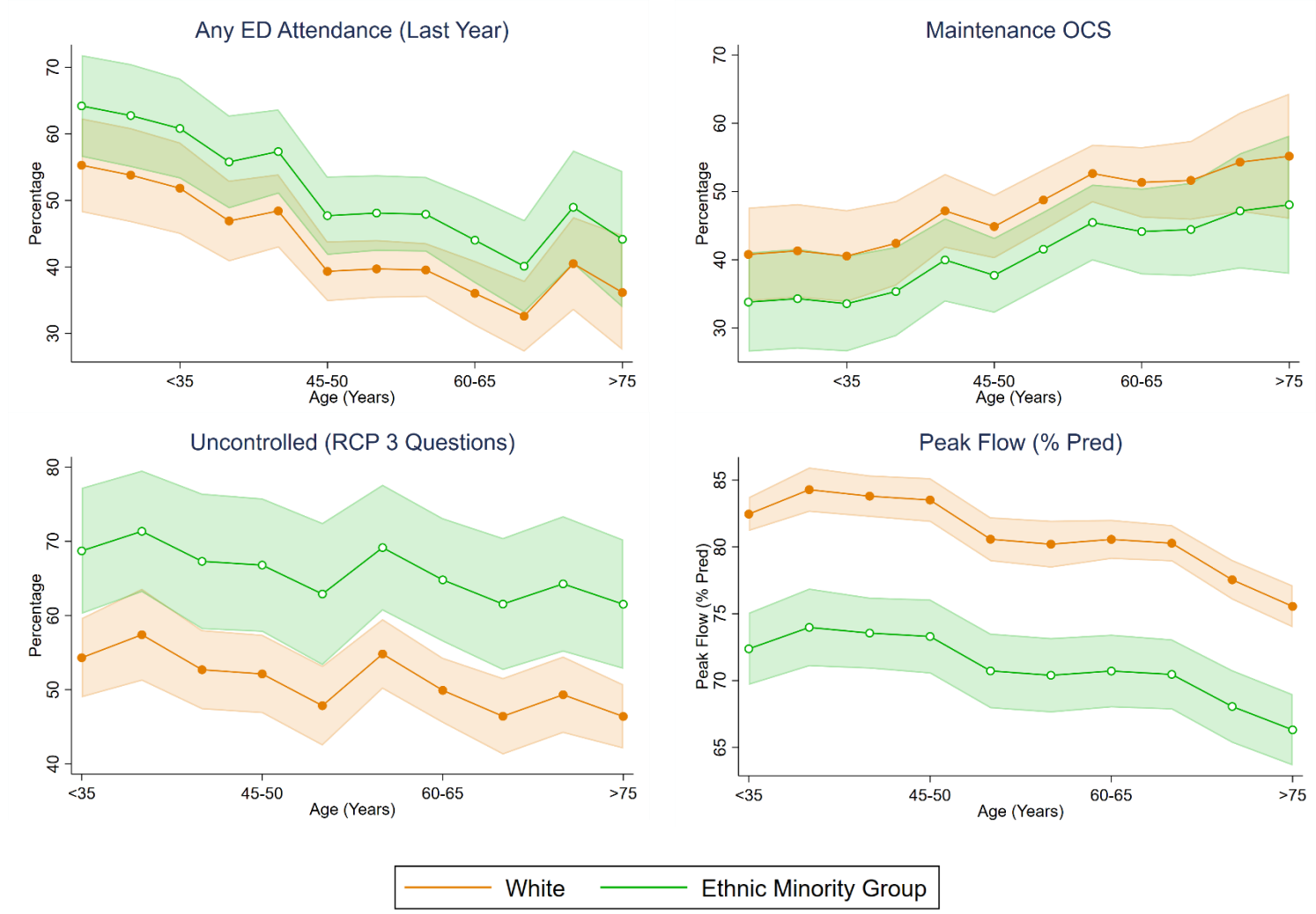
Figure 2: Model-based predications of selected outcomes in the UKSAR and OPCRD analysis for White and ethnic minority group patients with severe asthma. Shaded area is 95% confidence interval.

