

Observational & Pragmatic Research Institute Pte Ltd
Final report: Assessing the use of fractional exhaled Nitric Oxide and blood eosinophils as biomarkers in predicting asthma exacerbations, and evaluating the subsequent healthcare resource utilisation

Observational and Pragmatic Research Institute Pte Ltd

Final Report

Final report for phase 1

AUREA

Assessing the Use of fractional exhaled Nitric Oxide and blood eosinophils as biomarkers in predicting asthma exacerbations, and Evaluating the subsequent healthcare resource utilisation

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Final report: Assessing the use of fractional exhaled Nitric Oxide and blood eosinophils as biomarkers in predicting asthma exacerbations, and evaluating the subsequent healthcare resource utilisation

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List of abbreviations

ADEPT	Anonymous Data Ethics Protocols and Transparency
ATS/ERS	American Thoracic Society/European Respiratory Society
BEC	Blood Eosinophil Count
BMI	Body mass index
CCI	Charlson comorbidity index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ICD	International Classification of Disease
ICS	Inhaled corticosteroids
FeNO	Fractional exhaled Nitric Oxide
GERD	Gastro-esophageal reflux disease
GINA	Global initiative for asthma
LABA	Long-acting $\beta 2$ agonist
LAMA	Long acting muscarinic antagonist
LTRA	Leukotriene receptor antagonist
OCS	Oral corticosteroids
OPCRD	Optimum Patient Care Research Database
OPRI	Observational and Pragmatic Research Institute
PEF	Peak expiratory flow
REC	Research Ethics Committee
REG	Respiratory Effectiveness Group
RR	Rate ratio
SABA	Short-acting $\beta 2$ agonist
SAMA	Short-acting muscarinic antagonist

1.0 Executive summary

1.1 Introduction

Blood eosinophil counts and fractional exhaled nitric oxide (FeNO) are established biomarkers in asthma (3). While patients with raised blood eosinophil counts were found to be at increased risk of asthma exacerbations (10), it is not clear whether raised FeNO further increases the risk.

1.2 Study aims and objectives

To determine if raised blood eosinophil counts combined with raised FeNO levels are associated with increased frequency of severe asthma exacerbations.

Primary objective:

To compare the rate of severe asthma exacerbations in different patient groups characterised by biomarker levels* in the year prior to the FeNO measurement.

Secondary objective:

To describe demographic characteristics, lung function, comorbidities, respiratory medication, and health care resource utilisation in patient groups characterised by biomarkers levels.

Exploratory objective:

To describe demographic characteristics, lung function, comorbidities, respiratory medication, and health care resource utilisation in currently smoking patients characterised by biomarkers levels.

1.3 Methods

This was a cross sectional study using a bespoke dataset from Optimum Patient Care Research Database (OPCRD).

The study population included asthma patients with a FeNO reading with a prescription for

* 6 patient groups will be categorised by eosinophils ($\geq 0.3 \times 10^9/L$ and $< 0.3 \times 10^9/L$) and FeNO levels (≥ 50 ppb – high, ≥ 25 ppb < 50 ppb – medium, < 25 ppb - low). Combinations of these groups can be considered e.g. low FeNO/high eosinophil + medium FeNO/low eosinophil + medium FeNO/high eosinophils.

ICS in the year prior, and a stable blood eosinophil count (BEC)* within 5 years. Patients were divided into groups based on their FeNO reading and the closest BEC.

Two criteria were used to define the groups.

The first categorisation (categorisation 1) was based on the ATS guidelines for FeNO readings (high FeNO was defined as ≥ 50 ppb, medium FeNO as ≥ 25 and < 50 ppb, low FeNO as < 25 ppb) a cut-off for a high BEC defined as $\geq 300/\mu\text{L}$.

The second categorisation (categorisation 2) was based on expert opinion from the steering committee where high FeNO readings were defined as ≥ 35 ppb, and low FeNO was < 35 ppb. The cut-off for a high BEC remained $\geq 300/\mu\text{L}$.

Characterisation and subsequent matched analyses of study outcomes were performed based on the above defined two criteria. Patients were matched 1:1 on age, sex, and smoking status.

The primary outcome was the severe exacerbation rate during the year prior to the FeNO reading.

Patients with high BEC and high FeNO readings were compared to matched patients with low BEC and low FeNO (reference group) readings for both categorisation 1 and 2.

Patients with either high BEC ($\geq 300/\mu\text{L}$) or high FeNO (≥ 50 ppb) were compared to matched patients in the reference group ($< 300/\mu\text{L}$ BEC and < 25 ppb FeNO) under categorisation 1.

Two additional matched comparisons were carried out under categorisation 2. Firstly, patients with high BEC ($\geq 300/\mu\text{L}$), were compared with matched patients in the reference group ($< 300/\mu\text{L}$ BEC and < 35 ppb FeNO). Secondly, patients with high FeNO (≥ 35 ppb) were compared with matched patients in the reference group ($< 300/\mu\text{L}$ BEC and < 35 ppb FeNO).

1.4 Results

The rate of severe exacerbations was significantly higher during the year preceding the FeNO readings for patients with high BEC and high FeNO readings compared to matched reference patients with categorisation 1 (RR: 3.67 [95% CI 1.49, 9.04], p value = 0.005) and categorisation 2 (RR: 1.72 [95% CI 1.00, 2.93] p value = 0.050).

The severe exacerbation rate was numerically higher (but not statistically significant [p value = 0.081] for patients with high BEC or high FeNO readings compared to the matched reference patients for categorisation 1 (RR 1.31 [95% CI 0.97-1.76]. For categorisation 2, patients with

* Stable blood eosinophil readings are blood eosinophil readings without a prescription of oral corticosteroids in the 2 weeks prior

high BEC had a numerically higher (but not statistically significant [p value = 0.124]) severe exacerbation rate (RR of 1.41 [95% CI 0.91-2.19]) compared to matched reference patients with low BEC and low FeNO readings. Under the categorisation 2, patients with high FeNO showed a numerically higher (but not statistically significant [p value = 0.054]) severe exacerbation rate (RR 1.35 [95% CI 0.99-1.84]) compared to matched reference patients.

1.5 Conclusion

The presence of raised FeNO in addition to a high BEC was associated with a higher rate of severe exacerbations compared to the absence of raised FeNO and raised BEC. The association between patients with both high FeNO and high BEC and a higher severe exacerbation rate was stronger compared to high BEC alone, or high FeNO alone.

2.0 Background

An estimated 5-10% of the 300 million people who suffer from asthma worldwide have a severe form of the disease, defined as those patients treated with high dose inhaled corticosteroids (ICS) who continue to be uncontrolled. Approximately 40–60% of this population with severe asthma have eosinophilic airway inflammation (1).

Eosinophils, proliferation and survival of which are elicited by interleukin 5 (IL-5), are considered a key effector arm of the allergic response in asthma. ICS subdues the cellular inflammatory response and encourages the anti-inflammatory response in the airway, but in some patients, the allergic response is under-responsive to ICS (2). Fractional exhaled nitric oxide (FeNO) and sputum eosinophilia have been identified as biomarkers for T-helper 2 (Th2)-driven allergic airway inflammation in patients with asthma, and both are considered reliable predictors of responsiveness to ICS (3). Although FeNO levels are correlated with blood and sputum eosinophil counts in patients with mild-to-moderate asthma (3, 4), this association attenuates in patients with severe asthma.

This study explores whether the presence of high FeNO readings and high BEC can provide additional insight into asthma severity compared to high BEC alone. Prescription of ICS reduces FeNO in a dose dependent manner in asthma patients with elevated FeNO levels: however, FeNO is still detectable when patients are treated with high doses of ICS (5). A reduction in FeNO readings has been positively correlated with improvement and in asthma symptoms and Asthma Control Questionnaire scores (ACQ) (5-7). High FeNO readings are associated with poorer adherence to ICS, which may partially explain the presence of uncontrolled severe asthma (8).

This suggests that the measurement of FeNO may provide additional predictive value to eosinophilia for severe exacerbations in patients with a strong Th2 allergic response.

Assessment of sputum eosinophilia is impractical in non-specialised settings without a physiotherapist or access to bronchial lavage whereas a blood eosinophil count (BEC) is easily obtained. A high BEC ($\geq 300/\mu\text{L}$) has been found to be a useful predictor of sputum eosinophilia ($\geq 2\%$) in patients with severe asthma (9). A significant reduction in severe exacerbations has also been seen in patients with severe asthma with blood eosinophils $\geq 300/\mu\text{L}$ treated with an IL-5 receptor antagonist (10).

A previous OPRI study found a count–response relation between BECs and asthma-related outcomes, suggesting a causal relationship between eosinophilic inflammation and lack of asthma control (11, 12).

Results from two large mepolizumab trials showed that a BEC greater than or equal to 150 cells/ μL was non inferior to sputum counts $\geq 3\%$ in predicting treatment response to anti-IL5 therapy, and suggested that a high BEC may even be a better predictor of therapy response than sputum eosinophils (13).

The presence of raised FeNO levels and/or high BECs, despite adherence to medium to high doses of ICS, may identify corticosteroid-resistant asthma patients who continue to suffer from severe exacerbations. These patients may be candidates for drugs targeting immunoglobulin E (IgE), interleukin - 4 (IL-4), interleukin - 5 (IL-5) or interleukin – 13 (IL-13) which have yielded positive outcomes in severe asthma patients with evidence of Th2 airway inflammation (11, 14, 15).

This study aims to determine if a high BEC combined with high FeNO reading is associated with the increased risk of severe asthma exacerbations.

Two categorisations were used to group patients.

The first categorisation is based on the ATS grouping for high, low and medium FeNO levels in conjunction with the cutoff for a high BEC as 300/ μL or above.

The second categorisation was chosen after discussion with the steering committee, where it was suggested that a simple high/low format for FeNO levels would be more easily implemented in clinical practice compared to a high/medium/low categorisation for FeNO. The 35ppb cut-off for FeNO readings was chosen based on prior research in patients who were considered to present an at risk asthma phenotype(4).

3.0 Study hypothesis and objective

3.1 Hypothesis

Assessment of both FeNO and the BEC together may help to identify patients at higher risk of severe exacerbations.

3.2 Objective

3.2.1 Primary objective:

To find the rate of severe exacerbations in patient groups characterised by different biomarker levels in the year prior to the FeNO measurement.

3.2.2 Secondary objective:

To describe demographic characteristics, lung function, comorbidities, respiratory medication in patient groups characterised by biomarker levels.

3.2.3 Exploratory objective:

To describe demographic characteristics, lung function, comorbidities, respiratory medication, and health care resource utilisation in currently smoking patients categorised by biomarkers.

3.2.4 Health care Resource Utilisation objective:

To describe the health care resource utilisation in patient groups categorised by biomarkers.

4.0 Study design

This was a historical cross-sectional study of patients with evidence of asthma, a valid blood eosinophil count, a FeNO reading, and a prescription for inhaled corticosteroids in the year prior to the FeNO reading. Only a BEC within 5 years prior to the date of FeNO was considered. Any BEC within 2 weeks of an oral corticosteroid prescription was disregarded because the BEC would be reduced. The study period, over which both the patient characteristics and outcome (severe exacerbations) were observed, consisted of the year prior to the latest documented FeNO reading.

