EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original research article

Benefits of specialist severe asthma management: demographic and geographic disparities

Charlene Redmond, Liam G. Heaney, Rekha Chaudhuri, David J. Jackson, Andrew Menzies-Gow, Paul Pfeffer, John Busby

Please cite this article as: Redmond C, Heaney LG, Chaudhuri R, *et al*. Benefits of specialist severe asthma management: demographic and geographic disparities. *Eur Respir J* 2022; in press (https://doi.org/10.1183/13993003.00660-2022).

Title: Benefits of specialist severe asthma management: demographic and geographic disparities

Authors: Charlene Redmond [1], Liam G. Heaney [1,2], Rekha Chaudhuri[3], David J. Jackson [4,5], Andrew Menzies-Gow [6], Paul Pfeffer [7], John Busby [1] on behalf of the UK Severe Asthma Registry

Affiliations:

[1] School of Medicine, Dentistry and Biomedical Sciences, Queen's University, Belfast, UK

[2] Belfast Health & Social Care NHS Trust, Belfast, UK

[3] Gartnavel General Hospital, Glasgow, UK

[4] Guy's Severe Asthma Centre, Guy's and St Thomas' Hospitals, London, United Kingdom

[5] School of Immunology & Microbial Sciences, King's College London, United Kingdom

[6] Royal Brompton and Harefield Hospitals, London, UK

[7] Barts Health NHS Trust, London, UK

Correspondence: John Busby, Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen's University, Belfast, UK. Tel: +44 28 9097 6019. Email: john.busby@qub.ac.uk

Take home message: Specialist assessment and management of patients with severe asthma leads to substantially improved patient outcomes, which are broadly consistent across demographic groups although vary substantially across hospitals.

Abstract

Introduction: The benefits of specialist assessment and management have yet to be evaluated within the biologic era of UK severe asthma treatment, and potential disparities have not been considered.

Methods: In an uncontrolled before-and-after study, we compared asthma symptoms (asthma control questionnaire [ACQ6]), exacerbations, unscheduled secondary care use, lung function (FEV_1) and oral corticosteroid (OCS) dose after one year. We compared outcomes by sex, age (18-34, 35-49, 50-64, 65+ years), ethnicity (Caucasian vs. Non- Caucasian) and hospital site after adjusting for demographics and variation in biologic therapy use.

Results: 1,140 patients were followed-up for 1,370 person-years from twelve specialist centres. At annual review, ACQ6 score was reduced by a median of 0.7 (IQR:0.0, 1.5), exacerbations by 75% (IQR: 33%, 100%) and unscheduled secondary care by 100% (IQR:67%, 100%). FEV_1 increased by a median of 20ml (IQR:-200, 340) while OCS dose decreased for 67% of patients. Clinically meaningful improvements occurred across almost all patients, including those not receiving biologic therapy. There was little evidence of differences across demographic groups, although those aged over 65 demonstrated larger reductions in exacerbations (69% vs. 52%; $p<0.001$) and unscheduled care use (77% vs. 50%; $p<0.001$) compared to patients aged under 34 years. There were more than 2-fold differences between the best and worst performing centres across all study outcomes.

Conclusions: Specialist assessment and management is associated with substantially improved patient outcomes which are broadly consistent across demographic groups, and are not restricted to those receiving biologic therapy. Significant variation exists between hospitals which requires further investigation.

Introduction

Asthma is a heterogeneous respiratory disease estimated to affect over 330 million people worldwide [1], with around 5% of these having severe disease [2]. Severe asthma is defined as asthma that remains uncontrolled despite patient adherence to optimized therapies (high dose inhaled corticosteroids, long-acting beta-agonists, and the treatment of contributory factors) or asthma which worsens when high dose treatment is reduced/stepped down [3]. The British Thoracic Society (BTS), European Respiratory Society (ERS) and American Thoracic Society (ATS) have highlighted the need for patients with difficult or severe asthma to be systematically evaluated by specialists [4, 5]. Within the UK, care for patients with severe asthma is currently provided by specialists based within regional centres.

There has been much interest investigating the benefits of specialist assessment and management since it was recommended for difficult to control asthma over thirty years ago [6]. Studies in the USA, France, Australia and the Netherlands [7-13] have demonstrated that specialist assessment can lead to improved asthma control, reduced exacerbations and a lowering of maintenance oral corticosteroid dose (mOCS) dose. These findings have been replicated within several UK-based studies and, most recently, Gibeon et. al demonstrated that dedicated severe asthma centres led to a significant improvement in asthma symptoms (median ACQ from 3.4 to 2.8), a reduction in the proportion of patients admitted to hospital (48% vs. 38%) and a lowering of mOCS dose (15mg vs. 10mg) [14]. Crucially, only 12% of this study cohort were receiving biologic therapy as this analysis used data collected from patients registered during 2009 and 2010. Recent evidence from the UK and elsewhere has highlighted potential disparities in asthma morbidity based on patient's gender, ethnicity and socioeconomic status [15-18]. However, the moderating impact of demographic and geographic factors on outcomes among those treated in specialist asthma centres has yet to be assessed. Consequently, an updated analysis is required to estimate the benefits of specialist assessment for people with severe asthma in the 'biologic-era', and to assess if these benefits are observed equally across patient groups.

The primary aim of this study is to estimate the benefits of specialist assessment of patients with severe asthma. As a secondary objective we investigate if these benefits are observed equally across patient groups and seek to identify evidence of unmet need.

Methods

Study population and design

The UK Severe Asthma Registry (UKSAR) collects standardised data on patients with severe asthma that have been referred to specialist services in England, Scotland, and Northern Ireland. Variables contained within the dataset include demographic characteristics, patient medical history, current treatment regimes, lung function and inflammatory biomarkers. Further details about the registry can be found elsewhere [19, 20]. The UKSAR has database ethical approval from the Office of Research Ethics Northern Ireland (15/NI/0196) and all patients provide written informed consent. All patients in this analysis were first seen between 2016-2020 and assessed as meeting ERS/ATS severe asthma guidelines [19]. Patients were included if they were aged 18 or older at first assessment, had at least one annual review (within 9 to 24 months of their baseline assessment), and were not receiving biologic therapy at the time of their baseline assessment. This was an uncontrolled before-and-after study.

Exposures, outcomes, and covariates

Comparisons were made between the baseline and first annual review visit. The outcomes of interest were ACQ6 improvement, exacerbation reduction (%), reduction in unscheduled care utilisation (%), FEV_1 improvement (measured in millilitres) and OCS discontinuation (%). Exacerbation reduction compared the number of times the patient required rescue corticosteroids in the 12 months prior to baseline against the 12 months prior to the annual review visit. Unscheduled care reduction was also based on the 12 months prior to the relevant study visit, and was a composite measure of ED attendances and hospital admissions. The OCS discontinuation outcome was restricted to patients on maintenance OCS at baseline, and was defined as not receiving any maintenance OCS at the time of their annual review. We created a composite measure to quantify the distribution of improvements across patients. Patients were categorised according to the number of domains in which they had a material improvement in over the study period: asthma symptoms (ACQ improvement ≥0.5 or well controlled [ACQ <0.75] at annual review); exacerbations (reduction ≥50% or no exacerbations in the 12 month prior to annual review); unscheduled care (reduction ≥50% or no unscheduled care in the 12 month prior to annual review); FEV_1 (≥100ml improvement); OCS (dose reduction ≥50% or not a mOCS user at annual review).

Our secondary objective compared improvement across groups based on age (18-34, 35-49, 50-64, 65+ years), sex (female vs. male) and ethnicity. The ethnicity of patients in the UKSAR is recorded according to Global Lung Initiative criteria, although to increase statistical power in the current study,

we made comparisons between Caucasian (White) and non-Caucasian (Southeast Asian, Northeast Asian, African, mixed, and other) patients [16]. We compared improvements by biologic prescription and assessed the reason for patients not progressing to biologic therapy by applying current National Institute for Health and Care Excellence (NICE) access criteria which are used across the UK. We also compared outcomes among hospitals to explore geographic variation. To ensure an acceptable level of precision around the hospital-specific estimates, sites were only included in this analysis if they had at least 30 eligible patients in the analysis. Consequently, each analysis had a different number of hospitals included.

Statistical analyses

Our primary analyses compared the change in study outcomes between baseline and first annual review. Descriptive statistics were calculated using means (standard deviation [SD]), medians (inter quartile ranges [IQR]) and counts (percentages) as appropriate. Differences in characteristics between patients that did, or did not, receive biologic treatment were tested for statistical significance using chi-square tests, t-tests and Wilcoxon-Mann-Whitney tests as appropriate.