Figure 1: Summary of multivariate regression results in the UKSAR and OPCRD comparing White and ethnic minority group severe asthmatics[a]



[a] Adjusting for hospital, year seen, age (5 year groups) and gender
[b] Odds Ratio
[c] 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/µl and recent systemic OCS exposure (≥4 rescue steroids in the previous year or mOCS use)[48]. 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, FEV_1<80% and within the IgE/weight prescribing range.[49]

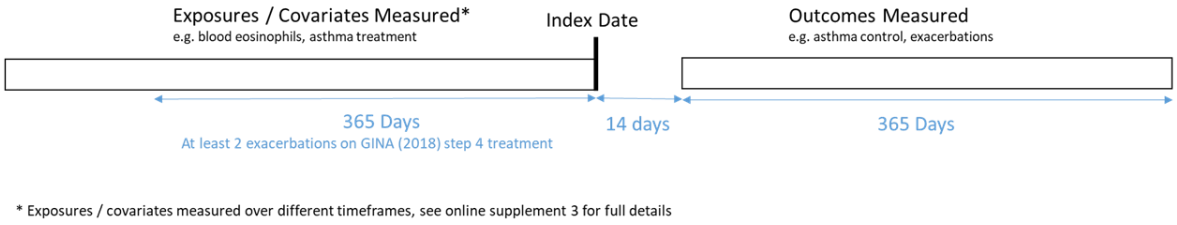
OPCRD Study Population

From the OPCRD 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 (≥2 exacerbations within a year) on step 4 treatment or who require maintenance oral corticosteroids (OCS) to achieve control.[18] 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.[50] 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.[51] 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 OPCRD 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.[52] 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 OPCRD (post-2008) we repeated our analysis of the OPCRD restricting to patients meeting the uncontrolled severe asthma definition after 1st January 2014. Lastly, we repeated our analysis comparing outcomes between White patients and those form each individual ethnicity (Asian, Black, Mixed and Other) to explore if important differences existed.

We conducted a further analysis within the OPCRD 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 (±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

Ethnicity	Read Code Description	Read Code
White	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
Mixed	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
Asian	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
Black	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
Exposures			
Ethnicity	Read codes were grouped in five categories: White, Asian (including Asian British), Black (including Black British), Chinese and Mixed (see **Error! Not a valid result for table.**). 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
Outcomes			
Asthma Control	Measured using the Royal College of Physicians 3 questions [53]. 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
Asthma Exacerbation	Read code indicating an 'Asthma Exacerbation' or 'Asthma Attack, prescription of acute oral corticosteroids (OCS), or a lower respiratory infection requiring antibiotics. We applied an algorithm based on number of days medication given, strength of tablet, diagnosis codes recorded during the prescribing visit, dosing instruction and frequency of OCS prescription to differentiate 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
Asthma Review	Read code list recognised within the Quality and Outcomes Framework: Asthma annual review (Read code: XaIeq), Asthma follow-up (XaIer), Asthma monitoring by nurse (XaIu5), Asthma monitoring by doctor (XaIu6), Asthma medication review (XaIfK) or Asthma monitoring check done (XE2Nb).	1 year from start of FUP	1 year before referral
Blood Eosinophil Count	Blood eosinophil count measured in cells per litre (10^9/L).	1 year from start of FUP	1 year before referral
Peak Flow	Percent predicted values were calculated using raw measurements and the formula specified by Knudson et al. [51] 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
Respiratory Referral	Read code for respiratory referral (Read Codes: XaAfm, XaAcS, XaAfl)	1 year from start of FUP	N/A
Treatment Adherence (GP)	Using Read Codes and based on clinical impression	1 year from start of FUP	1 year before referral

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

Table E3: Summary of asthma treatments by GINA (2018) Step[a]