Time BEC reading taken relative to index date	Number
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Less than 1 year	348
Between 1 and 2 years	126
Between 2 and 3 years	66
Between 3 and 4 years	36
4 years plus	36

Cohorts were categorised per two criteria:

1. The first categorisation consisted of using the ATS classification(16) for FeNO readings (<25ppb = low, 25-<50ppb = medium, ≥50ppb = high) and a BEC cut-off ≥300/μL/<300/ μL
2. The second categorisation was recommended upon discussion with the steering committee. The final criteria were composed of a cut off ≥35ppb/<35ppb for FeNO readings, and a BEC cut-off ≥300/μL/<300/μL

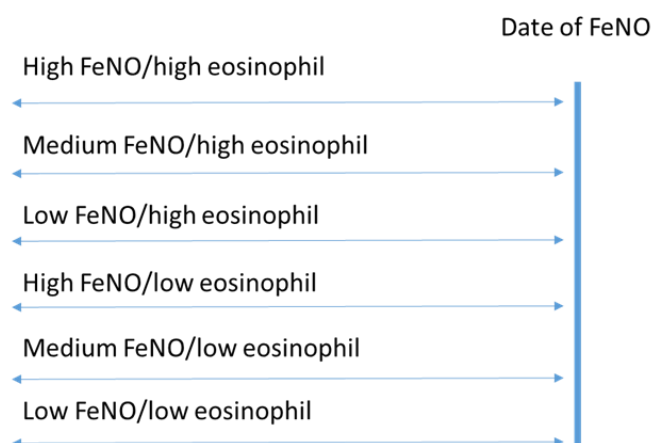


Figure 1: ATS criteria for patient groups

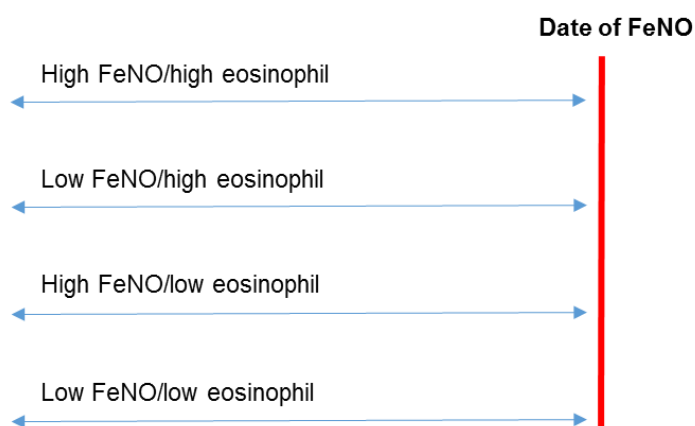


Figure 2: Steering committee criteria for patient groups

5.0 Study population

The study population consisted of patients with evidence of asthma, registered at general practices providing data to Optimum Patient Care across England, Scotland, Wales, and Northern Ireland with a FeNO reading, a BEC recorded in the database 5 years prior, and an ICS prescription in the year prior.

5.1 Inclusion and exclusion criteria

Inclusion criteria

- A diagnostic Read code for asthma qualifying for inclusion in the register of patients with asthma, which GP practices in the UK maintain for the Quality Outcomes Framework (QOF)(17) OR active asthma with ≥ 1 prescriptions for asthma medication in the year prior to the index date and no recorded FEV1/FVC <0.7 or COPD Read code and LAMA prescription
- Age 18-80 on date of FeNO reading
- ≥ 1 valid BEC measurement available without a prescription of an acute course of oral corticosteroids (OCS) within 2 weeks prior to the measurement, at most 5 years prior to the FeNO reading
- Valid continuous data for one year prior to latest FeNO reading

Exclusion criteria

- Diagnosis Read code for any of the following chronic lower respiratory conditions: pulmonary sarcoidosis; hypersensitivity pneumonitis; bronchiolitis; malignancy of the lungs; interstitial lung disease, and; cystic fibrosis
- Prescription of maintenance oral corticosteroids during the study period

Table 1: Inclusion/exclusion criteria

5.2 Data source

The study used patient data from the Optimum Patient Care Research Database (OPCRD). At the time of study execution, there were over 2.4 million patient records available from over

560 practices. The study team work with anonymous data removed of any patient identifiable information.

The database has received a favourable opinion from the Health Research Authority for clinical research use (REC reference: 15/EM/0150). Governance is provided by The Anonymous Data Ethics Protocols and Transparency (ADEPT) committee, an independent body of experts and regulators commissioned by the Respiratory Effectiveness Group (REG)* to govern the standard of research conducted on internationally renowned recognised databases. The study is registered under the established study database the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP) under the registration number EUPAS16891. The ADEPT code is ADEPT1017.

6.0 Study variables and study outcomes

6.1 Exposure

The exposure of interest was the level of BEC and FeNO.

Categorisation 1 (ATS criteria):

A high BEC was defined as $\geq 300/\mu\text{L}$

A low BEC was defined as $< 300/\mu\text{L}$

High FeNO was defined as $\geq 50\text{ppb}$

Medium FeNO was defined as 25 to $< 50\text{ppb}$

Low FeNO was defined as $< 25\text{ppb}$

Categorisation 2 (Steering committee criteria)

A high BEC was defined as $\geq 300/\mu\text{L}$

A low BEC was defined as $< 300/\mu\text{L}$

High FeNO was defined as $\geq 35\text{ppb}$

Low FeNO was defined as $< 35\text{ppb}$

The main analysis compared the rate of exacerbation between those with a high BEC and high FeNO readings against those with low BECs and low FeNO levels (the reference group) for categorisation 1 and categorisation 2.

Further analysis for the ATS criteria compared the rate of exacerbation between those with

* Respiratory Effectiveness Group (REG) (<http://effectivenessevaluation.org/>)

high BEC or high FeNO readings against those in the reference group.

An exploratory analysis of patients who were documented as smokers was also carried out using categorisation 1. Only exploratory characterisation was carried out because the small numbers in the high BEC, high FeNO reading precluded meaningful analysis (6 patients), and was not extended to categorisation 2.

Further analysis for categorisation 2 compared the rate of exacerbation between those with a high BEC against those in the reference group. In addition, the rate of exacerbation in patients with a high FeNO reading was compared against those in the reference group. Health economic costs were compared as part of the characterisation for categorisation 2.

6.2 Primary outcome

The primary outcome was the annual rate of severe asthma exacerbations. This was defined as the number of severe exacerbations in the study period per patient. A severe exacerbation was defined in line with the European Respiratory Society/American Thoracic Society Position Statement as:

- a) An acute prescription of oral corticosteroids OR
- b) An unplanned lower respiratory related hospitalisation OR
- c) An accident and emergency attendance associated with a lower respiratory code or primary care consultation within 14 days

6.3 Healthcare Resource Utilisation

The healthcare resource utilisation outcome incorporated both healthcare costs due to resource utilisation and respiratory related medication costs.

Resource utilisation was based on the Personal Social Services Research Unit (PSSRU) document 2016. The average costs included qualification costs and direct care staff costs. The average cost per hour of patient contact was estimated at £236, with each GP led consultation taking an average of 9.22 minutes. The costs for respiratory related services were obtained from the publication of the National Health Service (NHS) reference cost schedule from 2015-2016.

Prices assigned to drugs were taken from the NHS dictionary of medicines and devices (DM+D) browser (found at <http://dmd.medicines.org.uk>). DM+D provides up to date costs for Systematized Nomenclature of Medicine Clinical Terms (SnoMed) codes, and for the purposes of this study were taken in December 2016. Read codes were mapped to SnoMed

codes and costs were calculated for the following asthma medications:

- Short-acting beta2-agonists (SABA)
- Short-acting muscarinic antagonists (SAMA)
- Long-acting beta2-agonists (LABA)
- Long-acting muscarinic antagonists (LAMA)
- Inhaled corticosteroids (ICS)
- Inhaled combination therapy
 - LABA / ICS
 - LABA / ICS / LAMA
 - LABA / LAMA
 - LAMA / ICS
- Oral corticosteroids
- Theophylline
- Antibiotics prescribed for lower respiratory events

6.4 Demographic variables

The following characteristics were summarised for each group comparison.

6.4.1 Demographics

<i>Age group</i>	At index date
<i>Sex</i>	
<i>Smoking status</i>	Read code closest to and within 5 years prior to index date, grouped as; <i>never smoker, ex-smoker, current smoker</i>
<i>Body Mass Index (BMI)</i>	Calculated in adults (≥ 18 years) only from height and weight data, if available, and taken from practice-recorded BMI if not, within 10 years of the index date. Defined as the ratio of weight (kg) to squared height (m^2), and categorised as <i>underweight</i> ($< 18.5 \text{ kg}/m^2$), <i>normal weight</i> ($\geq 18.5 \text{ kg}/m^2$ and $< 25 \text{ kg}/m^2$), <i>overweight</i> ($\geq 25 \text{ kg}/m^2$ and $< 30 \text{ kg}/m^2$) and <i>obese</i> ($\geq 30 \text{ kg}/m^2$)

6.4.2 Comorbidities

The following comorbidities were based on a diagnostic Read code recorded prior to the index date:

<i>Allergic/non-allergic rhinitis</i>	<i>never, active* or ever</i>
<i>Atopic eczema diagnosis</i>	<i>never, active, or ever</i>
<i>Chronic Obstructive Pulmonary Disease (COPD)</i>	<i>Ever</i>
<i>Gastro-oesophageal reflux disease (GERD)</i>	<i>never, active, or ever</i>
<i>Diabetes Mellitus type II</i>	Read coded ever
<i>Osteoporosis</i>	Read coded ever
<i>Heart failure</i>	Read coded ever
<i>Hypertension</i>	Read coded ever
<i>Ischaemic heart disease</i>	Read coded ever
<i>Cardiovascular disease</i>	Read coded ever (including ischaemic heart disease, cerebrovascular disease)
<i>Myocardial Infarct</i>	Read coded ever
<i>Psychiatric conditions / Anxiety / Depression</i>	Read coded ever
<i>Chronic kidney disease</i>	Read coded ever

6.4.3 Other clinical characteristics

The following characteristics within the one year study period were summarised in the comparison cohorts:

<i>Current peak flow</i>	<i>Most recent documented peak flow reading</i>
<i>Predicted peak flow</i>	<i>Predicted peak flow based on gender, height and age</i>
<i>Percentage predicted peak flow</i>	<i>Observed peak flow/predicted peak flow</i>
<i>PEF% predicted (categorised)</i>	<i>Most recent measurement prior to index date, grouped as; ≤33%, 33-50%, ≥50%</i>
<i>FEV1</i>	<i>Forced Expiratory Volume in the first second (L), and the % of the predicted normal value for age, gender and height. Most recent observed FEV1 values</i>
<i>FVC</i>	<i>Forced Vital Capacity (L). Most recent observed FVC values</i>
<i>FEV1 % predicted</i>	<i>Most recent observed FEV1 values/predicted FEV1 values</i>
<i>FEV1 % predicted (categorised)</i>	<i>FEV1% predicted grouped as ≤50%, 50-80%, ≥80%</i>
<i>Standalone inhaled corticosteroids (ICS) prescription</i>	<i>Any standalone ICS prescription</i>
<i>Combination inhaled corticosteroid (ICS/LABA) prescription</i>	<i>Any ICS/LABA prescription</i>
<i>Standalone LAMA prescriptions per patient</i>	<i>Any standalone LAMA prescription</i>
<i>LTRA prescriptions</i>	<i>Any LTRA prescription</i>
<i>Theophylline prescriptions</i>	<i>Any theophylline prescription</i>

* Active defined as diagnosis in year prior to FeNO reading or relevant medication AND Read coded diagnosis ever

<i>SABA inhalers</i>	<i>Number of SABA inhalers listed on prescriptions</i>
<i>SABA inhalers (categorised)</i>	<i>Number of SABA inhalers categorised into 0, 1-3, 4-6, 7+</i>
<i>SABA prescriptions</i>	<i>Number of prescriptions containing SABA inhalers</i>
<i>SABA prescriptions (categorised)</i>	<i>Number of prescriptions containing SABA inhalers categorised into 0, 1-3, 4-6, 7+</i>
<i>SABA daily dose</i>	<i>Number of inhalers (typically 200 doses of 100) over study period/365 shown as unit doses and µg</i>
<i>SABA daily dose (categorised)</i>	<i>Mean daily dose categorised into <100µg, 100-200µg, 201-400µg, >400µg</i>
<i>ICS daily dose</i>	<i>Total number of ICS containing inhalers, multiplied by number of ICS doses in the study year, divided by 365</i>
<i>ICS daily dose (categorised)</i>	<i>Mean daily ICS dose grouped into <250µg, 250-500µg, >500µg</i>
<i>ICS inhalers</i>	<i>Number of ICS inhalers listed on prescriptions</i>
<i>ICS inhalers (categorised)</i>	<i>Number of ICS inhalers categorised into 0, 1-3, 4-6, 7+</i>
<i>ICS prescriptions</i>	<i>Number of prescriptions containing ICS inhalers</i>
<i>ICS prescriptions (categorised)</i>	<i>Number of prescriptions containing ICS inhalers categorised into 0, 1-3, 4-6, 7+</i>
<i>Acute respiratory events</i>	<i>Count of acute respiratory events defined as: Acute prescription of oral corticosteroids OR Antibiotic prescription associated with a primary care consultation lower respiratory infection OR Lower respiratory related Accident and Emergency admission OR Unplanned lower respiratory related inpatient admission</i>
<i>Acute respiratory events (categorised)</i>	<i>Acute respiratory events categorised into 0, 1, 2, 3, 4+</i>
<i>ICS adherence</i>	<i>Medication Possession Ratio (MPR), calculated by dividing the total of one day's supply by the total number of days evaluated, multiplied by 100%. The evaluation period for every person is 365 days in the study year.</i>
<i>Number of severe exacerbations</i>	<i>During study year, defined according to ATS/ERS Task Force position statement as a respiratory-related inpatient admission, A&E attendance or a prescription for a course of acute oral corticosteroids (OCS).</i>
<i>Respiratory-related primary care consultations</i>	<i>Number in study period</i>
<i>Respiratory related accident and emergency admission</i>	<i>Number in study period</i>
<i>Respiratory related inpatient attendance</i>	<i>Number in study period</i>