For our secondary objective we used hierarchical linear (ACQ6 score, FEV_1), Poisson (exacerbations, unscheduled care) and logistic (OCS discontinuation) regression analysis to compare improvements by age, sex, ethnicity and hospital site. Adjusted models included time-period (follow-up vs. annual review), year of baseline visit, hospital, age, sex, ethnicity, biologic prescription prior to annual review, and baseline value of the metric (e.g., baseline ACQ score, baseline OCS dose). Each patient was included as a random-intercept in the model which allowed their responses to vary, and appropriately accounted for the non-independence of observations. Crucially, our models included an interaction term between time-period and each candidate demographic / geographic variable, which captured variation in improvement across the groups of interest. Model coefficients were converted to adjusted predictions which represent the improvement in each group of interest, assuming all other variables in the model were fixed [21]. All analyses were conducted under a complete-case framework using STATA 16 (StataCorp, College Station, TX, USA).

Sensitivity analyses

We re-ran our regression models omitting the biologic therapy variable to investigate the importance of differing biologic prescription pattern across demographic groups in driving potential disparities. Recent evidence has shown that a substantial proportion of patients experience adrenal insufficiency

when tapering their mOCS dose [22], therefore we repeated our analysis classifying OCS discontinuance as complete withdrawal of mOCS or remaining on 5mg or less at annual review.

Results

Patient characteristics

1,140 patients were followed-up for 1,370 person-years from twelve specialist centres. The median time between their baseline and annual review visit was 406 days (IQR; 363-497 days). Data completeness was generally good, although a lower percentage of patients had FEV_1 (83.8%) and ACQ6 (81.5%) available at follow-up (Table E1). The majority of our patient cohort were female (61.1%), with an average age at first assessment of 50.6 years. Most patients were Caucasian (80.4%) and had never smoked (67.7%). At baseline, patients exhibited substantial morbidity, including high symptom burden (median ACQ6: 3.0; IQR: 2.0, 4.0), impaired lung function (mean FEV_1 66.6% predicted) and frequent exacerbations in the prior year (median: 5; IQR: 3, 8). A substantial proportion of patients attended ED (38.9%) and/or were hospitalised (38.8%) for their asthma in the year prior to assessment. Biomarkers of type-2 inflammation including blood eosinophils (0.40 $N/10^9L$), FeNO (41 ppb) and IgE (154 IU/mL) were frequently elevated at time of registration. Over half of patients (56.3%) were receiving maintenance OCS at baseline (median dose 10mg), whilst the majority (81.3%) progressed to biologics by the time of their annual review visit (Table 1). Four different biologic therapies were prescribed to patients in this cohort, with the majority receiving Mepolizumab (65.7%), Benralizumab (19.7%) or Omalizumab (14.4%) (Table 1). Over 40% of those who did not receive biologic therapy failed to meet the UK access criteria set by NICE. Of the remainder, 47% required optimisation of current treatment and 33% had issues with medication adherence.

Benefits of specialist severe asthma assessment and management

There were significant improvements achieved across all study outcomes. In particular, the median ACQ6 score was reduced by 0.7 (IQR: 0.0, 1.5), exacerbations reduced by 75% (IQR: 33%, 100%) and unscheduled care reduced by 100% (IQR: 67%, 100%). mOCS dose was reduced in the majority of patients (67%), and for some patients (20.2%) was discontinued altogether, however limited changes were noted for FEV_1 (median increase 20ml [IQR: -200ml, 340ml]) (Table 2). A median reduction of 80% (IQR: 28%, 98%) in blood eosinophils was achieved among patients receiving a biologic compared to no change among those who were not (median reduction: 0%; IQR:-68%, 50%). Almost all (97.3%) patients had a material improvement in at least one study outcome, and the median improvement

was 3 outcomes (IQR: 2, 4). A substantial minority of patients (15.5%) experienced an improvement across all five outcomes (Table 2 & Figure E1).

We observed greater improvement among those receiving biologics. In particular, they experienced a larger reduction in symptoms (ACQ6 improvement 0.8 vs. 0.3, p<0.001) and exacerbations (75% vs. 54% reduction, p<0.001). A larger proportion of the patients on biologics discontinued their mOCS (20.8% vs. 16.0%, p=0.003) compared to those not receiving biologics. A much larger proportion of the biologic patients also experienced material improvement across all five domains (17.3% vs. 6.3%, p<0.001) compared to the non-biologic cohort (Tables 1 & 2; Figure E1). However, it is important to note that clinically important benefits were still observed among a substantial proportion of patients who did not receive a biologic, with over half (57.6%) showing material improvement across at least 3 domains.

Potential disparities by demographic factors

In general, considerable benefits were observed across all demographic groups, with little evidence of substantial differences after accounting for potential confounders (Figure 1). At the population level, all groups had a *minimum* ACQ6 decrease of 0.6, 50% reduction in exacerbations and unscheduled care, 55ml increase in FEV_1, and a 18% OCS discontinuance rate. However, we did observe some potentially important differences between groups. Females achieved a larger ACQ6 improvement compared to males (0.87 vs. 0.61; p=0.004), although this trend was reversed in exacerbation reduction (57% vs. 64%; p=0.001). Variation was also observed by age category, with patients aged over 65 demonstrating larger reductions in exacerbations (69% vs. 52%; p<0.001) and unscheduled care use (77% vs. 50%; p<0.001) when compared to those aged 18 to 34 years (Figure 1; Table E2). Importantly, this larger improvement among the older-aged patients was observed despite substantially reduced exacerbation and health care utilisation at baseline (Table E3).

Potential disparities by centre

Improvements were observed across all sites; however, the magnitude of these improvements differed substantially, even after adjustment for covariates (Figure 2). For example, although seven out of eight sites achieved a mean ACQ6 improvement in excess of 0.5, the improvements ranged from 1.39 (CI: 1.01, 1.77) to 0.33 (95% CI: -0.16, 0.81) between the best and worst performing hospitals (p=0.002). Similar trends were observed for reductions in exacerbations and unscheduled care use where, despite substantial improvements across all hospitals of at least 35%, 2-fold differences persisted. Substantial variation was also observed in the proportion of patients discontinuing

maintenance OCS, ranging from 11% (95% CI: 7, 16) in the lowest hospital to 37% (95% CI: 23, 51) in the highest ($p<0.001$).

Sensitivity analyses

Omitting biologic therapy use from our models led to small changes in estimates and did not alter our conclusions (Table E2). A much larger proportion (48.4%) of patients met our expanded definition of OCS discontinuance, which included those receiving 5mg or less at follow-up, however there was no variation by demographic groups and the magnitude of inter-hospital variation was similar to our primary analysis (Figure E2).

Discussion

This large study of 1,140 severe asthma patients demonstrates that assessment and management by severe asthma specialists leads to substantial benefits for the majority of patients, including reduced symptoms, healthcare utilisation and maintenance oral corticosteroid dose. Benefits were greater among those receiving biologics, however, we also observed clinically meaningful improvement among the majority of patients who did not receive these medications. The magnitude of benefits were generally consistent across demographic groups, however there was some evidence of a larger improvement among older-aged patients. Significant variation existed across hospital sites for all outcomes.

The British Thoracic Society, European Respiratory Society and American Thoracic Society have highlighted the need for patients with difficult or severe asthma to be systematically evaluated by specialists [4, 5]. There are several potential benefits of this approach including confirmation of diagnosis, identification of the mechanism driving symptoms, and assessment of adherence to maintenance medications. Although there is no standardised pathway, assessment may lead to a broad range of potentially effective interventions including changes to treatment regimen, adherence counselling, psychological therapy, physiotherapy referral, or biologic therapy initiation. Our findings that specialist assessment is associated with substantially improved outcomes highlights the importance of appropriate referral from primary and secondary care, particularly as biologic therapies can only be prescribed by specialists within the UK. In that context, recent evidence demonstrating that a large number of patients with potential severe asthma are hidden within UK primary care is concerning [23].

Our findings are consistent with other evidence from the USA, France, Australia and the Netherlands [7-13] which have demonstrated that specialist assessment can lead to improved asthma control, reduced exacerbations and a lowering of mOCS dose. Our results are also in broad agreement with evidence from the UK [24, 25], including within the most recent study by *Gibeon et al* [14] which used data collected from UK severe asthma centres between 2009 and 2010. However, we reported a larger improvement in median ACQ6 score (1.0 vs. 0.6), and a lower proportion of patients with an exacerbation (66% vs 77%) or hospital admission (17% vs. 33%) in the year prior to follow-up. Whilst the study by *Gibeon et al* did not report any reduction in median blood eosinophil level at follow-up, we reported median reductions of 73% across the cohort, driven by 80% reductions among those receiving biologics, which suggests that these advances are likely driven by a reduction in type-2 inflammatory pathways due to the widespread use of anti-IL5 and anti-IL5R biologic therapy.