GINA (2018) treatment step	Asthma treatment
Step 1	only β-agonist OR only muscarinic agonist
Step 2	low dose ICS without other controllers OR LTRA without other controllers OR low dose theophylline all without other controllers
Step 3	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)
Step 4	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 ≥3 controllers (without ICS)
Step 5	Maintenance OCS plus any other asthma treatment

[a]ICS: inhaled corticosteroid; LABA: long-acting β2-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[a]

Variable	N	Univariate		Multivariate		Multiple Imputation	
		Ratio (95% CI)	P-value	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value
Type-2 Biomarkers							
Blood Eosinophil Count (10^9/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
Lung Function							
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
Asthma Control							
Uncontrolled Asthma (ACQ6>1.5)[b]	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
Phenotype							
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
Medications							
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[b]	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		
Healthcare Utilisation							
Exacerbation[c]	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)[b]	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)[b]	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

[a]Adjusting for hospital, year seen, age (5 year groups) and gender

[b]Odds Ratio

[c] Rate Ratio

Table E5: Multivariate analysis comparing ethnic minority group to White patients in the OPCRD[a]

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
Type-2 Biomarkers									
Blood Eosinophils (10^9/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
Lung Function									
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
Asthma Control									
Uncontrolled (RCP 3Q)[b]	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
Phenotype									
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
Medications									
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
Healthcare Utilisation									
Exacerbations[c]	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