6.4.4 Health care resource utilisation

Consultations counted as distinct dates with clinical codes (excluding admin codes)

<i>Asthma related consultation</i>	<i>Any Lower GP respiratory consultation</i>
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<i>Asthma related accident and emergency attendance</i>	<i>Count of accident and emergency attendances with a lower respiratory code or on the same day as a GP respiratory consultation</i>
<i>Asthma related hospitalisations</i>	<i>Count of inpatient admissions for a lower respiratory code or generic inpatient code on same day as a GP respiratory consultation</i>

7.0 Statistical analysis

7.1 Software used

All statistical analyses have been conducted using Stata SE version 14.2 and R version 3.0.2. A statistically significant result was defined as a $P \leq 0.05$.

7.2 Power calculation

The study protocol originally considered multiple outcomes showing a 20% difference as being relevant. The sample size was calculated by accounting for multiple testing with a Bonferonni correction. With 4 comparisons, and an alpha of 0.0125, 800 patients were necessary to show at least 20% difference between groups with a 90% power. This was later revised to detect a difference in a single outcome only namely a 20% in exacerbation rate between two groups of interest. When the sample size is 807 in each group, a single group t-test with a 0.050 two sided significance level will have 90% power to detect the difference between a mean of 0.8 in the control group* and 0.96 in the comparator group assuming that the standard deviation is 1.4. When the sample size is 603 in each group, a single t-test with a 0.050 two-sided significance level will have 80% power to detect the difference between the two means.

7.3 Methods of analyses

Characteristics and analyses of study outcomes were performed using the following two categorisations:

1. FeNO readings grouped as low (<25ppb), medium (≥ 25 and <50ppb) and high (≥ 50 ppb), and BEC as low (<300/ μ L) and high (≥ 300 / μ L)
2. FeNO readings grouped as low (<35ppb) and high (≥ 35 ppb), and BEC as low (<300/ μ L) and high (≥ 300 / μ L)

A subpopulation of current smokers was characterised using the first categorisation. Further

* Based on patients prescribed fixed dose combination inhalers (Tuncelli O, Williams SA, Kern DM et al. Comparative effectiveness of budesonide-formoterol combination and fluticasone-salmeterol combination for asthma management: a United States retrospective database analysis. J Allergy Clin Immunol Pract. 2014. 2 (6) 719-26

analysis in this smoking subpopulation was not carried out because of limited patient numbers. Healthcare resource utilisation were assessed only using both criteria, but costs were calculated only for the second categorisation, as this was considered the most relevant criteria to practicing physicians.

Patients were directly matched 1:1 on age (within 10 years), sex, and smoking status. Cases that were missing these variables were dropped from the analysis.

7.4 Methods of characterisation

Descriptive statistics of all characteristics were computed for each group of patients within the cohorts using both categorisations.

Continuous variables were summarised using the number and percentage of non-missing observations, mean and standard deviation for normally distributed variables and, median and inter-quartile range (difference between the 25th and 75th percentile) for non-normally distributed variables.

Binary and categorical variables were summarised using the number and percentage of non-missing observations and the count and percentage by category.

Characteristics were compared between different patient groups: Pearson's Chi square test was used to compare percentages between different groups. In case of a small number of observations per groups a Fisher test was used. Student t-test to compare a continuous variable between two groups. In case, of small number of observations per groups, a non-parametric test of Mann-Whitney was used. In case the continuous variable was compared between more than two groups a non-parametric Kruskal-Wallis test was used where sample size does not allow an ANOVA test.

7.5 Analysis of study outcomes

7.5.1 Main analysis

The number of severe exacerbations was compared between matched patients in the groups of interest. The analysis for categorisation 1 compared patients with:

- A high BEC and high FeNO vs a low BEC and low FeNO (reference group)
- A high BEC OR high FeNO vs the reference group

The analysis for categorisation 2 compared patients with:

- A high BEC and high FeNO vs the reference group

- A high BEC vs the reference group
- High FeNO vs the reference group

Conditional Poisson regression analyses were performed to estimate the rate ratio (RR) between the groups of interest, with a 95% confidence interval.

8.0 Characterisation

8.1 Patient population

Patient numbers	Inclusion/exclusion Criteria	Number of patients excluded
2 423 445	All patients in OPCR	
1 268	Patients with FeNO readings	2 422 177
1 120	Asthma diagnosis or evidence of asthma treatment, with no evidence of COPD*	148
1 015	At least one ICS prescription	105
822	Age between 18 and 80 inclusive	193
656	No blood eosinophil reading 5 years prior to the index date	166
637	One year of data prior to FeNO reading	19
621	No other chronic respiratory condition	16
612	No maintenance OCS	9
610	Not an outlier	2

Table 2: Patient population

After applying inclusion and exclusion criteria (Table 2), 610 patients were included in the study population. The number of FeNO readings per practice can be found in the appendix (Table 227).

8.2 Unmatched characteristics of study population

All 610 patients that met the inclusion/exclusion criteria were grouped according to their biomarker values. Comparisons were initially unmatched for the purposes of exploring the main differences between patient groups, and providing data for the steering committee to decide which patient groups to compare. The description of the main differences between unmatched groups is provided in section 8.2.1 and 8.2.2. Tables of the relevant characteristics in the unmatched patient groups are provided in the appendix, sections 15.1 to 15.2.

8.2.1 Categorisation 1: ATS categorisation of FeNO as low/medium/high

A summary of demographics and comorbidities of the population grouped by categorisation 1

can be seen in Table 33. Of these 610 patients, 296 were in the low BEC, low FeNO reference group. There were 27 patients in the high BEC, high FeNO group. There were 242 patients in the high eosinophil OR high FeNO group.

Significant differences were seen between the groups in terms of gender ($p = 0.0028$), categorised age group ($p < 0.0001$), smoking status ($p = 0.0007$) and BMI ($p = 0.0022$). For the comorbidities, there was a significant difference between the number of patients with an eczema ($p = 0.0405$), rhinitis ($p = 0.0270$), and active GERD diagnosis ($p = 0.0223$). In terms of lung function, the current peak flow ($p = 0.0285$), predicted peak flow ($p = 0.0032$), and categorised FEV₁ predicted ($p = 0.0456$) were significantly different between the groups. The number of asthma related primary care consultations differed significantly across the groups ($p = 0.0446$), as did the asthma related inpatient attendances ($p = 0.0163$). The number of ICS/LABA prescriptions was significantly different ($p = 0.0096$), as was the number of total ICS inhalers ($p = 0.0165$), prescriptions ($p = 0.0165$) and mean ICS daily dose ($p = 0.00454$). The categorised ICS inhalers ($p = 0.0010$), categorised mean daily ICS ($p = 0.0026$) were also significantly different. These differences are summarised in the appendix, section 15.1.1 and 15.2.1.

The characterisation for the subpopulation of current smokers is provided in the appendix, section 15.13.

8.2.2 Categorisation 2: Steering committee categorisation of patients using the cut off ≥ 35 ppb for high FeNO, and < 35 ppb as low FeNO, and $\geq 300/\mu\text{L}$ as a high BEC, $< 300/\mu\text{L}$ as a low BEC

There were 55 patients in the high BEC, high FeNO reading group, 161 patients in the high BEC, low FeNO reading group, 47 patients in the low BEC and high FeNO reading group, and 347 patients in the low blood eosinophil and low FeNO reading group (Table 50).

In the unmatched categorisation of the study population, we observed differences in the gender ($p = 0.0177$), smoking status ($p = 0.0115$), BMI ($p = 0.0005$), and whether the patients were prescribed oral corticosteroids in the study year ($p = 0.0486$). In terms of the comorbidities, there was a significant difference in the rhinitis diagnosis ever variable ($p = 0.0422$). For the lung function tests, the predicted peak flow ($p = 0.0038$), the percentage predicted peak flow (0.0418) and FEV₁/FVC ratio differed across groups ($p = 0.0386$). There were low numbers of asthma related accident and emergency attendances ($p = 0.0177$) and asthma related unplanned inpatient attendances ($p = 0.0002$).

In terms of the asthma medication, the number of ICS/LABA prescriptions varied ($p = 0.0056$)

between patient groups. The total number of ICS inhalers ($p = 0.0219$), ICS prescriptions ($p = 0.01$) and the mean ICS daily dose ($p = 0.0153$) was different across the groups. Likewise, the categorised versions of ICS daily dose also differed ($p = 0.0133$). The asthma related medication cost differed between groups ($p = 0.0062$).

8.3 Paired unmatched comparison of study population

The main analysis focused on a comparator vs a reference group. The comparators differed depending on the categorisation. Categorisation 1 comparators included the patients with a high BEC *and* a high FeNO reading, and those with a high BEC *or* a high FeNO reading. The reference group consisted of those with low BEC and a low FeNO reading. There were more patients in the comparator population than in the reference population. Unmatched comparisons were made to help decide on the eventual matching criteria. The written summary of statistically significant differences is included in sections 8.3.1 to 8.3.5. The tables are listed in the appendix in section 15.3.

8.3.1 Categorisation 1: Unmatched comparison between high BEC/high FeNO reading ($\geq 300/\mu\text{L}$ and $\geq 50\text{ppb}$) vs low BEC/low FeNO reading ($< 300/\mu\text{L}$ and $< 25\text{ppb}$)

There were 27 patients in the comparator group ($\text{BEC} \geq 300/\mu\text{L}$ and $\text{FeNO} \geq 50\text{ppb}$), and 296 patients in the reference group ($\text{BEC} < 300/\mu\text{L}$ and $\text{FeNO} < 25\text{ppb}$). Differences between groups were seen, with a greater proportion under 35 ($p < 0.0001$), a lower BMI ($p = 0.0098$), more acute oral corticosteroid prescriptions ($p = 0.0406$), fewer GERD diagnosis ever ($p = 0.0408$) and fewer GERD active ($p = 0.0202$), a lower categorised percent predicted peak flow ($p = 0.0054$) in the comparator group. The numbers of primary care asthma consultations ($p = 0.0363$) and asthma related inpatient admissions ($p = 0.0009$) were higher in the comparator group. The number of ICS/LABA and standalone ICS inhalers, daily ICS dosage and categorised ICS dosage was consistent with fewer patients in a higher ICS usage comparator group. The number of categorised ($p = 0.0063$) and non categorised ($p = 0.0049$) severe exacerbations, also differed, with more exacerbations in the comparator group.