Our finding that improvements were observed similarly across demographic groups is reassuring, particularly given recent findings of substantially higher asthma morbidity among ethnic minority groups presenting to UK severe asthma services [16]. There was some evidence that older patients had a larger reduction in exacerbations and unscheduled care utilisation than younger patients. The reasons for this remain unclear, however it does not appear to be related to higher healthcare utilisation at baseline. It is known that adherence often deteriorates after biologic commencement, which can reduce the effectiveness of these medications [26]. It may be that older patients, who are known to have better adherence across all severities of asthma, are less susceptible to this phenomenon [27]. Differences in asthma phenotype have also been related to treatment response and, naturally, the early onset phenotype is likely to be more prevalent among younger adults referred to specialist clinics [28, 29].

Our findings of geographic variation in asthma outcomes requires further investigation. It has been shown elsewhere that the patients presenting to these centres vary substantially in terms of demographic and clinical characteristics [30], however, it is unlikely that this is driving all of the differences observed in our study, and may instead reflect regional differences in referral practices or care pathways. In particular, wide variation in mOCS discontinuation rates may reflect differences in local protocols or variation in biologic prescribing patterns. It should be noted that our data was collected before publication of the PONENTE study, which demonstrated the effectiveness of a personalised dosage-reduction algorithm among patients initiating benralizumab, and might be expected to change mOCS tapering practices going forwards [22]. The UK Severe Asthma Registry was established to provide data which would support quality improvement in severe asthma management. In response to potential variation among patient outcomes, the UK severe asthma community continues to undertake initiatives which share best-practice amongst service providers [31].

Our study is novel, being first to investigate potential disparities in specialist severe asthma care outcomes, and is at least three times larger than other similar analyses. It is the first to investigate this issue within the 'biologic era' of UK severe asthma treatment, and uses real-world data from the majority of specialist severe asthma centres in the UK. The primary weakness of our study is the lack of a comparison group meaning that some of the improvements observed in our study could be due to regression to the mean [32]. However, due to the magnitude and consistency of the effects observed we do not think this statistical phenomenon is the primary driver of our results. A randomized controlled trial is required to fully address this issue, however, given the consensus that

specialist assessment of severe asthma is beneficial, this is unlikely to be ethically viable. It is unclear if our results can be generalised to countries outside the UK due to significant heterogeneity between severe asthma populations and treatment patterns worldwide [33, 34].

In conclusion, specialist assessment and management leads to substantially improved patient outcomes, which are broadly consistent across demographic groups and are not restricted to those receiving biologic therapy. The magnitude of these improvements are larger than those observed in previous studies of UK severe asthmatics, which is likely mediated by a reduction in type-2 inflammatory pathways due to the widespread use of anti-IL5 and anti-IL5R biologic therapy. Significant variation was observed between hospitals, which requires further investigation.

Declarations

CR & JB declare no competing interests.

LGH is Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma which involves industrial partnerships with a number of pharmaceutical companies.

AMG has consultancy agreements with Astra Zeneca and Sanofi, he is participating in research funded by Astra Zeneca, he has received lecture fees from Teva, Astra Zeneca, Novartis and Sanofi attended advisory boards for Novartis, Sanofi, Glaxo SmithKline, Astra Zeneca and Teva and attended international conferences with Teva.

DJJ has received advisory board and speaker fees from AstraZeneca plc, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline plc, Napp Pharmaceuticals Limited, Novartis International.

PEP has attended advisory board for AstraZeneca, GlaxoSmithKline and Sanofi; 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.

RC has received lecture fees from GSK, AstraZeneca, Teva, Chiesi, Sanofi and Novartis; honoraria for Advisory Board Meetings from GSK, AstraZeneca, Teva, Chiesi, Novartis; sponsorship to attend international scientific meetings from Chiesi, Napp, Sanofi and GSK and a research grant to her Institute from AstraZeneca for a UK multi-centre study.

Acknowledgements

We thank the UKSAR Steering committee for access to the UKSAR dataset, along with their helpful comments in guiding our research.

Support statement

This work was supported by a PhD studentship from the Department for the Economy (DfE), Northern Ireland, awarded to Charlene Redmond.

Collaborators

Dr Thomas Brown, Portsmouth Hospitals NHS Trust; Dr Mitesh Patel, University Hospitals Plymouth NHS Trust; Dr Hassan Burhan, Liverpool Royal Hospital NHS Foundation Trust; Dr James Dodd, Southmead Hospital; Prof Salman Siddiqui, Glenfield Hospital; Dr Simon Doe, Newcastle Upon Tyne Hospitals NHS Foundation Trust; Dr Deepak Subramanian, Royal Derby Hospital.

Tables and Figures

Table 1 – Baseline patient characteristics, presented for both the entire cohort as well as stratified by biologic treatment

	Entire Cohort	Received Biologic		P-value
		No	Yes	
Number of Patients	1,140	213	927	
Age At First Assessment (Years)	50.6 (14.6)	48.2 (14.7)	51.1 (14.5)	0.010
Age of Onset (Years)	25.4 (19.3)	25.2 (19.2)	25.5 (19.3)	0.847
Gender				0.163
Female	696 (61.1%)	139 (65.3%)	557 (60.1%)	
Male	444 (38.9%)	74 (34.7%)	370 (39.9%)	
Ethnicity				0.002
Caucasian	913 (80.4%)	155 (72.8%)	758 (82.1%)	
Non-Caucasian	223 (19.6%)	58 (27.2%)	165 (17.9%)	
BMI (kg/m^2)	30.7 (7.1)	30.9 (7.7)	30.7 (6.9)	0.725
Smoking Status				0.004
Never smoked	756 (67.7%)	132 (62.6%)	624 (69.0%)	
Ex-smoker	321 (28.8%)	64 (30.3%)	257 (28.4%)	
Current smoker	39 (3.5%)	15 (7.1%)	24 (2.7%)	
Atopic Disease	628 (55.7%)	123 (58.3%)	505 (55.1%)	0.404
FEV_1 (L)	2.00 (0.78)	2.00 (0.73)	2.00 (0.79)	0.944
FEV_1 (% Predicted)	66.6 (21.0)	68.3 (20.9)	66.2 (21.0)	0.190
FVC (L)	3.15 (1.02)	3.02 (0.99)	3.18 (1.02)	0.034
FVC (% Predicted)	84.3 (18.9)	83.5 (18.8)	84.5 (18.9)	0.497
FEV_1/FVC	63.7 (18.5)	66.5 (12.4)	63.1 (19.5)	0.017
ACQ6 Score	3.0 (2.0,4.0)	3.0 (2.0,4.0)	3.0 (2.0,3.8)	0.702
Uncontrolled Asthma (ACQ6>1.5)	811 (82.2%)	161 (82.6%)	650 (82.1%)	0.872
EuroQoL Utility	0.73 (0.48,0.88)	0.73 (0.56,0.86)	0.73 (0.45,0.88)	0.674
Exacerbations (Prior Year)	5 (3,8)	4 (2,6)	5 (3,8)	<0.001
Any ED Attendance (Prior Year)	435 (38.9%)	98 (47.1%)	337 (37.0%)	0.007
Any Hospital Admissions (Prior Year)	437 (38.8%)	79 (37.4%)	358 (39.1%)	0.659
Invasive Ventilations (Ever)	117 (10.5%)	18 (8.7%)	99 (10.9%)	0.345
Eczema	27 (2.4%)	3 (1.4%)	24 (2.6%)	0.307
Nasal Polyps	211 (18.5%)	27 (12.7%)	184 (19.8%)	0.015
Gastro-oesophageal Reflux	207 (18.2%)	43 (20.2%)	164 (17.7%)	0.394
Depression or Anxiety	109 (9.6%)	23 (10.8%)	86 (9.3%)	0.496
Blood Eosinophil Count ($N/10^9L$)	0.40 (0.20,0.60)	0.30 (0.18,0.50)	0.40 (0.20,0.63)	<0.001
Highest Blood Eosinophil Count ($N/10^9L$)	0.68 (0.40,1.05)	0.55 (0.30,0.90)	0.70 (0.46,1.10)	<0.001
FeNO (ppb)	41 (22,73)	36 (19,62)	42 (24,75)	0.007
IGE (IU/mL)	154 (53,438)	147 (51,501)	155 (53,420)	0.866
mOCS	639 (56.3%)	81 (38.2%)	558 (60.5%)	<0.001
mOCS (prednisolone equivalent /mg)	10 (8,15)	10 (5,15)	10 (8,15)	0.049
ICS Dose (BDP equivalent/ug)	2000 (1600,2000)	2000 (1600,2000)	2000 (1600,2000)	0.005
LAMA	646 (57.4%)	104 (49.3%)	542 (59.2%)	0.008
Theophylline	279 (24.7%)	38 (18.0%)	241 (26.2%)	0.013
Leukotriene Receptor Antagonists	568 (51.2%)	120 (58.5%)	448 (49.5%)	0.019
Maintenance Macrolides	82 (7.4%)	10 (4.9%)	72 (7.9%)	0.128
Nebuliser	232 (20.7%)	38 (18.3%)	194 (21.3%)	0.335
Biologic Therapy	927 (81.3%)	0 (0.0%)	927 (100.0%)	N/A
Biological Therapy Medication				N/A
Mepolizumab	591 (65.7%)	0 (0.0%)	591 (65.7%)	
Benralizumab	177 (19.7%)	0 (0.0%)	177 (19.7%)	
Omalizumab	130 (14.4%)	0 (0.0%)	130 (14.4%)	
Dupilumab	2 (0.2%)	0 (0.0%)	2 (0.2%)	