[a] Adjusted for year, age (5 year groups) and gender

[b] Odds Ratio

[c] Rate Ratio

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

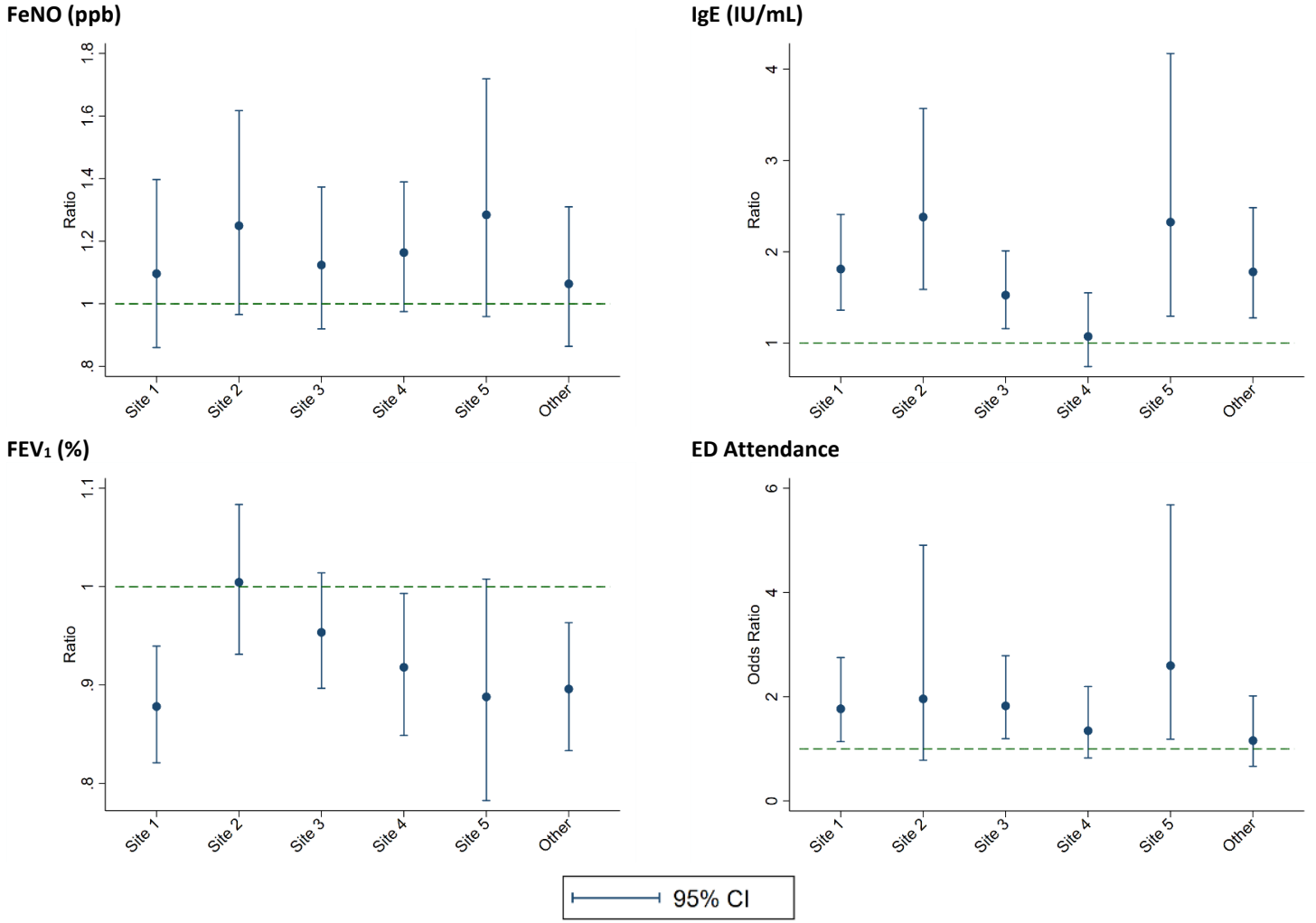


Figure E2: Multivariate analysis comparing biomarkers of ethnic minority group to White patients in the UKSAR with sequential adjustment

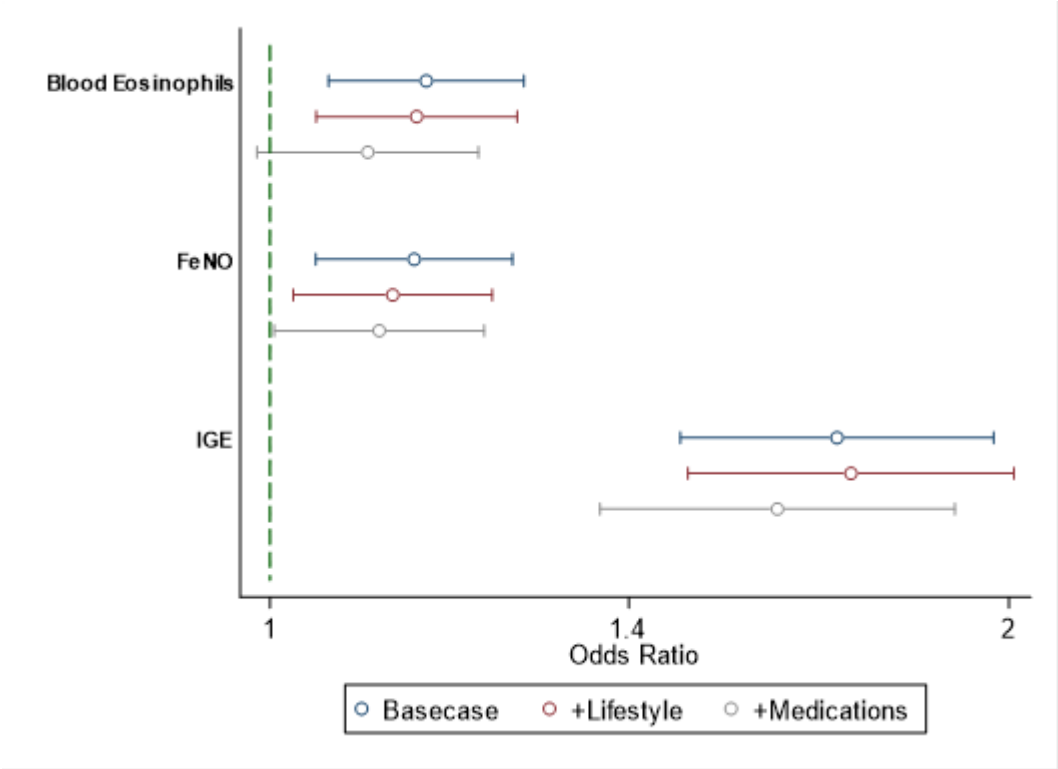


Table E6: Comparison of patients with a respiratory referral (cases) to those with no respiratory referral (controls) in OPCRD