8.3.2 Categorisation 1: Unmatched comparison between high BEC ($\geq 300/\mu\text{L}$) or high FeNO ($\geq 50\text{ppb}$) vs low BEC/low FeNO reading ($< 300/\mu\text{L}$ and $< 25\text{ppb}$)

There were 296 patients in the reference group ($< 25\text{ppb}$ FeNO AND $< 300/\mu\text{L}$ BEC). There were 242 patients in the comparator group ($\text{BEC} \geq 300/\mu\text{L}$ or $\text{FENO} \geq 50\text{ppb}$). There were differences in the gender ($p = 0.0003$) and categorised age group ($p = 0.0163$), with the reference group having more females, and being in an older age group. In addition, the mean

height of reference group was smaller ($p = 0.0006$). The proportion of patients with hypertension was higher in the reference group. The median BEC was 0.4 compared to 0.2 in the reference group. GERD diagnosis ever ($p = 0.0489$), or active GERDs was higher in the reference group ($p = 0.0195$). In terms of lung function, the current peak flow was lower in the reference group ($p = 0.0105$), as was the predicted peak flow ($p = 0.0001$). This could be partly explained by the older, shorter, more female reference group. The FEV1 percent predicted ($p = 0.0448$), and the FEV1/FVC ratio ($p = 0.0278$) were lower in the comparator group. There were fewer standalone ICS prescriptions for the comparator group ($p = 0.0178$).

8.3.3 Categorisation 2: Unmatched comparison between high BEC ($\geq 300/\mu\text{L}$) and high FeNO ($\geq 35\text{ppb}$) vs low BEC/low FeNO reading ($< 300/\mu\text{L}$ and $< 35\text{ppb}$)

There were 347 patients in the reference group ($< 35\text{ppb}$ FeNO AND $< 300/\mu\text{L}$ BEC). There were 55 patients in the comparator group (BEC $\geq 300/\mu\text{L}$ AND FENO $\geq 35\text{ppb}$). The age groups differed, with a lower proportion of patients aged 35-65 in the comparator group ($p = 0.0015$). The BMI was lower in the comparator group ($p = 0.0002$). More patients were prescribed OCS in the comparator group ($p = 0.0107$). There were more asthma related accident emergency attendances ($p = 0.0119$) and asthma related inpatient admissions ($p = 0.0004$) in the comparator group. The number of severe exacerbations ($p = 0.0063$) and acute respiratory events ($p = 0.0061$) was higher in the comparator group.

8.3.4 Categorisation 2: Unmatched comparison between high BEC ($\geq 300/\mu\text{L}$) vs low BEC/low FeNO reading ($< 300/\mu\text{L}$ and $< 35\text{ppb}$)

There were 347 patients in the reference group ($< 35\text{ppb}$ FeNO AND $< 300/\mu\text{L}$ BEC). There were 218 patients in the comparator group (BEC $\geq 300/\mu\text{L}$). The proportion of male patients was higher in the comparator group ($p = 0.0015$), which also featured more patients with a rhinitis diagnosis ($p = 0.0369$), eczema diagnosis ($p = 0.0237$) and fewer with a hypertension diagnosis ($p = 0.0487$). Both the mean current peak flow ($p = 0.0213$) and mean predicted peak flow ($p = 0.0015$) were higher in the comparator group. Patients averaged fewer standalone ICS prescriptions in the comparator group ($p = 0.0380$).

8.3.5 Categorisation 2: Unmatched comparison between high FeNO ($\geq 35\text{ppb}$) vs low BEC/low FeNO reading ($< 300/\mu\text{L}$ and $< 35\text{ppb}$)

There were 103 patients with a high FeNO reading (the comparator group) and 347 patients in the reference group. There was a greater proportion of males in the comparator group ($p =$

0.0378). The comparator group was older ($p = 0.0236$), had a lower BMI ($p < 0.0001$) and more cardiovascular ($p = 0.0480$) and GERD diagnoses ($p = 0.0236$). The predicted peak flow was higher ($p = 0.0327$) as was the FVC in the comparator group ($p = 0.0424$). There were more asthma related admissions in the comparator group ($p = 0.0093$). The mean ICS dose ($p = 0.0226$), number of ICS prescriptions ($p = 0.0065$), and number of inhalers ($p = 0.0159$) was lower in the comparator group. The categorised ICS prescriptions ($p = 0.0139$) and ICS inhalers ($p = 0.0337$) also showed a greater proportion of patients in the lower ICS usage categories for the comparator group.

8.4 Characterisation of matched patient groups

Patients were matched 1:1 on age (within 10 years), gender and smoking status. Further criteria to match were not included to preserve numbers in the cohort of interest. The statistically significant differences between patient groups of interest are summarised in section 8.4.1 to 8.4.5 along with tables showing only the covariates that were significantly different. Full tables can be found in the appendix, section 15.8 to 15.12.

8.4.1 Categorisation 1: High BEC ($\geq 300/\mu\text{L}$) AND high FeNO ($\geq 25\text{ppb}$) vs matched low BEC ($< 300/\mu\text{L}$) and low FeNO ($< 25\text{ppb}$)

There were 27 patients directly matched between the two groups. The statistically significant differences were limited to the OCS and ICS prescription. There were more patients in higher OCS usage categories ($p = 0.0427$) and more patients using OCS ($p = 0.0242$) in the comparator group (Table 3). The distribution of ICS/LABA and standalone ICS prescriptions showed a greater proportion of patients in the lower use categories in the comparator group. The distribution of ICS/LABA or standalone ICS inhalers also showed a greater proportion in the lower usage category in the comparator group.

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*
Acute oral corticosteroid prescriptions	N (% non-missing)	27 (100.0)	27 (100.0)	0.0427
	0	21 (77.8)	13 (48.1)	
	1	6 (22.2)	8 (29.6)	
	2	0 (0.0)	5 (18.5)	
	3+	0 (0.0)	1 (3.7)	
Acute oral corticosteroid use (yes/no)	N (% non-missing)	27 (100.0)	27 (100.0)	0.0242
	Yes	6 (22.2)	14 (51.9)	
Number of ICS/LABA or mono ICS prescriptions	N (% non-missing)	27 (100.0)	27 (100.0)	
	1-3	12 (44.4)	11 (40.7)	

	4-6	4 (14.8)	12 (44.4)	0.0259
	>=7	11 (40.7)	4 (14.8)	
Number of ICS/LABA or mono ICS inhalers	N (% non-missing)	27 (100.0)	27 (100.0)	0.0147
	1-3, n (%)	11 (40.7)	7 (25.9)	
	4-6, n (%)	4 (14.8)	14 (51.9)	
	>=7, n (%)	12 (44.4)	6 (22.2)	

Table 3: High BEC and high FeNO compared to matched reference Categorisation 1: High BEC ($\geq 300/\mu\text{L}$) OR high FeNO ($\geq 25\text{ppb}$) vs matched low BEC ($< 300/\mu\text{L}$) and low FeNO ($< 25\text{ppb}$)

8.4.2 Categorisation 1: High BEC ($\geq 300/\mu\text{L}$) OR high FeNO ($\geq 25\text{ppb}$) vs matched low BEC ($< 300/\mu\text{L}$) and low FeNO ($< 25\text{ppb}$)

Patients were matched on age (within 10 years), gender and smoking status. Further criteria to match were not included to preserve numbers in the cohort of interest. There were 200 patients in each group. There was a lower number of patients prescribed standalone ICS ($p = 0.0112$) and SAMA ($p = 0.0137$) in the comparator group (Table 4). There was a significantly greater proportion of patients in the higher severe exacerbation categories in the comparator group ($p = 0.0481$).

		Low eosinophil/low FeNO (n=200)	High eosinophil/high FeNO (n=200)	P value*
Mono ICS prescriptions per patient	N (% non-missing)	200 (100.0)	200 (100.0)	0.0112
	Mean (SD)	1.4 (2.7)	0.6 (1.6)	
	Median (IQR)	0.0 (1.0)	0.0 (0.0)	
SAMA prescription (yes/no)	N (% non-missing)	200 (100.0)	200 (100.0)	0.0137
	Yes	6 (3.0)	0 (0.0)	
Asthma ATS exacerbations	N (% non-missing)	173 (100.0)	173 (100.0)	0.0481
	0, n (%)	120 (69.4)	120 (69.4)	
	1, n (%)	41 (23.7)	28 (16.2)	
	2, n (%)	11 (6.4)	19 (11.0)	
	3, n (%)	0 (0.0)	5 (2.9)	

Table 4: Statistically significant differences between high BEC or high FeNO vs matched reference population

8.4.3 Categorisation 2: High BEC ($\geq 300/\mu\text{L}$) and high FeNO ($\geq 35\text{ppb}$) vs low BEC ($< 300/\mu\text{L}$) and low FeNO ($< 35\text{ppb}$)

Patients were matched on age (within 10 years), gender and smoking status. Further criteria to match were not included to preserve numbers in the cohort of interest. There were 53 patients. Patients in the comparator group had a lower BMI ($p = 0.0386$), and a lower

proportion were in the lowest ICS category (<250µg), and the highest ICS category (p = 0.0396; Table 5).

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*
BMI	N (% non-missing)	52 (98.1)	51 (96.2)	0.0386
	Mean (SD)	29.0 (5.9)	26.8 (5.6)	
	Median (IQR)	28.4 (8.3)	25.6 (7.1)	
Mean daily ICS dosage (mcg)	N (% non-missing)	53 (100.0)	53 (100.0)	0.0396
	<250	20 (37.7)	14 (26.4)	
	250-<500	10 (18.9)	22 (41.5)	
	>=500	23 (43.4)	17 (32.1)	

Table 5: High BEC and high FeNO vs matched reference group, statistically significant differences in patient groups

8.4.4 Categorisation 2: High FeNO (≥35/µL) vs low BEC (<300/µL) and low FeNO (<35ppb)

There were 98 directly matched patients in each group. The BMI was lower in the comparator group (p = 0.0063) along with the number of standalone ICS prescriptions per patient (p = 0.0295; Table 6).

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*
BMI	N (% non-missing)	96 (98.0)	94 (95.9)	0.0063
	Mean (SD)	29.3 (6.2)	26.9 (5.8)	
	Median (IQR)	27.9 (8.6)	25.7 (7.6)	
Mono ICS prescriptions per patient	N (% non-missing)	98 (100.0)	98 (100.0)	0.0295
	Mean (SD)	1.6 (2.8)	0.9 (1.9)	
	Median (IQR)	0.0 (2.0)	0.0 (1.0)	

Table 6: High FeNO vs matched reference group, statistically significant differences in patient groups

8.4.5 Categorisation 2: High BEC (≥300/µL) vs low BEC (<300/µL) and low FeNO (<25ppb)

There were 186 matched patients in each group. Patients had a lower BMI (p = 0.0492), along with fewer SAMA (p = 0.0076) and standalone ICS prescriptions (p = 0.0362) in the comparator group. The proportion of rhinitis diagnosis was higher in the comparator group (p = 0.0272). The number of ICS/LABA prescriptions per patient was also higher in the

comparator group (p = 0.0404; Table 7).