Footnote: Abbreviations: FEV1 (Forced expiratory volume in the first second), FVC (Forced vital capacity), ACQ6 (Asthma Control Questionnaire 6), ED (Emergency Department), FeNO (Fractional exhaled nitric oxide), IGE (Immunoglobulin E), mOCS (Maintenance oral corticosteroids), ICS (Inhaled corticosteroids), LAMA (Long-acting muscarinic antagonists), SABA (Short-acting beta-agonists)

Table 2 – Patient characteristics at follow-up review, presented for both the entire cohort and stratified by biologic treatment (No/Yes)

	Entire Cohort	Received Biologic		P-value
		No	Yes	
Number of Patients	1,140	213	927	
Follow-up Time (Days)	406 (363,497)	413 (357,511)	405 (363,494)	0.586
BMI (kg/m^2)	31.1 (7.2)	31.4 (8.3)	31.0 (6.9)	0.465
Exacerbations (Prior Year)	1 (0,3)	2 (0,4)	1 (0,3)	0.129
0	371 (33.7%)	63 (31.2%)	308 (34.3%)	
1	205 (18.6%)	35 (17.3%)	170 (18.9%)	
2	152 (13.8%)	21 (10.4%)	131 (14.6%)	
3	109 (9.9%)	30 (14.9%)	79 (8.8%)	
4+	264 (24.0%)	53 (26.2%)	211 (23.5%)	
Any ED Attendance (Prior Year)	170 (15.6%)	43 (21.4%)	127 (14.3%)	0.012
Any Hospital Admissions (Prior Year)	187 (17.2%)	44 (21.8%)	143 (16.1%)	0.053
Blood Eosinophil Count (N/10^{9}L)	0.10 (0.01,0.23)	0.30 (0.15,0.50)	0.08 (0.00,0.19)	<0.001
FeNO (ppb)	36 (20,67)	33 (21,55)	36 (20,70)	0.362
FEV_1 (L)	2.10 (0.79)	2.06 (0.75)	2.11 (0.80)	0.458
FEV_1 (% Predicted)	70.3 (20.9)	70.6 (19.5)	70.3 (21.2)	0.871
FVC (L)	3.17 (1.03)	3.06 (1.03)	3.19 (1.03)	0.150
FVC (% Predicted)	84.9 (19.3)	84.0 (18.8)	85.2 (19.4)	0.497
FEV_1/FVC	66.4 (13.3)	67.9 (12.1)	66.1 (13.6)	0.115
ACQ6 Score	2.0 (0.8,3.3)	2.8 (1.5,3.8)	1.8 (0.8,3.2)	<0.001
Uncontrolled Asthma (ACQ6>1.5)	556 (59.8%)	112 (74.7%)	444 (57.0%)	<0.001
EuroQoL Utility	0.76 (0.49,0.92)	0.73 (0.43,0.88)	0.78 (0.50,0.94)	0.175
mOCS	587 (51.6%)	84 (39.6%)	503 (54.3%)	<0.001
mOCS (prednisolone equivalent/mg)	8 (5,13)	10 (5,10)	8 (5,13)	0.270
Difference from Baseline				
ACQ6 Score improvement	0.7 (0.0,1.5)	0.3 (-0.7,0.8)	0.8 (0.0,1.7)	<0.001
EuroQoL Utility	0.02 (-0.07,0.15)	0.01 (-0.09,0.12)	0.02 (-0.06,0.16)	0.306
Exacerbations (Prior Year)	-75.0 (-100.0,-33.3)	-54.2 (-100.0,0.0)	-75.0 (-100.0,-40.0)	<0.001
ED / Hospitalisation (Prior Year)	-100.0 (-100.0,-66.7)	-100.0 (-100.0,-25.0)	-100.0 (-100.0,-66.7)	0.030
Blood Eosinophil Count (N/109L)	-73.3 (-95.1,0.0)	0.0 (-50.0,67.9)	-80.0 (-97.7,-27.9)	<0.001
FeNO (ppb)	-8.0 (-41.4,43.5)	-5.7 (-34.4,30.8)	-8.6 (-42.2,49.4)	0.671
FEV_1 (ml)	20.0 (-200.0,340.0)	0.0 (-200.0,285.0)	30.0 (-200.0,350.0)	0.279
mOCS Change				0.003
Discontinue	129 (20.2%)	13 (16.0%)	116 (20.8%)	
Decrease Dose	301 (47.2%)	27 (33.3%)	274 (49.2%)	
Maintain Dose	148 (23.2%)	29 (35.8%)	119 (21.4%)	
Increase Dose	60 (9.4%)	12 (14.8%)	48 (8.6%)	
Clinically important differences				
ACQ Improvement	523 (62.5%)	59 (41.8%)	464 (66.7%)	<0.001
Exacerbation Reduction	746 (69.0%)	117 (60.0%)	629 (71.0%)	0.003
Unscheduled Care Reduction	915 (85.5%)	151 (77.0%)	764 (87.4%)	<0.001
FEV_1	402 (42.5%)	63 (37.5%)	339 (43.6%)	0.149
OCS	738 (64.9%)	143 (67.1%)	595 (64.4%)	0.450
Number of Positive Outcomes	3 (2,4)	3 (2,4)	3 (2,4)	<0.001
0	18 (2.7%)	1 (0.9%)	17 (3.0%)	
1	57 (8.4%)	14 (12.6%)	43 (7.6%)	
2	125 (18.4%)	32 (28.8%)	93 (16.4%)	
3	172 (25.4%)	31 (27.9%)	141 (24.9%)	
4	201 (29.6%)	26 (23.4%)	175 (30.9%)	
5	105 (15.5%)	7 (6.3%)	98 (17.3%)	

Table 2 Footnote: Definitions of clinically important differences: ACQ Improvement >=0.5 or Well Controlled (ACQ <=0.75); Exacerbation Reduction >=50% or No Exacerbations; Unscheduled Care Reduction >=50% or No Unscheduled Care; FEV_1 increase >=100ml; OCS Dose Decrease >=50% or not receiving mOCS at follow-up