	Controls (n=6,541)	Cases (n=1,426)	P-value
Age (Years, N=7967)	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%)	
Gender (N=7967)			0.967
Female	4,129 (63.1%)	901 (63.2%)	
Male	2,412 (36.9%)	525 (36.8%)	
Ethnic Minority Group (N=5593)	255 (5.5%)	75 (7.7%)	0.008
BMI (Kg/M^2, N=7075)	29.1 (6.2)	29.3 (6.5)	0.292
Alcohol Consumption (Weekly Units, N=5192)	2.0 (0.0,10.0)	1.0 (0.0,8.0)	<0.001
Smoking Status (N=7875)			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%)	
IMD Decile (N=7947)			<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%)	
Comorbidities (N=7967)			
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
Atopic Disease (N=7967)	883 (13.5%)	192 (13.5%)	0.972
Peak Flow (% Predicted, N=5803)	87.9 (73.8,100.5)	80.4 (64.9,93.6)	<0.001
Blood Eosinophils (10^9/L, N=3742)	0.20 (0.10,0.30)	0.20 (0.10,0.32)	0.459
Uncontrolled (RCP 3Q, N=4717)	1,486 (39.4%)	630 (66.6%)	<0.001
Exacerbations (N=7967)	0.0 (0.0,1.0)	1.0 (0.0,2.0)	<0.001
Any Exacerbations (N=7967)	1,967 (30.1%)	805 (56.5%)	<0.001
Asthma Review (N=7967)	4,925 (75.3%)	1,230 (86.3%)	<0.001
Treatment Adherent (Clinical Impression, N=944)	710 (91.3%)	154 (92.8%)	0.526
Treatment Adherent (MPR≥70%, N=7272)	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
Ethnic Minority Group	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
Smoking Status							
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
Comorbidities[a]							
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
Peak Flow (%)							
<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
Uncontrolled (RCP 3Q)	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
Any Exacerbations	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[a]

Variable	N	Univariate		Multivariate		Primary Analysis (Multivariate)	
		Ratio (95% CI)	P-value	Ratio (95% CI)	P-value	Ratio (95% CI)	P-value
Type-2 Biomarkers							
Blood Eosinophils (10^9/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
Lung Function							
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
Asthma Control							
Uncontrolled (RCP 3Q)[b]	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
Phenotype							
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
Medications							
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
Healthcare Utilisation							
Exacerbations[c]	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

[a] Adjusted for year, age (5 year groups) and gender

[b] Odds Ratio

[c] Rate Ratio

Table E9: Multivariate analysis comparing individual ethnicities to White patients in the UKSAR[a]

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
Type-2 Biomarkers								
Blood Eosinophil Count (10^9/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
Lung Function								
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
Asthma Control								
Uncontrolled Asthma (ACQ6>1.5)[b]	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
Phenotype								
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
Medications								
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[b]	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
Healthcare Utilisation	0.92 (0.86,0.97)	0.002	1.15 (1.05,1.26)	0.002	1.19 (1.03,1.38)	0.018	1.05 (0.99,1.12)	0.130
Exacerbation[c]	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)[b]	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)[b]	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

[a] Adjusted for year, age (5 year groups) and gender

[b] Odds Ratio

[c] Rate Ratio

Table E10: Multivariate analysis comparing individual ethnicities to White patients in the OPCRD[a]

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
Type-2 Biomarkers								
Blood Eosinophils (10^9/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
Lung Function								
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
Asthma Control								
Uncontrolled (RCP 3Q)[b]	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
Phenotype								
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
Medications								
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
Healthcare Utilisation								
Exacerbations[c]	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

[a] Adjusted for year, age (5 year groups) and gender

[b] Odds Ratio

[c] Rate Ratio