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*
BMI	N (% non-missing)	184 (98.4)	184 (98.4)	0.0492
	Mean (SD)	30.1 (6.3)	29.0 (6.7)	
	Median (IQR)	29.5 (9.0)	27.8 (7.8)	
SAMA prescriptions per patient	N (% non-missing)	186 (100.0)	186 (100.0)	0.0076
	Mean (SD)	0.1 (0.6)	0.0 (0.0)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	
Rhinitis diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.0272
	Yes	67 (36.0)	88 (47.3)	
ICS/LABA prescriptions per patient	N (% non-missing)	186 (100.0)	186 (100.0)	0.0404
	Mean (SD)	3.8 (3.9)	4.4 (3.8)	
	Median (IQR)	3.0 (6.0)	4.0 (5.0)	
Mono ICS prescriptions per patient	N (% non-missing)	186 (100.0)	186 (100.0)	0.0362
	Mean (SD)	1.3 (2.5)	0.7 (1.6)	
	Median (IQR)	0.0 (1.0)	0.0 (1.0)	

Table 7: High BEC vs reference group (categorisation 2) statistically significant differences in patient groups

9.0 Results

9.1.1 High BEC/high FeNO vs reference (categorisation 1)

The estimated rate of exacerbations in patients with $\geq 300/\mu\text{L}$ BEC and $\geq 50\text{ppb}$ FeNO compared to matched patients in the reference group was statistically significantly higher (Tables 8 and 9).

n=27	Rate ratio of exacerbations*	P value†	Lower CI (95%)	Higher CI (95%)
$\geq 300/\mu\text{L}$ eosinophil and $\geq 50\text{ppb}$ FeNO	3.67	0.005	1.49	9.04

Table 8: Rate ratio of high BEC and high FeNO vs low BEC and low FeNO reference group using conditional logistic regression (categorisation 1)

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*
Asthma ATS exacerbations	N (% non-missing)	27 (100.0)	27 (100.0)	0.0427
	0, n (%)	21 (77.8)	13 (48.1)	
	1, n (%)	6 (22.2)	8 (29.6)	
	2, n (%)	0 (0.0)	4 (14.8)	
	3, n (%)	0 (0.0)	2 (7.4)	
Asthma ATS exacerbations	Mean (SD)	0.2 (0.4)	0.8 (1.0)	0.0109
	Median (IQR)	0.0 (0.0)	1.0 (1.0)	

Table 9: Frequency matched patients for high BEC and high FeNO vs low BEC and low FeNO reference group (categorisation 1)

9.1.2 High BEC or high FeNO vs reference (categorisation 1)

The estimated exacerbation rate between patients with $\geq 300/\mu\text{L}$ BEC OR $\geq 50\text{ppb}$ FeNO (comparator group) compared to matched patients in the reference group was higher. The rate ratio was 1.31, the p-value was 0.081 and the lower confidence interval was 0.97, so a definitive statement on the association of high BEC with the exacerbation rate could not be made (Table 10). There were significantly more patients in higher exacerbation categories in the high BEC or high FeNO group compared to the reference group (p-value = 0.0481; Table 11).

n=200	Rate ratio of exacerbations*	P value	Lower CI (95%)	Higher CI (95%)
$\geq 300/\mu\text{L}$ eosinophil OR $\geq 50\text{ppb}$ FeNO	1.31	0.081	0.97	1.76

Table 10: *Compared to low eosinophil and low FeNO group (reference group) using conditional Poisson regression (categorisation 2)

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*
Asthma ATS exacerbations	N (% non-missing)	173 (100.0)	173 (100.0)	0.0481
	0, n (%)	120 (69.4)	120 (69.4)	
	1, n (%)	41 (23.7)	28 (16.2)	
	2, n (%)	11 (6.4)	19 (11.0)	
	3, n (%)	0 (0.0)	5 (2.9)	
	4+, n (%)	1 (0.6)	1 (0.6)	
Asthma ATS exacerbations	Mean (SD)	0.4 (0.6)	0.5 (0.8)	0.3423
	Median (IQR)	0.0 (1.0)	0.0 (1.0)	

Table 11: Frequency matched patients for high BEC or high FeNO vs low BEC and low FeNO reference group (categorisation 1)

9.1.3 High BEC/high FeNO vs reference (categorisation 2)

The estimated rate of exacerbations in patients with $\geq 300/\mu\text{L}$ BEC and $\geq 35\text{ppb}$ FeNO compared to matched patients in the reference group was statistically significantly higher (Tables 12 and 13).

n=53	Rate ratio of exacerbations*	P value†	Lower CI (95%)	Higher CI (95%)
≥300/μL eosinophil and ≥35ppb FeNO	1.72	0.050	1.00	2.93

Table 12: *Compared to low eosinophil and low FeNO group †Using conditional Poisson regression (categorisation 2)

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*
Asthma ATS exacerbations	N (% non-missing)	53 (100.0)	53 (100.0)	0.3080
	0, n (%)	36 (67.9)	29 (54.7)	
	1, n (%)	12 (22.6)	14 (26.4)	
	2, n (%)	5 (9.4)	8 (15.1)	
	3, n (%)	0 (0.0)	2 (3.8)	
	Mean (SD)	0.4 (0.7)	0.7 (0.9)	0.1166
	Median (IQR)	0.0 (1.0)	0.0 (1.0)	

Table 13: Frequency matched patients for high BEC and high FeNO vs low BEC and low FeNO reference group (categorisation 2)

9.1.4 High BEC vs reference (categorisation 2)

There was a higher estimated exacerbation rate in patients with ≥300/μL BEC compared to matched patients in the reference group. The rate ratio was 1.41, the p-value was 0.124 and the lower confidence interval was 0.91, so a definitive statement on the association of high BEC alone with the exacerbation rate could not be made in this study (Table 14).

n=186	Rate ratio of exacerbations*	P value	Lower CI (95%)	Higher CI (95%)
High eosinophil	1.41	0.124	0.91	2.19

Table 14: * Compared to low eosinophil and low FeNO group †Using conditional Poisson regression (categorisation 2)

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*
Asthma ATS exacerbations	N (% non-missing)	186 (100.0)	186 (100.0)	0.2149
	0, n (%)	134 (72.0)	128 (68.8)	
	1, n (%)	36 (19.4)	31 (16.7)	
	2, n (%)	15 (8.1)	20 (10.8)	
	3, n (%)	1 (0.5)	6 (3.2)	
	Mean (SD)	0.4 (0.7)	0.5 (0.9)	0.3134
	Median (IQR)	0.0 (1.0)	0.0 (1.0)	

Table 15: Frequency matched patients for high BEC vs low BEC and low FeNO reference group (categorisation 2)

9.1.5 High FeNO vs reference (categorisation 2)

There was an estimated higher exacerbation rate in patients with a FeNO reading ≥ 35 ppb compared to matched patients in the reference group. The rate ratio was 1.35, the p-value was 0.054 and the lower confidence interval was 0.99, so a definitive statement on the association of high FeNO alone with a higher exacerbation rate could not be made in this study (Table 16).

n=98	Rate ratio of exacerbations*	P value	Lower CI (95%)	Higher CI (95%)
High FeNO	1.35	0.054	0.99	1.84

*Table 16: *Compared to low eosinophil and low FeNO group using conditional Poisson regression*

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*
Asthma ATS exacerbations	N (% non-missing)	98 (100.0)	98 (100.0)	0.3126
	0, n (%)	72 (73.5)	63 (64.3)	
	1, n (%)	20 (20.4)	24 (24.5)	
	2, n (%)	6 (6.1)	9 (9.2)	
	3, n (%)	0 (0.0)	2 (2.0)	
	4, n (%)	0 (0.0)	0 (0.0)	
	Mean (SD)	0.3 (0.6)	0.5 (0.7)	0.1332
	Median (IQR)	0.0 (1.0)	0.0 (1.0)	

Table 17: Frequency matched patients for high FeNO vs low BEC and low FeNO reference group (categorisation 2)

10.0 Discussion and overall conclusions

This was a historical cross-sectional study to investigate the relationship between BEC, FeNO readings and the severe exacerbation rate in patients prescribed ICS for asthma.

In categorisation 1, patients with a BEC $\geq 300/\mu\text{L}$ and a FeNO reading ≥ 50 ppb had a statistically significantly higher estimated rate of severe exacerbations compared to the reference population (BEC $< 300/\mu\text{L}$ and a FeNO reading of < 25 ppb) (RR = 3.67 [95% CI 1.49-9.04] p-value = 0.005). This was more pronounced than the rate ratio between patients with either a BEC $\geq 300/\mu\text{L}$ or a FeNO reading ≥ 50 ppb and the reference population (RR 1.31 [95% CI 0.97 – 1.76] p-value = 0.081).

In categorisation 2, patients with a BEC $\geq 300/\mu\text{L}$ and a FeNO reading $\geq 35\text{ppb}$ had a statistically significantly higher estimated rate of severe exacerbations compared to the reference population (BEC $< 300/\mu\text{L}$ and a FeNO reading of $< 35\text{ppb}$) (RR = 1.72 [95% CI 1.00-2.93], p-value = 0.05). This was more pronounced than the estimated rate ratio between patients with BEC $\geq 300/\mu\text{L}$ alone compared to the reference population (RR 1.41 [95% CI 0.91-2.19] p-value = 0.124). It was also more pronounced than the rate ratio between patients with a FeNO reading $\geq 35\text{ppb}$ compared to the reference population (RR 1.35 [95% CI 0.99 – 1.84] p-value = 0.054).

The number of patients with both FeNO readings and blood eosinophil counts was low. Only 610 patients fulfilled the inclusion criteria which was lower than the 800 patients required for 90% power to detect a 20% difference between 4 groups. The matching process reduced the number of patients further. Only 27 high FeNO/high BEC patients were compared to the reference populations in categorisation 1. A post-hoc power calculation with an alpha of 0.025, showed that this number of patients would have only provided 80% power to detect a rate ratio of 5.3. The estimated rate ratio of exacerbations in high FeNO or high BEC patients compared to the reference population was 1.31, inferred from 200 patients. A post-hoc power calculation indicated that 200 patients gave 80% power to detect a rate ratio of 1.8.

In categorisation 2, there were more patients in the comparison of high FeNO/high BEC patients to the reference population (n = 53) compared to categorisation 1. A retrospective power calculation shows that this would have 80% power to detect a rate ratio of 3.1.

Although there was a low number of patients, there was a statistically significant association of raised BEC and raised FeNO with a raised exacerbation rate. The higher estimated exacerbation rate was more significant in categorisation 1 (p-value = 0.005) compared to categorisation 2 (p-value = 0.05), indicating that a higher FeNO reading ($\geq 50\text{ppb}$ vs $\geq 35\text{ppb}$) in the presence of raised BEC was associated with a higher exacerbation rate. The association of high BEC and high FeNO together was stronger than high BEC alone, or high FeNO alone in both categories.

The total healthcare resource costs (with and without ICS/LABA prescriptions) and medication costs (with and without ICS/LABA prescriptions) were not significantly different in categorisation 2 between patients with high FeNO/high BEC and the matched reference population. The total healthcare resource costs were also not statistically significantly different between patients with high BEC and the matched reference population, and the high FeNO population and matched reference population.

It should be noted that this cohort of patients was not a population with severe asthma, but

any patient with asthma with a prescription for asthma and recent BEC and FeNO readings.

The strength of the study is that it is based on real-life data that were obtained from a well-validated, high-quality database.

11.0 Limitations

Power analyses performed at the protocol stage of this study showed that more patients were required for sufficient power to show a difference between groups than were available.

The study dataset comprised of information collected for clinical and routine use rather than specifically for research purposes. Although extensive quality control and validity checks are conducted at the practice level, the validity and completeness of individual patient records can be limited.

The study included only patients who had a recorded blood eosinophil measurement. Such measurements are not collected routinely, so it is possible that patients with asthma who have had blood eosinophils measured, are not representative of the overall asthma population.

A limitation of all observational studies is the possibility of confounding of the results, arising from systematic differences between the patients being compared. In this study, confounding was minimised where possible by fitting multivariate models which were adjusted patient characteristics that may have varied between patient groups. Despite the measures taken, confounding by unmeasured variables may be present.