Figure 1

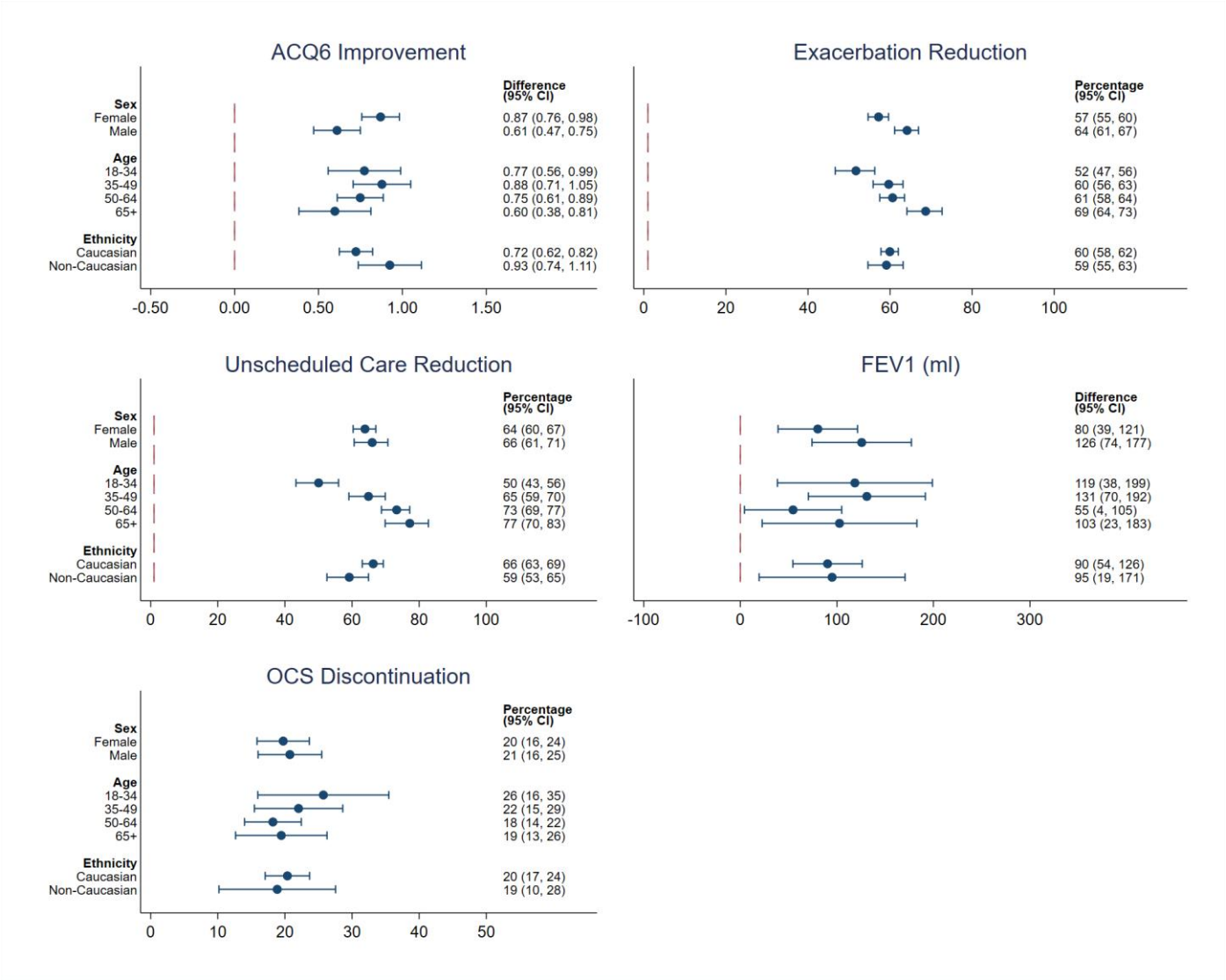
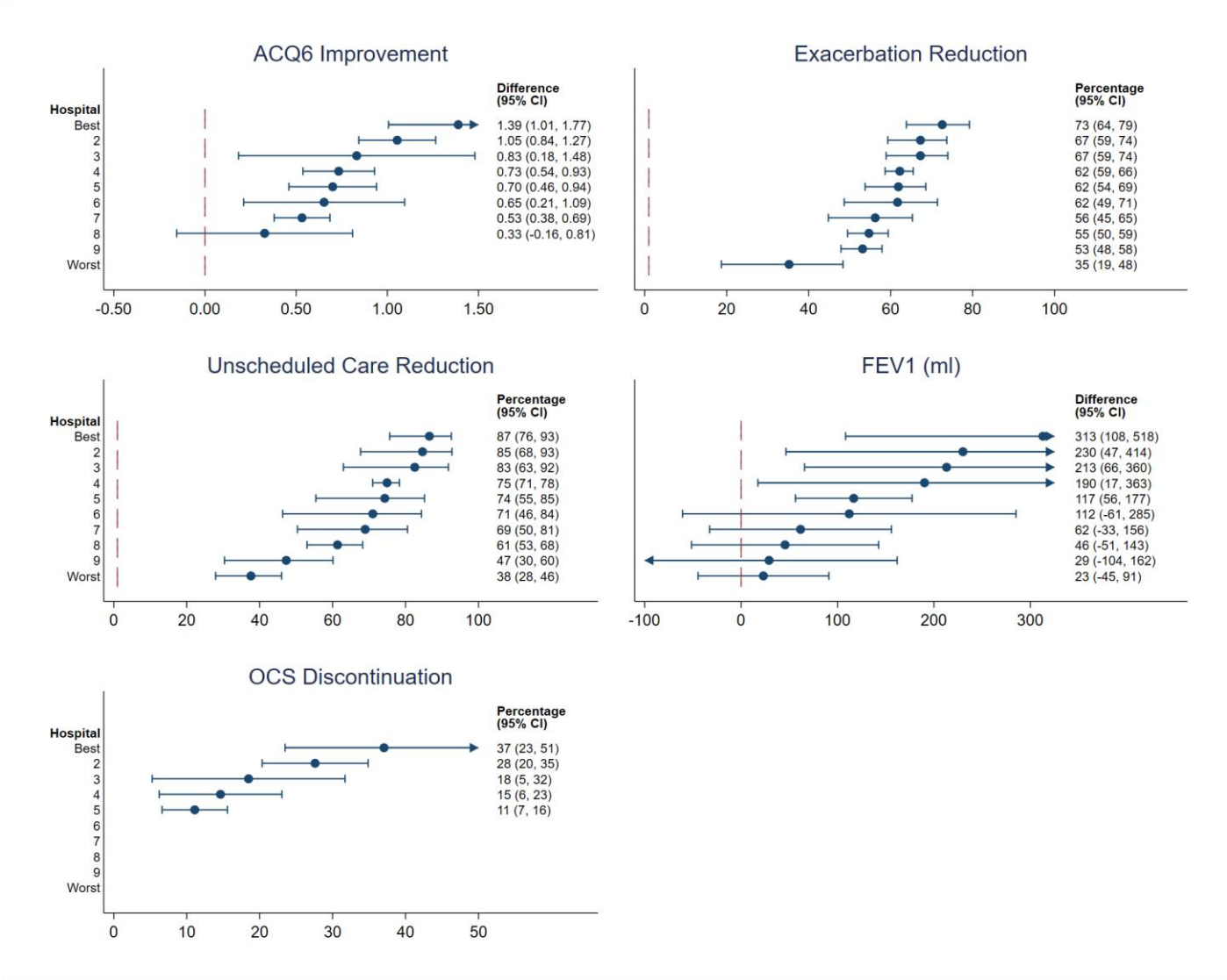

ACQ6 Improvement
Difference (95% CI)
Sex
Female 0.87 (0.76, 0.98)
Male 0.61 (0.47, 0.75)
Age
18-34 0.77 (0.56, 0.99)
35-49 0.88 (0.71, 1.05)
50-64 0.75 (0.61, 0.89)
65+ 0.60 (0.38, 0.81)
Ethnicity
Caucasian 0.72 (0.62, 0.82)
Non-Caucasian 0.93 (0.74, 1.11)
-0.50 0.00 0.50 1.00 1.50
Exacerbation Reduction
Percentage (95% CI)
57 (55, 60)
64 (61, 67)
52 (47, 56)
60 (56, 63)
61 (58, 64)
69 (64, 73)
60 (58, 62)
59 (55, 63)
0 20 40 60 80 100
Unscheduled Care Reduction
Percentage (95% CI)
Sex
Female 64 (60, 67)
Male 66 (61, 71)
Age
18-34 50 (43, 56)
35-49 65 (59, 70)
50-64 73 (69, 77)
65+ 77 (70, 83)
Ethnicity
Caucasian 66 (63, 69)
Non-Caucasian 59 (53, 65)
0 20 40 60 80 100
FEV1 (ml)
Difference (95% CI)
80 (39, 121)
126 (74, 177)
119 (38, 199)
131 (70, 192)
55 (4, 105)
103 (23, 183)
90 (54, 126)
95 (19, 171)
-100 0 100 200 300
OCS Discontinuation
Percentage (95% CI)
Sex
Female 20 (16, 24)
Male 21 (16, 25)
Age
18-34 26 (16, 35)
35-49 22 (15, 29)
50-64 18 (14, 22)
65+ 19 (13, 26)
Ethnicity
Caucasian 20 (17, 24)
Non-Caucasian 19 (10, 28)
0 10 20 30 40 50

Figure 2


ACQ6 Improvement
Hospital
Difference (95% CI)
Best 1.39 (1.01, 1.77)
2 1.05 (0.84, 1.27)
3 0.83 (0.18, 1.48)
4 0.73 (0.54, 0.93)
5 0.70 (0.46, 0.94)
6 0.65 (0.21, 1.09)
7 0.53 (0.38, 0.69)
8 0.33 (-0.16, 0.81)
9
Worst
-0.50 0.00 0.50 1.00 1.50
Exacerbation Reduction
Percentage (95% CI)
73 (64, 79)
67 (59, 74)
67 (59, 74)
62 (59, 66)
62 (54, 69)
62 (49, 71)
56 (45, 65)
55 (50, 59)
53 (48, 58)
35 (19, 48)
0 20 40 60 80 100
Unscheduled Care Reduction
Hospital
Percentage (95% CI)
Best 87 (76, 93)
2 85 (68, 93)
3 83 (63, 92)
4 75 (71, 78)
5 74 (55, 85)
6 71 (46, 84)
7 69 (50, 81)
8 61 (53, 68)
9 47 (30, 60)
Worst 38 (28, 46)
0 20 40 60 80 100
FEV1 (ml)
Difference (95% CI)
313 (108, 518)
230 (47, 414)
213 (66, 360)
190 (17, 363)
117 (56, 177)
112 (-61, 285)
62 (-33, 156)
46 (-51, 143)
29 (-104, 162)
23 (-45, 91)
-100 0 100 200 300
OCS Discontinuation
Hospital
Percentage (95% CI)
Best 37 (23, 51)
2 28 (20, 35)
3 18 (5, 32)
4 15 (6, 23)
5 11 (7, 16)
6
7
8
9
Worst
0 10 20 30 40 50