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Final report: Assessing the use of fractional exhaled Nitric Oxide and blood eosinophils as biomarkers in predicting asthma exacerbations, and evaluating the subsequent healthcare resource utilisation

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15.0 Appendix

15.1 Unmatched characterisation (categorisation 1)

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Gender	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0028
	Male	93 (31.4)	25 (34.7)	14 (53.8)	52 (42.6)	37 (55.2)	10 (37.0)	
Age	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0671
	Mean (SD)	52.9 (12.8)	50.9 (14.4)	46.8 (15.4)	51.7 (12.8)	53.2 (13.2)	43.3 (19.0)	
	Median (IQR)	55.0 (17.0)	55.0 (26.0)	47.5 (30.0)	52.0 (20.0)	56.0 (21.0)	41.0 (37.0)	
Age group	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	<0.0001
	Under 35	28 (9.5)	12 (16.7)	8 (30.8)	12 (9.8)	6 (9.0)	12 (44.4)	
	35-65	229 (77.4)	49 (68.1)	14 (53.8)	90 (73.8)	48 (71.6)	9 (33.3)	
Smoking status	66-80	39 (13.2)	11 (15.3)	4 (15.4)	20 (16.4)	13 (19.4)	6 (22.2)	0.0007
	N (% non-missing)	245 (82.8)	62 (86.1)	22 (84.6)	101 (82.8)	60 (89.6)	22 (81.5)	
	Non-smoker	110 (44.9)	36 (58.1)	15 (68.2)	30 (29.7)	32 (53.3)	14 (63.6)	
	Ex-smoker	35 (14.3)	7 (11.3)	3 (13.6)	29 (28.7)	6 (10.0)	2 (9.1)	
Height	Current smoker	100 (40.8)	19 (30.6)	4 (18.2)	42 (41.6)	22 (36.7)	6 (27.3)	0.0003
	N (% non-missing)	285 (96.3)	70 (97.2)	25 (96.2)	119 (97.5)	63 (94.0)	27 (100.0)	
	Mean (SD)	1.66 (0.09)	1.68 (0.09)	1.71 (0.09)	1.67 (0.09)	1.70 (0.07)	1.67 (0.09)	
Weight	Median (IQR)	1.64 (0.14)	1.67 (0.12)	1.72 (0.12)	1.65 (0.13)	1.70 (0.10)	1.67 (0.13)	0.1523
	N (% non-missing)	282 (95.3)	71 (98.6)	24 (92.3)	118 (96.7)	64 (95.5)	26 (96.3)	
	Mean (SD)	82.4 (18.9)	83.2 (20.7)	77.7 (19.5)	85.7 (22.0)	81.7 (20.7)	75.8 (20.8)	
	Median (IQR)	80.4 (26.5)	79.6 (26.0)	72.2 (24.3)	83.0 (33.0)	79.4 (17.0)	71.8 (23.2)	

Table 18: Demographic summary (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
BMI	N (% non-missing)	280 (94.6)	70 (97.2)	24 (92.3)	118 (96.7)	63 (94.0)	26 (96.3)	0.0022
	Mean (SD)	30.0 (6.7)	29.5 (6.1)	26.3 (5.3)	30.8 (7.6)	28.2 (7.1)	26.9 (6.4)	
	Median (IQR)	29.0 (9.1)	29.6 (8.2)	25.2 (7.8)	29.0 (9.1)	26.8 (6.7)	25.5 (8.4)	
BMI	N (% non-missing)	280 (94.6)	70 (97.2)	24 (92.3)	118 (96.7)	63 (94.0)	26 (96.3)	0.1119
	Underweight	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.8)	1 (1.6)	1 (3.8)	
	Normal	68 (24.3)	20 (28.6)	12 (50.0)	27 (22.9)	19 (30.2)	10 (38.5)	
	Overweight	89 (31.8)	16 (22.9)	5 (20.8)	35 (29.7)	23 (36.5)	8 (30.8)	
	Obese	122 (43.6)	34 (48.6)	7 (29.2)	55 (46.6)	20 (31.7)	7 (26.9)	
FENO value	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	<0.0001
	Mean (SD)	14.1 (5.7)	32.8 (6.3)	80.6 (41.5)	14.2 (5.7)	34.0 (7.2)	73.1 (28.4)	
	Median (IQR)	14.0 (10.0)	31.0 (8.0)	64.0 (32.0)	13.0 (10.0)	33.0 (11.0)	65.0 (22.0)	
Eosinophil count	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	<0.0001
	Mean (SD)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.4 (0.2)	0.5 (0.3)	0.5 (0.2)	
	Median (IQR)	0.2 (0.1)	0.2 (0.1)	0.2 (0.0)	0.4 (0.1)	0.4 (0.2)	0.5 (0.2)	
COPD diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.2727
	Yes	5 (1.7)	1 (1.4)	1 (3.8)	3 (2.5)	0 (0.0)	2 (7.4)	

Table 19: Clinical measurements (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Acute oral corticosteroid prescriptions	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0782
	0	213 (72.0)	56 (77.8)	20 (76.9)	89 (73.0)	50 (74.6)	13 (48.1)	
	1	53 (17.9)	10 (13.9)	4 (15.4)	15 (12.3)	9 (13.4)	8 (29.6)	
	2	25 (8.4)	2 (2.8)	2 (7.7)	13 (10.7)	6 (9.0)	5 (18.5)	

	3	3 (1.0)	4 (5.6)	0 (0.0)	5 (4.1)	1 (1.5)	0 (0.0)	
	4	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (3.7)	
Acute oral corticosteroid prescriptions >14 days apart	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.1656
	0	213 (72.0)	56 (77.8)	20 (76.9)	89 (73.0)	50 (74.6)	13 (48.1)	
	1	60 (20.3)	10 (13.9)	5 (19.2)	15 (12.3)	12 (17.9)	8 (29.6)	
	2	20 (6.8)	5 (6.9)	1 (3.8)	14 (11.5)	4 (6.0)	5 (18.5)	
	3	2 (0.7)	1 (1.4)	0 (0.0)	4 (3.3)	0 (0.0)	1 (3.7)	
	4	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	
Acute oral corticosteroid use (yes/no)	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0926
	Yes	83 (28.0)	16 (22.2)	6 (23.1)	33 (27.0)	17 (25.4)	14 (51.9)	
Antibiotics	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.8819
	Mean (SD)	1.3 (1.8)	1.4 (2.0)	1.3 (2.0)	1.4 (1.8)	1.1 (1.5)	1.0 (1.4)	
	Median (IQR)	1.0 (2.0)	1.0 (2.0)	1.0 (2.0)	1.0 (2.0)	1.0 (2.0)	0.0 (2.0)	
Antibiotic courses	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.9804
	0	131 (44.3)	33 (45.8)	12 (46.2)	52 (42.6)	31 (46.3)	15 (55.6)	
	1	70 (23.6)	19 (26.4)	7 (26.9)	29 (23.8)	19 (28.4)	4 (14.8)	
	2	43 (14.5)	7 (9.7)	2 (7.7)	19 (15.6)	6 (9.0)	5 (18.5)	
	3	19 (6.4)	4 (5.6)	2 (7.7)	8 (6.6)	6 (9.0)	2 (7.4)	
	4+	33 (11.1)	9 (12.5)	3 (11.5)	14 (11.5)	5 (7.5)	1 (3.7)	

Table 20: Acute asthma treatment (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Active eczema diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.5140
	Yes	9 (3.0)	2 (2.8)	2 (7.7)	6 (4.9)	1 (1.5)	2 (7.4)	

Active rhinitis diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.1324
	Yes	85 (28.7)	21 (29.2)	3 (11.5)	36 (29.5)	26 (38.8)	11 (40.7)	
Eczema diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0405
	Yes	78 (26.4)	23 (31.9)	5 (19.2)	49 (40.2)	17 (25.4)	11 (40.7)	
Rhinitis diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0270
	Yes	114 (38.5)	24 (33.3)	5 (19.2)	52 (42.6)	36 (53.7)	13 (48.1)	
Cardiovascular diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.4444
	Yes	42 (14.2)	8 (11.1)	1 (3.8)	14 (11.5)	8 (11.9)	1 (3.7)	
IHD diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.8121
	Yes	15 (5.1)	3 (4.2)	0 (0.0)	8 (6.6)	3 (4.5)	1 (3.7)	
Heart failure diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.4968
	Yes	1 (0.3)	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)	
Hypertension diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.2113
	Yes	79 (26.7)	20 (27.8)	4 (15.4)	26 (21.3)	12 (17.9)	3 (11.1)	

Table 21: Comorbidities 1 (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value
Diabetes diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.3785
	Yes	27 (9.1)	4 (5.6)	1 (3.8)	10 (8.2)	8 (11.9)	0 (0.0)	
Osteoporosis diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.3185
	Yes	8 (2.7)	0 (0.0)	0 (0.0)	3 (2.5)	1 (1.5)	2 (7.4)	
GERD diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0342
	Yes	58 (19.6)	6 (8.3)	1 (3.8)	19 (15.6)	11 (16.4)	1 (3.7)	
GERD active diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0223
	Yes	50 (16.9)	5 (6.9)	1 (3.8)	13 (10.7)	10 (14.9)	0 (0.0)	
Anxiety or depression	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.4564

	Yes	120 (40.5)	29 (40.3)	10 (38.5)	49 (40.2)	20 (29.9)	7 (25.9)	
Chronic Kidney Disease	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.4630
	Yes	61 (20.6)	10 (13.9)	5 (19.2)	16 (13.1)	10 (14.9)	5 (18.5)	
Cerebrovascular disease	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.6708
	Yes	11 (3.7)	3 (4.2)	0 (0.0)	3 (2.5)	1 (1.5)	0 (0.0)	
Myocardial infarct	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.5161
	Yes	3 (1.0)	2 (2.8)	0 (0.0)	3 (2.5)	0 (0.0)	0 (0.0)	

Table 22: Comorbidities 2 (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Current peak flow	N (% non-missing)	160 (54.1)	49 (68.1)	19 (73.1)	57 (46.7)	42 (62.7)	20 (74.1)	0.0285
	Mean (SD)	401.3 (102.9)	403.6 (112.7)	431.1 (123.3)	423.6 (132.1)	469.8 (111.2)	406.0 (142.4)	
	Median (IQR)	392.5 (115.0)	390.0 (160.0)	435.7 (140.0)	430.0 (200.0)	450.0 (150.0)	400.0 (92.5)	
Predicted peak flow	N (% non-missing)	158 (53.4)	49 (68.1)	19 (73.1)	57 (46.7)	42 (62.7)	20 (74.1)	0.0032
	Mean (SD)	495.7 (71.4)	503.2 (79.3)	542.6 (60.1)	526.8 (81.3)	534.8 (69.7)	505.8 (74.9)	
	Median (IQR)	472.5 (121.1)	480.6 (123.5)	563.0 (109.4)	485.8 (136.7)	547.6 (130.6)	478.3 (127.7)	
Percentage predicted peak flow	N (% non-missing)	158 (53.4)	49 (68.1)	19 (73.1)	57 (46.7)	42 (62.7)	20 (74.1)	0.3489
	Mean (SD)	81.1 (15.9)	79.8 (16.5)	78.8 (18.7)	79.7 (19.1)	87.7 (16.4)	79.5 (22.4)	
	Median (IQR)	81.9 (22.1)	83.3 (24.5)	78.8 (19.1)	78.3 (32.3)	87.2 (27.3)	82.3 (25.5)	
% predicted PF groups	N (% non-missing)	158 (53.4)	49 (68.1)	19 (73.1)	57 (46.7)	42 (62.7)	20 (74.1)	0.6204
	<=33%	4 (2.5)	2 (4.1)	1 (5.3)	2 (3.5)	0 (0.0)	2 (10.0)	
	>33% to <50%	45 (28.5)	16 (32.7)	5 (26.3)	20 (35.1)	9 (21.4)	5 (25.0)	
	>=50%	109 (69.0)	31 (63.3)	13 (68.4)	35 (61.4)	33 (78.6)	13 (65.0)	

Table 23: Peak flow (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value
FeV ₁	N (% non-missing)	53 (17.9)	10 (13.9)	4 (15.4)	28 (23.0)	13 (19.4)	4 (14.8)	0.2774
	Mean (SD)	11.1 (25.0)	2.2 (1.2)	2.6 (0.5)	7.6 (20.8)	3.1 (0.9)	2.4 (1.1)	
	Median (IQR)	2.3 (1.2)	2.1 (1.1)	2.8 (0.6)	2.4 (1.4)	3.2 (1.1)	2.0 (1.5)	
FVC	N (% non-missing)	87 (29.4)	13 (18.1)	6 (23.1)	39 (32.0)	19 (28.4)	4 (14.8)	0.1489
	Mean (SD)	3.3 (0.9)	3.8 (1.1)	3.7 (0.5)	3.4 (0.9)	4.0 (1.3)	3.2 (1.3)	
	Median (IQR)	3.2 (1.2)	3.5 (1.0)	3.9 (0.8)	3.3 (1.3)	4.1 (1.8)	3.3 (1.7)	
FEV ₁ /FVC_ratio	N (% non-missing)	40 (13.5)	9 (12.5)	4 (15.4)	16 (13.1)	11 (16.4)	4 (14.8)	0.0670
	Mean (SD)	0.8 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.8 (0.1)	
	Median (IQR)	0.8 (0.1)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)	0.8 (0.2)	0.8 (0.2)	
FEV ₁ Percent Predicted	N (% non-missing)	55 (18.6)	10 (13.9)	4 (15.4)	28 (23.0)	13 (19.4)	5 (18.5)	0.2960
	Mean (SD)	71.8 (40.1)	74.3 (32.2)	55.0 (38.7)	59.7 (44.3)	34.0 (46.5)	66.4 (38.7)	
	Median (IQR)	83.0 (44.0)	81.0 (32.9)	68.0 (54.0)	72.5 (94.5)	1.0 (91.0)	81.0 (25.0)	
FEV1 % predicted groups	N (% non-missing)	55 (18.6)	10 (13.9)	4 (15.4)	28 (23.0)	13 (19.4)	5 (18.5)	0.0456
	50% or less	12 (21.8)	1 (10.0)	1 (25.0)	10 (35.7)	9 (69.2)	1 (20.0)	
	>50% to <80%	13 (23.6)	4 (40.0)	1 (25.0)	8 (28.6)	0 (0.0)	1 (20.0)	
	80% to <100%	15 (27.3)	4 (40.0)	2 (50.0)	3 (10.7)	2 (15.4)	3 (60.0)	
	100%+	15 (27.3)	1 (10.0)	0 (0.0)	7 (25.0)	2 (15.4)	0 (0.0)	

Table 24: Lung function (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value
Asthma consultations	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0446
	Mean (SD)	1.8 (1.5)	2.3 (1.8)	2.5 (2.6)	1.7 (1.3)	1.9 (2.0)	2.3 (1.4)	

	Median (IQR)	1.5 (1.0)	2.0 (2.0)	1.5 (2.0)	2.0 (1.0)	1.0 (1.0)	2.0 (2.0)	
Asthma consultations	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.4902
	0	34 (11.5)	7 (9.7)	3 (11.5)	17 (13.9)	9 (13.4)	3 (11.1)	
	1	114 (38.5)	20 (27.8)	10 (38.5)	43 (35.2)	27 (40.3)	5 (18.5)	
	2+	148 (50.0)	45 (62.5)	13 (50.0)	62 (50.8)	31 (46.3)	19 (70.4)	
Asthma related accident and emergency attendance	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.1499
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	
Asthma related accident and emergency attendance	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.1499
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	
Asthma related unplanned inpatient attendance	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0163
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (3.7)	
Asthma related unplanned inpatient attendance	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0163
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (3.7)	

Table 25: Healthcare Resource Utilisation (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value
LAMA prescriptions per patient	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.4825
	Mean (SD)	0.0 (0.4)	0.1 (0.4)	0.2 (1.2)	0.3 (1.5)	0.0 (0.0)	0.1 (0.8)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	
ICS/LABA prescriptions per patient	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0096
	Mean (SD)	4.2 (4.1)	3.2 (3.5)	2.5 (3.0)	4.9 (3.9)	4.2 (4.3)	3.2 (2.5)	
	Median (IQR)	3.0 (6.0)	2.0 (5.5)	1.5 (4.0)	4.0 (5.0)	3.0 (6.0)	3.0 (5.0)	
Mono ICS prescriptions per patient	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.1344
	Mean (SD)	1.2 (2.5)	1.1 (2.2)	0.4 (1.2)	0.5 (1.4)	0.7 (1.5)	1.0 (2.2)	

	Median (IQR)	0.0 (1.0)	0.0 (1.5)	0.0 (0.0)	0.0 (0.0)	0.0 (1.0)	0.0 (1.0)	
LTRA prescriptions per patient	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.4427
	Mean (SD)	0.7 (2.3)	0.6 (2.0)	0.0 (0.0)	0.9 (2.8)	0.6 (2.2)	0.9 (2.4)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	
THEO prescriptions per patient	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.8200
	Mean (SD)	0.1 (1.0)	0.1 (0.6)	0.0 (0.0)	0.2 (1.7)	0.1 (1.0)	0.0 (0.0)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	

Table 26: Asthma prescriptions per patient (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
LABA prescription (yes/no)	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.6326
	Yes	8 (2.7)	0 (0.0)	1 (3.8)	2 (1.6)	1 (1.5)	0 (0.0)	
LAMA prescription (yes/no)	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.4906
	Yes	5 (1.7)	2 (2.8)	1 (3.8)	5 (4.1)	0 (0.0)	1 (3.7)	
SAMA prescription (yes/no)	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.5826
	Yes	7 (2.4)	1 (1.4)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	
LTRA prescription (yes/no)	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.4315
	Yes	38 (12.8)	10 (13.9)	0 (0.0)	17 (13.9)	8 (11.9)	5 (18.5)	
Theophylline prescription (yes/no)	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.8187
	Yes	6 (2.0)	2 (2.8)	0 (0.0)	4 (3.3)	1 (1.5)	0 (0.0)	

Table 27: Asthma prescriptions yes/no (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
SABA prescriptions	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.4641
	Mean (SD)	3.0 (3.2)	3.3 (4.1)	2.5 (2.6)	3.4 (3.9)	2.9 (3.6)	4.3 (4.4)	
	Median (IQR)	2.0 (3.5)	2.0 (3.0)	1.5 (3.0)	2.0 (4.0)	2.0 (3.0)	3.0 (4.0)	
SABA inhalers	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.5290
	Mean (SD)	3.6 (4.3)	4.0 (4.9)	3.1 (4.2)	3.6 (4.1)	3.7 (5.4)	5.0 (5.6)	
	Median (IQR)	2.0 (4.0)	2.0 (4.5)	1.5 (3.0)	2.0 (4.0)	2.0 (4.0)	3.0 (3.0)	
SABA daily dose	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.5237
	Mean (SD)	1.0 (1.2)	1.1 (1.4)	0.9 (1.2)	1.0 (1.1)	1.0 (1.5)	1.4 (1.5)	
	Median (IQR)	0.6 (1.1)	0.6 (1.2)	0.4 (0.8)	0.6 (1.1)	0.6 (1.1)	0.8 (0.8)	
SABA dosage	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.5237
	Mean (SD)	197.6 (238.6)	216.9 (271.2)	170.7 (230.6)	196.5 (222.2)	198.8 (293.5)	272.3 (305.8)	
	Median (IQR)	109.6 (219.2)	109.6 (246.6)	82.2 (164.4)	109.6 (219.2)	109.6 (219.2)	164.4 (164.4)	

Table 28: SABA usage (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Number of SABA prescriptions	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.8253
	0	68 (23.0)	16 (22.2)	6 (23.1)	27 (22.1)	17 (25.4)	2 (7.4)	
	1-3	136 (45.9)	34 (47.2)	13 (50.0)	51 (41.8)	35 (52.2)	14 (51.9)	
	4-6	54 (18.2)	10 (13.9)	4 (15.4)	22 (18.0)	7 (10.4)	6 (22.2)	
	>=7	38 (12.8)	12 (16.7)	3 (11.5)	22 (18.0)	8 (11.9)	5 (18.5)	
Number of SABA inhalers	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.7606
	0	68 (23.0)	16 (22.2)	6 (23.1)	27 (22.1)	17 (25.4)	2 (7.4)	
	1-3	119 (40.2)	31 (43.1)	12 (46.2)	47 (38.5)	31 (46.3)	12 (44.4)	
	4-6	58 (19.6)	9 (12.5)	5 (19.2)	22 (18.0)	9 (13.4)	8 (29.6)	

	>=7	51 (17.2)	16 (22.2)	3 (11.5)	26 (21.3)	10 (14.9)	5 (18.5)	
Mean daily SABA dosage (mcg)	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.7535
	<100	109 (36.8)	30 (41.7)	13 (50.0)	48 (39.3)	27 (40.3)	6 (22.2)	
	100-200	80 (27.0)	17 (23.6)	5 (19.2)	27 (22.1)	21 (31.3)	8 (29.6)	
	201-400	68 (23.0)	12 (16.7)	6 (23.1)	30 (24.6)	11 (16.4)	8 (29.6)	
	>400	39 (13.2)	13 (18.1)	2 (7.7)	17 (13.9)	8 (11.9)	5 (18.5)	

Table 29: Categorised SABA usage (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
ICS daily dose	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0454
	Mean (SD)	586.9 (503.5)	549.4 (477.0)	357.4 (349.2)	623.2 (497.7)	588.3 (523.4)	443.6 (342.1)	
	Median (IQR)	427.4 (602.7)	402.7 (569.9)	219.2 (246.6)	493.1 (591.8)	438.4 (608.2)	350.7 (252.0)	
ICS inhalers	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0165
	Mean (SD)	7.0 (5.2)	5.9 (3.9)	4.3 (4.3)	6.9 (4.6)	6.9 (5.4)	5.1 (2.8)	
	Median (IQR)	6.0 (7.0)	5.0 (5.5)	3.0 (3.0)	6.0 (7.0)	5.0 (7.0)	5.0 (3.0)	
ICS prescriptions	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0043
	Mean (SD)	5.6 (3.8)	4.5 (3.3)	3.3 (3.1)	5.5 (3.6)	5.1 (3.9)	4.4 (2.3)	
	Median (IQR)	5.0 (6.0)	3.0 (4.0)	2.0 (4.0)	5.0 (5.0)	4.0 (4.0)	5.0 (4.0)	
ICS adherence	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0988
	Mean (SD)	70.1 (65.8)	69.5 (67.6)	51.6 (54.5)	62.5 (42.8)	74.0 (68.5)	52.3 (32.9)	
	Median (IQR)	64.4 (69.9)	50.7 (71.2)	37.0 (30.1)	54.8 (60.3)	65.8 (63.0)	49.3 (35.7)	

Table 30: ICS usage (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Number of ICS containing inhalers	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0010
	1-3	90 (30.4)	24 (33.3)	17 (65.4)	36 (29.5)	23 (34.3)	7 (25.9)	
	4-6	76 (25.7)	25 (34.7)	4 (15.4)	27 (22.1)	16 (23.9)	14 (51.9)	
	>=7	130 (43.9)	23 (31.9)	5 (19.2)	59 (48.4)	28 (41.8)	6 (22.2)	
Mean daily ICS dosage (mcg)	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0026
	<250	89 (30.1)	22 (30.6)	16 (61.5)	30 (24.6)	21 (31.3)	8 (29.6)	
	250-<500	74 (25.0)	24 (33.3)	4 (15.4)	32 (26.2)	19 (28.4)	14 (51.9)	
	>=500	133 (44.9)	26 (36.1)	6 (23.1)	60 (49.2)	27 (40.3)	5 (18.5)	
ICS adherence (%)	N (% non-missing)	295 (99.7)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.5376
	<40	95 (32.2)	24 (33.3)	13 (50.0)	44 (36.1)	17 (25.4)	10 (37.0)	
	40-79	90 (30.5)	26 (36.1)	9 (34.6)	40 (32.8)	22 (32.8)	12 (44.4)	
	80-120	76 (25.8)	15 (20.8)	2 (7.7)	28 (23.0)	20 (29.9)	4 (14.8)	
	>120	34 (11.5)	7 (9.7)	2 (7.7)	10 (8.2)	8 (11.9)	1 (3.7)	

Table 31: Categorized ICS usage (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Asthma ATS exacerbations	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0971
	0	213 (72.0)	56 (77.8)	20 (76.9)	89 (73.0)	50 (74.6)	13 (48.1)	
	1	60 (20.3)	10 (13.9)	5 (19.2)	15 (12.3)	11 (16.4)	8 (29.6)	
	2	20 (6.8)	5 (6.9)	1 (3.8)	14 (11.5)	5 (7.5)	4 (14.8)	
	3	2 (0.7)	1 (1.4)	0 (0.0)	4 (3.3)	0 (0.0)	2 (7.4)	
	4	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	
N (% non-missing)		296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0691

Asthma ATS exacerbations	Mean (SD)	0.4 (0.7)	0.3 (0.67)	0.3 (0.5)	0.5 (0.8)	0.4 (0.8)	0.8 (1.0)	
Acute respiratory event	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.5152
	0	117 (39.5)	30 (41.7)	11 (42.3)	44 (36.1)	29 (43.3)	12 (44.4)	
	1	83 (28.0)	18 (25.0)	8 (30.8)	30 (24.6)	21 (31.3)	3 (11.1)	
	2	44 (14.9)	10 (13.9)	3 (11.5)	27 (22.1)	5 (7.5)	9 (33.3)	
	3	23 (7.8)	4 (5.6)	1 (3.8)	10 (8.2)	5 (7.5)	1 (3.7)	
	4+	29 (9.8)	10 (13.9)	3 (11.5)	11 (9.0)	7 (10.4)	2 (7.4)	
Acute respiratory event	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.8639
	Mean (SD)	1.3 (1.6)	1.4 (1.9)	1.3 (1.7)	1.4 (1.6)	1.1 (1.4)	1.2 (1.4)	