Abbreviations: ED (Emergency Department), FeNO (Fractional exhaled nitric oxide), FEV_1 (Forced expiratory volume in the first second), FVC (Forced vital capacity), ACQ6 (Asthma Control Questionnaire 6), mOCS (Maintenance oral corticosteroids)

References

1. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2163-96.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2021.
3. Difficult-to-treat & Severe Asthma in adolescent and adult patients. Diagnosis and Management. Global Initative for Asthma; 2019.
4. SIGN 158 British guideline on the management of asthma: A national clinical guideline. In: Scottish Intercollegiate Guidelines Network & British Thoracic Society, editor.: Healthcare Improvement Scotland; 2019.
5. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. European Respiratory Journal. 2014;43(2):343-73.
6. Barnes PJ, Chung KF. Difficult asthma. Br Med J. 1989;299(6701):695-8.
7. van der Meer AN, Pasma H, Kempenaar-Okkema W, et al. A 1-day visit in a severe asthma centre: effect on asthma control, quality of life and healthcare use. European Respiratory Journal. 2016;48(3):726-33.
8. Irwin RS, Curley FJ, French CL. Difficult-to-control asthma - Contributing factors and outcome of a systematic management protocol. Chest. 1993;103(6):1662-9.
9. Bratton DL, Price M, Gavin L, et al. Impact of a multidisciplinary day program on disease and healthcare costs in children and adolescents with severe asthma: a two-year follow-up study. Pediatr Pulmonol. 2001;31(3):177-89.
10. Krupp NL, Weist A, Fiscus CD, et al. Efficacy, cost effectiveness, and sustainability of a pediatric high risk asthma clinic. Pediatr Pulmonol. 2018;53(5):538-43.
11. Tay TR, Lee J, Radhakrishna N, et al. A Structured Approach to Specialist-referred Difficult Asthma Patients Improves Control of Comorbidities and Enhances Asthma Outcomes. Journal of Allergy and Clinical Immunology-in Practice. 2017;5(4):956-+.
12. Begne C, Justet A, Dupin C, et al. Evaluation in a severe asthma expert center improves asthma outcomes regardless of step-up in asthma therapy. Journal of Allergy and Clinical Immunology-in Practice. 2020;8(4):1439-+.
13. Denton E, Lee J, Tay T, et al. Systematic Assessment for Difficult and Severe Asthma Improves Outcomes and Halves Oral Corticosteroid Burden Independent of Monoclonal Biologic Use. Journal of Allergy and Clinical Immunology-in Practice. 2020;8(5):1616-24.
14. Gibeon D, Heaney LG, Brightling CE, et al. Dedicated severe asthma services improve health-care use and quality of life. Chest. 2015;148(4):870-6.
15. Busby J, Price D, Al-Lehebi R, et al. Impact of Socioeconomic Status on Adult Patients with Asthma: A Population-Based Cohort Study from UK Primary Care. J Asthma Allergy. 2021;14:1375-88.
16. Busby J, Heaney LG, Brown T, et al. Ethnic Differences in Severe Asthma Clinical Care and Outcomes: An Analysis of United Kingdom Primary and Specialist Care. J Allergy Clin Immunol Pract. 2021.
17. Redmond C, Akinoso-Imran AQ, Heaney LG, et al. Socioeconomic disparities in asthma health care utilization, exacerbations, and mortality: A systematic review and meta-analysis. J Allergy Clin Immunol. 2021.
18. Chowdhury NU, Guntur VP, Newcomb DC, et al. Sex and gender in asthma. Eur Respir Rev. 2021;30(162).
19. Jackson DJ, Busby J, Pfeffer PE, et al. Characterisation of patients with severe asthma in the UK Severe Asthma Registry in the biologic era. Thorax. 2021;76(3):220-7.
20. Heaney LG, Brightling CE, Menzies-Gow A, et al. Refractory asthma in the UK: cross-sectional findings from a UK multicentre registry. Thorax. 2010;65(9):787-94.
21. Williams R. Using the margins command to estimate and interpret adjusted predictions and marginal effects. The Stata Journal. 2012;12(2):308-31.

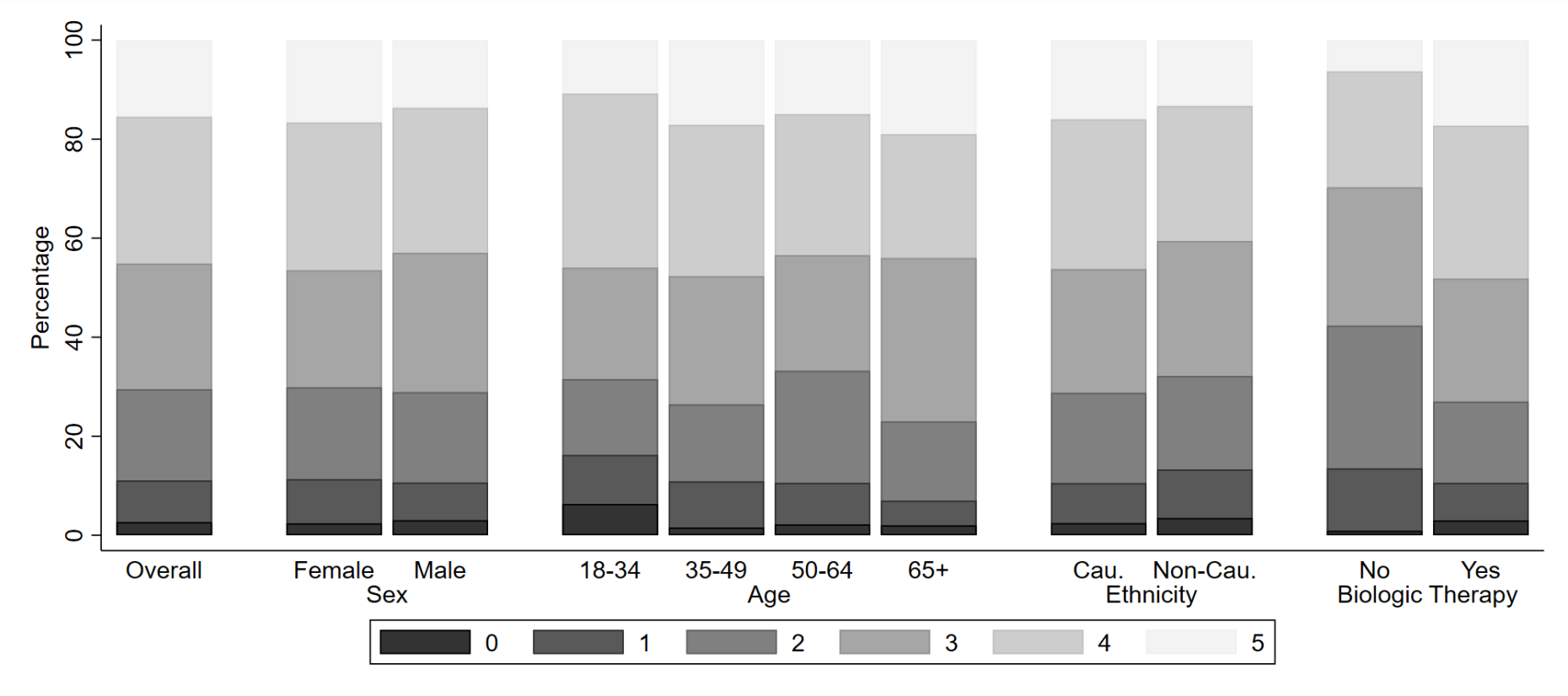
22. Menzies-Gow A, Gurnell M, Heaney LG, et al. Oral corticosteroid elimination via a personalised reduction algorithm in adults with severe, eosinophilic asthma treated with benralizumab (PONENTE): a multicentre, open-label, single-arm study. The Lancet Respiratory Medicine. 2022;10(1):47-58.
23. Ryan D, Heatley H, Heaney LG, et al. Potential Severe Asthma Hidden in UK Primary Care. Journal of Allergy and Clinical Immunology-in Practice. 2021;9(4):1612-+.
24. Patil VK, Townshend C, Mitchell F, et al. An outreaching model of tertiary difficult asthma care reduces adverse asthma outcomes and healthcare utilisation costs. European Respiratory Journal. 2016;47(6):1857-60.
25. Sweeney J, Brightling CE, Menzies-Gow A, et al. Clinical management and outcome of refractory asthma in the UK from the British Thoracic Society Difficult Asthma Registry. Thorax. 2012;67(8):754-6.
26. Ancona G, Kavanagh J, Roxas C, et al. Adherence to inhaled corticosteroids and clinical outcomes in mepolizumab therapy for severe asthma. European Respiratory Journal. 2020;55(5):1902259.
27. Dima AL, Hernandez G, Cunillera O, et al. Asthma inhaler adherence determinants in adults: systematic review of observational data. Eur Respir J. 2015;45(4):994-1018.
28. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008;178(3):218-24.
29. de Nijs SB, Venekamp LN, Bel EH. Adult-onset asthma: is it really different? Eur Respir Rev. 2013;22(127):44-52.
30. Busby J, Matthews JG, Chaudhuri R, et al. Factors affecting adherence with treatment advice in a clinical trial of patients with severe asthma. Eur Respir J. 2021.
31. Oxford Academic Health Science Network. Consultation: AAC Consensus Pathway for Uncontrolled and Severe Asthma 2022 [updated 01/02/22. Available from: https://www.oxfordahsn.org/our-work/asthma-biologics-toolkit/consultation-aac-consensus-pathway-for-uncontrolled-and-severe-asthma/.
32. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. Int J Epidemiol. 2005;34(1):215-20.
33. Porsbjerg CM, Menzies-Gow AN, Tran TN, et al. Global Variability in Administrative Approval Prescription Criteria for Biologic Therapy in Severe Asthma. J Allergy Clin Immunol Pract. 2022.
34. Wang E, Wechsler ME, Tran TN, et al. Characterization of Severe Asthma Worldwide: Data From the International Severe Asthma Registry. Chest. 2020;157(4):790-804.

Supplement

Table E1 - Data completeness

Characteristic	Baseline	Follow-up
Age at assessment	1,140 (100%)	N/A
Gender	1,140 (100%)	N/A
Ethnicity	1,136 (99.6%)	N/A
BMI	1,135 (99.6%)	903 (79.2%)
Smoking status	1,116 (97.9%)	N/A
FEV_1	1,124 (98.6%)	955 (83.8%)
FVC	1,113 (97.6%)	911 (79.9%)
FEV_1/FVC	1,113 (97.6%)	910 (79.8%)
ACQ6	987 (86.6%)	929 (81.5%)
Exacerbations (Prior year)	1,120 (98.3%)	1,101 (96.6%)
ED Attendance (Prior year)	1,120 (98.3%)	1,089 (95.5%)
Hospital Admissions (Prior year)	1,127 (98.9%)	1,090 (95.6%)
Blood Eosinophil Count	1,119 (98.2%)	705 (61.8%)
FeNO	898 (78.8%)	583 (51.1%)
IGE	1,100 (96.5%)	N/A
mOCS	1,134 (99.5%)	1,138 (99.8%)
mOCS dose	637 (99.7%)	585 (99.7%)
ICS dose	1,062 (93.2%)	N/A
Biologic Therapy	NA	1,140 (100%)

Figure E1 – Bar chart depicting the representative proportion of patients that achieved improvement across five patient outcomes*



***Outcomes included:** ACQ improvement of 0.5 or greater or Well Controlled (ACQ <=0.75), an exacerbation reduction >=50% or No Exacerbations, a 50% or greater reduction in unscheduled care (ED attendance/hospitalisation) or No Unscheduled Secondary Care, an FEV_1 increase of 100ml or greater, an OCS dose reduction of 50% or greater (or not receiving OCS at follow-up appointment).

Abbreviation: Cau (Caucasian)

Table E2 – Comparison of specialist referral benefit by demographic factors and biologic treatment status

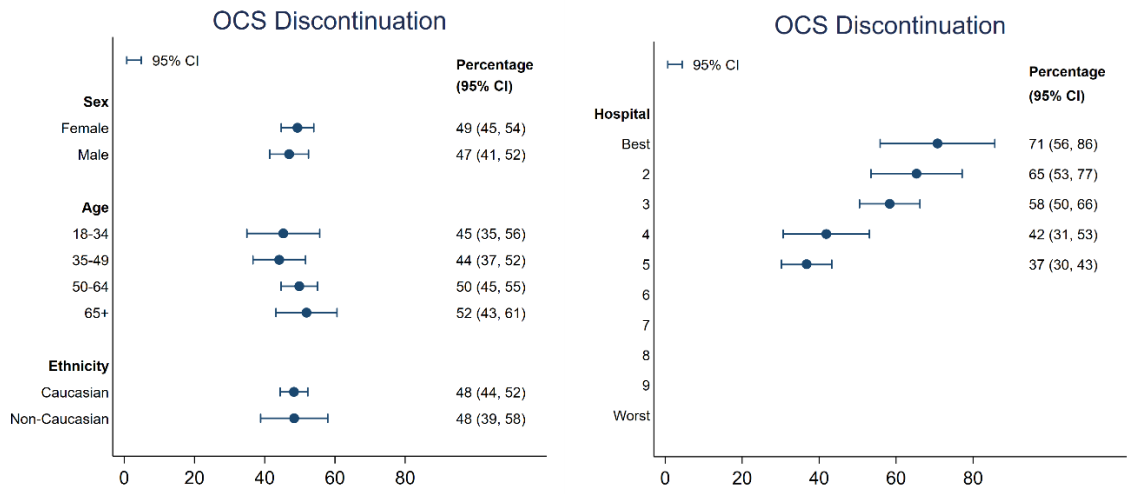
Exposure	ACQ6 Score [a]				Exacerbations [b]			
	Univariate	Multivariate (No biologic)	Multivariate	P-Value	Univariate	Multivariate (No biologic)	Multivariate	P-Value
Sex	**N=1079**	**N=1075**	**N=1075**		**N=1140**	**N=1136**	**N=1136**	
Female	Ref	Ref	Ref	.	Ref	Ref	Ref	.
Male	0.24 (0.06,0.42)	0.24 (0.05,0.42)	0.26 (0.08,0.44)	0.004	0.83 (0.75,0.91)	0.83 (0.75,0.91)	0.84 (0.76,0.93)	0.001
Age At First Assessment (Years)	**N=1079**	**N=1075**	**N=1075**		**N=1140**	**N=1136**	**N=1136**	
18-34	Ref	Ref	Ref	.	Ref	Ref	Ref	.
35-49	-0.13 (-0.41,0.15)	-0.13 (-0.41,0.15)	-0.10 (-0.38,0.17)	0.457	0.82 (0.72,0.94)	0.82 (0.72,0.94)	0.83 (0.73,0.95)	0.008
50-64	-0.01 (-0.27,0.25)	-0.01 (-0.27,0.25)	0.02 (-0.23,0.28)	0.850	0.80 (0.71,0.91)	0.80 (0.71,0.91)	0.82 (0.72,0.92)	0.001
65+	0.14 (-0.17,0.45)	0.14 (-0.17,0.45)	0.18 (-0.13,0.48)	0.258	0.63 (0.54,0.75)	0.63 (0.54,0.75)	0.65 (0.55,0.77)	0.000
Ethnicity	**N=1075**	**N=1075**	**N=1075**		**N=1136**	**N=1136**	**N=1136**	
Caucasian	Ref	Ref	Ref	.	Ref	Ref	Ref	.
Non-Caucasian	-0.12 (-0.33,0.10)	-0.12 (-0.33,0.10)	-0.20 (-0.41,0.01)	0.063	1.05 (0.93,1.18)	1.05 (0.93,1.18)	1.02 (0.91,1.15)	0.732

Exposure	Unscheduled Care Use [b]				OCS Discontinuation [c]			
	Univariate	Multivariate (No biologic)	Multivariate	P-Value	Univariate	Multivariate (No biologic)	Multivariate	P-Value
Sex	**N=1139**	**N=1135**	**N=1135**		**N=637**	**N=635**	**N=635**	
Female	Ref	Ref	Ref	.	Ref	Ref	Ref	.
Male	0.94 (0.79,1.12)	0.94 (0.79,1.12)	0.94 (0.79,1.12)	0.489	1.04 (0.69,1.56)	1.07 (0.71,1.62)	1.07 (0.71,1.62)	0.751
Age At First Assessment (Years)	**N=1139**	**N=1135**	**N=1135**		**N=637**	**N=635**	**N=635**	
18-34	Ref	Ref	Ref	.	Ref	Ref	Ref	.
35-49	0.70 (0.57,0.85)	0.70 (0.57,0.85)	0.70 (0.58,0.86)	0.001	0.83 (0.41,1.66)	0.81 (0.40,1.63)	0.80 (0.39,1.62)	0.534
50-64	0.53 (0.44,0.65)	0.54 (0.44,0.65)	0.53 (0.44,0.65)	0.000	0.62 (0.33,1.17)	0.62 (0.33,1.19)	0.62 (0.32,1.18)	0.143
65+	0.45 (0.33,0.61)	0.45 (0.33,0.61)	0.46 (0.34,0.62)	0.000	0.68 (0.33,1.43)	0.68 (0.32,1.42)	0.67 (0.32,1.42)	0.297
Ethnicity	**N=1135**	**N=1135**	**N=1135**		**N=635**	**N=635**	**N=635**	
Caucasian	Ref	Ref	Ref	.	Ref	Ref	Ref	.
Non-Caucasian	1.23 (1.03,1.46)	1.23 (1.03,1.46)	1.21 (1.01,1.45)	0.034	0.87 (0.45,1.69)	0.89 (0.45,1.73)	0.90 (0.46,1.77)	0.761

Table E2 Footnote: Univariate analysis adjusts for hospital site, year of baseline assessment and time. Multivariate analysis (no biologic) adjusts for hospital site, year of baseline assessment, time, sex, age and ethnicity. Multivariate analysis adjusts for hospital site, year of baseline assessment, time, sex, age, ethnicity, and biologic therapy. All models included an interaction term between time and the variable of interest.

[a] Mean difference; [b] Incidence rate ratio; [c] Odds ratio

Figure E2 – OCS discontinuation, defined as complete withdrawal of OCS or remaining on 5mg or less at annual review, stratified by patient demographic variables and hospital site



*All models are adjusted for sex, age category, ethnicity, biologic therapy, year of baseline assessment, hospital site, and base level of the relevant outcome of interest

**Analysis by site was restricted to hospitals with 30 or more patients per reported outcome.

***The terms best and worst refer to the magnitude of change for each outcome measured and are not consistent across panels.

Abbreviation: OCS (Oral corticosteroids)

Table E3 – Baseline patient characteristics stratified by age group at first assessment

	18-34	35-49	50-64	65+	P-value
Number of Patients	189	300	461	190	
Age At First Assessment (Years)	26.9 (4.6)	43.4 (4.2)	56.5 (4.2)	70.9 (6.9)	<0.001
Age of Onset (Years)	10.5 (8.3)	19.4 (13.6)	29.2 (18.5)	40.5 (22.5)	<0.001
Gender					<0.001
Female	142 (75.1%)	187 (62.3%)	270 (58.6%)	97 (51.1%)	
Male	47 (24.9%)	113 (37.7%)	191 (41.4%)	93 (48.9%)	
Ethnicity					0.007
Caucasian	152 (80.4%)	225 (75.3%)	366 (79.9%)	170 (89.5%)	
Non-Caucasian	37 (19.6%)	74 (24.7%)	92 (20.1%)	20 (10.5%)	
BMI (kg/m2)	29.9 (7.9)	31.1 (7.5)	31.2 (6.9)	29.6 (5.4)	0.013
Smoking Status					<0.001
Never smoked	137 (74.5%)	197 (67.0%)	293 (64.8%)	129 (69.4%)	
Ex-smoker	31 (16.8%)	85 (28.9%)	150 (33.2%)	55 (29.6%)	
Current smoker	16 (8.7%)	12 (4.1%)	9 (2.0%)	2 (1.1%)	
Atopic Disease	143 (75.7%)	187 (63.2%)	224 (49.0%)	74 (40.0%)	<0.001
FEV1 (ml)	2416.6 (801.6)	2159.6 (805.7)	1845.1 (711.5)	1709.3 (621.6)	<0.001
FEV1 (% Predicted)	70.3 (20.5)	67.1 (21.2)	64.3 (21.2)	67.7 (20.1)	0.008
FVC (ml)	3544.8 (934.2)	3348.7 (1061.6)	2979.5 (975.4)	2866.3 (954.6)	<0.001
FVC (% Predicted)	87.7 (16.5)	84.0 (19.1)	82.1 (18.9)	87.1 (19.9)	0.001
FEV1/FVC	67.6 (13.4)	64.7 (13.7)	62.7 (23.6)	60.7 (13.9)	0.002
ACQ6 Score	3.3 (2.3,4.3)	3.2 (2.2,4.2)	3.0 (1.8,3.8)	2.3 (1.3,3.2)	<0.001
Uncontrolled Asthma (ACQ6>1.5)	155 (90.6%)	214 (84.3%)	330 (82.9%)	112 (68.3%)	<0.001
EuroQoL Utility	0.73 (0.46,0.89)	0.74 (0.53,0.89)	0.70 (0.43,0.85)	0.78 (0.51,0.89)	0.483
Exacerbations (Prior Year)	6 (4,10)	5 (3,7)	4 (3,8)	5 (2,6)	<0.001
Any ED Attendance (Prior Year)	104 (55.9%)	129 (43.6%)	148 (33.0%)	54 (28.7%)	<0.001
Any Hospital Admissions (Prior Year)	96 (51.3%)	115 (38.9%)	156 (34.3%)	70 (37.0%)	0.008
Invasive Ventilations (Ever)	31 (16.8%)	31 (10.5%)	47 (10.4%)	8 (4.3%)	0.016
Eczema	11 (5.8%)	7 (2.3%)	6 (1.3%)	3 (1.6%)	0.006
Nasal Polyps	24 (12.7%)	54 (18.0%)	98 (21.3%)	35 (18.4%)	0.086
Gastro-oesophageal Reflux	29 (15.3%)	50 (16.7%)	87 (18.9%)	41 (21.6%)	0.375
Depression or Anxiety	23 (12.2%)	33 (11.0%)	48 (10.4%)	5 (2.6%)	0.004
Blood Eosinophil Count (N/109L)	0.40 (0.20,0.60)	0.41 (0.20,0.70)	0.33 (0.20,0.60)	0.31 (0.15,0.55)	0.009
Highest Blood Eosinophil Count (N/109L)	0.70 (0.40,1.10)	0.70 (0.40,1.18)	0.66 (0.40,1.00)	0.68 (0.44,1.10)	0.578
FeNO (ppb)	49 (21,87)	39 (20,75)	41 (25,69)	38 (19,63)	0.276
IGE (IU/mL)	204 (85,551)	152 (61,432)	147 (47,389)	145 (44,466)	0.013

mOCS	79 (41.8%)	156 (52.3%)	294 (64.2%)	110 (58.2%)	<0.001
mOCS (prednisolone equivalent/mg)	10 (10,20)	10 (10,20)	10 (8,15)	10 (5,10)	<0.001
ICS Dose (BDP equivalent/ug)	2000 (1600,2000)	2000 (1600,2000)	2000 (1600,2000)	2000 (1600,2000)	0.592
LAMA	111 (58.7%)	162 (54.4%)	254 (56.3%)	119 (63.3%)	0.098
Theophylline	45 (23.9%)	69 (23.2%)	129 (28.4%)	36 (18.9%)	0.075
Leukotriene Receptor Antagonists	107 (59.4%)	148 (50.7%)	224 (49.7%)	89 (47.6%)	0.095
Maintenance Macrolides	13 (7.2%)	12 (4.1%)	43 (9.4%)	14 (7.5%)	0.029
Nebuliser	42 (22.6%)	51 (17.0%)	102 (22.8%)	37 (19.8%)	0.029
Biologic Therapy	142 (75.1%)	242 (80.7%)	382 (82.9%)	161 (84.7%)	0.071
Biological Therapy Name					0.048
Mepolizumab	71 (52.6%)	151 (64.0%)	260 (69.9%)	109 (69.4%)	
Benralizumab	32 (23.7%)	49 (20.8%)	63 (16.9%)	33 (21.0%)	
Omalizumab	31 (23.0%)	36 (15.3%)	48 (12.9%)	15 (9.6%)	
Dupilumab	1 (0.7%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	

Footnote: Abbreviations: FEV1 (Forced expiratory volume in the first second), FVC (Forced vital capacity), ACQ6 (Asthma Control Questionnaire 6), ED (Emergency Department), FeNO (Fractional exhaled nitric oxide), IGE (Immunoglobulin E), mOCS (Maintenace oral corticosteroids), ICS (Inhaled corticosteroids), LAMA (Long-acting muscarinic antagonists), SABA (Short-acting beta-agonists)