Table 32: Exacerbations (categorisation 1)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

15.1.1 Statistically significant differences between unmatched patient groups (categorisation 1)

Characteristic		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Categorised age group	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	<0.0001
	Under 35	28 (9.5)	12 (16.7)	8 (30.8)	12 (9.8)	6 (9.0)	12 (44.4)	
	35-65	229 (77.4)	49 (68.1)	14 (53.8)	90 (73.8)	48 (71.6)	9 (33.3)	
	66-80	39 (13.2)	11 (15.3)	4 (15.4)	20 (16.4)	13 (19.4)	6 (22.2)	
Gender	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0028
	Male	93 (31.4)	25 (34.7)	14 (53.8)	52 (42.6)	37 (55.2)	10 (37.0)	
Smoking status	N (% non-missing)	245 (82.8)	62 (86.1)	22 (84.6)	101 (82.8)	60 (89.6)	22 (81.5)	0.0007
	Non-smoker	110 (44.9)	36 (58.1)	15 (68.2)	30 (29.7)	32 (53.3)	14 (63.6)	
	Ex-smoker	35 (14.3)	7 (11.3)	3 (13.6)	29 (28.7)	6 (10.0)	2 (9.1)	
	Current smoker	100 (40.8)	19 (30.6)	4 (18.2)	42 (41.6)	22 (36.7)	6 (27.3)	
BMI	N (% non-missing)	280 (94.6)	70 (97.2)	24 (92.3)	118 (96.7)	63 (94.0)	26 (96.3)	0.0022
	Mean (SD)	30.0 (6.7)	29.5 (6.1)	26.3 (5.3)	30.8 (7.6)	28.2 (7.1)	26.9 (6.4)	
	Median (IQR)	29.0 (9.1)	29.6 (8.2)	25.2 (7.8)	29.0 (9.1)	26.8 (6.7)	25.5 (8.4)	
Eczema diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0405

	Yes	78 (26.4)	23 (31.9)	5 (19.2)	49 (40.2)	17 (25.4)	11 (40.7)	
Rhinitis diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0270
	Yes	114 (38.5)	24 (33.3)	5 (19.2)	52 (42.6)	36 (53.7)	13 (48.1)	
GERD active diagnosis	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0223
	Yes	50 (16.9)	5 (6.9)	1 (3.8)	13 (10.7)	10 (14.9)	0 (0.0)	
Current peak flow	N (% non-missing)	160 (54.1)	49 (68.1)	19 (73.1)	57 (46.7)	42 (62.7)	20 (74.1)	0.0285
	Mean (SD)	401.3 (102.9)	403.6 (112.7)	431.1 (123.3)	423.6 (132.1)	469.8 (111.2)	406.0 (142.4)	
	Median (IQR)	392.5 (115.0)	390.0 (160.0)	435.7 (140.0)	430.0 (200.0)	450.0 (150.0)	400.0 (92.5)	
Predicted peak flow	N (% non-missing)	158 (53.4)	49 (68.1)	19 (73.1)	57 (46.7)	42 (62.7)	20 (74.1)	0.0032
	Mean (SD)	495.7 (71.4)	503.2 (79.3)	542.6 (60.1)	526.8 (81.3)	534.8 (69.7)	505.8 (74.9)	
	Median (IQR)	472.5 (121.1)	480.6 (123.5)	563.0 (109.4)	485.8 (136.7)	547.6 (130.6)	478.3 (127.7)	
FEV1 % predicted groups	N (% non-missing)	55 (18.6)	10 (13.9)	4 (15.4)	28 (23.0)	13 (19.4)	5 (18.5)	0.0456
	50% or less	12 (21.8)	1 (10.0)	1 (25.0)	10 (35.7)	9 (69.2)	1 (20.0)	
	>50% to <80%	13 (23.6)	4 (40.0)	1 (25.0)	8 (28.6)	0 (0.0)	1 (20.0)	
	80% to <100%	15 (27.3)	4 (40.0)	2 (50.0)	3 (10.7)	2 (15.4)	3 (60.0)	
	100%+	15 (27.3)	1 (10.0)	0 (0.0)	7 (25.0)	2 (15.4)	0 (0.0)	
Asthma consultations	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0446
	Mean (SD)	1.8 (1.5)	2.3 (1.8)	2.5 (2.6)	1.7 (1.3)	1.9 (2.0)	2.3 (1.4)	
	Median (IQR)	1.5 (1.0)	2.0 (2.0)	1.5 (2.0)	2.0 (1.0)	1.0 (1.0)	2.0 (2.0)	
Asthma related unplanned inpatient attendance	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0163
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (3.7)	
ICS/LABA prescriptions per patient	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0096
	Mean (SD)	4.2 (4.1)	3.2 (3.5)	2.5 (3.0)	4.9 (3.9)	4.2 (4.3)	3.2 (2.5)	
	Median (IQR)	3.0 (6.0)	2.0 (5.5)	1.5 (4.0)	4.0 (5.0)	3.0 (6.0)	3.0 (5.0)	
ICS daily dose	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0454
	Mean (SD)	586.9 (503.5)	549.4 (477.0)	357.4 (349.2)	623.2 (497.7)	588.3 (523.4)	443.6 (342.1)	
	Median (IQR)	427.4 (602.7)	402.7 (569.9)	219.2 (246.6)	493.1 (591.8)	438.4 (608.2)	350.7 (252.0)	
ICS inhalers	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0165
	Mean (SD)	7.0 (5.2)	5.9 (3.9)	4.3 (4.3)	6.9 (4.6)	6.9 (5.4)	5.1 (2.8)	
	Median (IQR)	6.0 (7.0)	5.0 (5.5)	3.0 (3.0)	6.0 (7.0)	5.0 (7.0)	5.0 (3.0)	

ICS prescriptions	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0043
	Mean (SD)	5.6 (3.8)	4.5 (3.3)	3.3 (3.1)	5.5 (3.6)	5.1 (3.9)	4.4 (2.3)	
	Median (IQR)	5.0 (6.0)	3.0 (4.0)	2.0 (4.0)	5.0 (5.0)	4.0 (4.0)	5.0 (4.0)	
Number of ICS containing inhalers	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0010
	1-3	90 (30.4)	24 (33.3)	17 (65.4)	36 (29.5)	23 (34.3)	7 (25.9)	
	4-6	76 (25.7)	25 (34.7)	4 (15.4)	27 (22.1)	16 (23.9)	14 (51.9)	
	>=7	130 (43.9)	23 (31.9)	5 (19.2)	59 (48.4)	28 (41.8)	6 (22.2)	
Mean daily ICS dosage (mcg)	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0026
	<250	89 (30.1)	22 (30.6)	16 (61.5)	30 (24.6)	21 (31.3)	8 (29.6)	
	250-<500	74 (25.0)	24 (33.3)	4 (15.4)	32 (26.2)	19 (28.4)	14 (51.9)	
	>=500	133 (44.9)	26 (36.1)	6 (23.1)	60 (49.2)	27 (40.3)	5 (18.5)	

Table 33: Unmatched comparison using categorisation 1, with significant differences between covariates illustrated. Comparison based on non-missing data

15.2 Unmatched characterisation (categorisation 2)

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
Gender	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0177
	Male	113 (32.6)	19 (40.4)	74 (46.0)	25 (45.5)	
Age	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.1825
	Mean (SD)	52.7 (13.0)	48.0 (14.9)	52.0 (12.9)	48.6 (17.0)	
	Median (IQR)	55.0 (17.0)	52.0 (28.0)	52.0 (20.0)	53.0 (31.0)	
Age group	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0014
	Under 35	36 (10.4)	12 (25.5)	16 (9.9)	14 (25.5)	
	35-65	264 (76.1)	28 (59.6)	117 (72.7)	30 (54.5)	
	66-80	47 (13.5)	7 (14.9)	28 (17.4)	11 (20.0)	
Smoking status	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0115
	Non-smoker	138 (39.8)	23 (48.9)	45 (28.0)	31 (56.4)	
	Ex-smoker	40 (11.5)	5 (10.6)	32 (19.9)	5 (9.1)	
	Current smoker	111 (32.0)	12 (25.5)	58 (36.0)	12 (21.8)	
Height	N (% non-missing)	336 (96.8)	44 (93.6)	156 (96.9)	53 (96.4)	0.0031

	Mean (SD)	165.93 (9.39)	170.14 (9.11)	167.86 (8.90)	164.74 (24.52)	
	Median (IQR)	165.00 (13.00)	170.10 (10.15)	167.00 (11.75)	167.00 (12.00)	
Weight	N (% non-missing)	333 (96.0)	44 (93.6)	156 (96.9)	52 (94.5)	0.0157
	Mean (SD)	82.4 (18.6)	81.2 (24.5)	85.6 (22.0)	75.9 (18.8)	
	Median (IQR)	80.0 (25.5)	75.0 (25.8)	82.3 (28.5)	74.9 (21.3)	

Table 34: Demographic summary (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
BMI	N (% non-missing)	331 (95.4)	43 (91.5)	155 (96.3)	51 (92.7)	0.0005
	Mean (SD)	29.9 (6.5)	27.8 (6.9)	30.4 (7.8)	26.7 (5.6)	
	Median (IQR)	29.0 (8.4)	25.9 (8.9)	28.8 (9.0)	25.6 (7.2)	
BMI	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0411
	Underweight	1 (0.3)	0 (0.0)	2 (1.2)	1 (1.8)	
	Normal	81 (23.3)	19 (40.4)	36 (22.4)	20 (36.4)	
	Overweight	102 (29.4)	8 (17.0)	48 (29.8)	18 (32.7)	
FENO value	Obese	147 (42.4)	16 (34.0)	69 (42.9)	12 (21.8)	
	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	<0.0001
	Mean (SD)	16.3 (7.6)	63.0 (36.6)	17.7 (8.1)	56.8 (25.7)	
Eosinophil count	Median (IQR)	15.0 (11.0)	51.0 (24.0)	17.0 (13.0)	49.0 (25.0)	
	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	<0.0001
	Mean (SD)	0.2 (0.1)	0.2 (0.1)	0.4 (0.2)	0.5 (0.3)	
COPD diagnosis	Median (IQR)	0.2 (0.1)	0.2 (0.1)	0.4 (0.2)	0.5 (0.3)	
	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.4614
	Yes	5 (1.4)	2 (4.3)	3 (1.9)	2 (3.6)	

Table 35: Clinical measurements (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
Acute oral corticosteroid prescriptions	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.3031
	0	254 (73.2)	35 (74.5)	121 (75.2)	31 (56.4)	
	1	58 (16.7)	9 (19.1)	19 (11.8)	13 (23.6)	
	2	27 (7.8)	2 (4.3)	15 (9.3)	9 (16.4)	
	3	6 (1.7)	1 (2.1)	5 (3.1)	1 (1.8)	
	4	2 (0.6)	0 (0.0)	1 (0.6)	1 (1.8)	
Acute oral corticosteroid prescriptions >14 days apart	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.1784
	0	254 (73.2)	35 (74.5)	121 (75.2)	31 (56.4)	
	1	65 (18.7)	10 (21.3)	20 (12.4)	15 (27.3)	
	2	24 (6.9)	2 (4.3)	15 (9.3)	8 (14.5)	
	3	3 (0.9)	0 (0.0)	4 (2.5)	1 (1.8)	
	4	1 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	
Acute oral corticosteroid use (yes/no)	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0486
	Yes	93 (26.8)	12 (25.5)	40 (24.8)	24 (43.6)	
Antibiotics	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.5845
	Mean (SD)	1.3 (1.9)	1.2 (1.8)	1.4 (1.8)	0.9 (1.3)	
	Median (IQR)	1.0 (2.0)	0.0 (2.0)	1.0 (2.0)	1.0 (2.0)	
Antibiotic courses	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.8116
	0	152 (43.8)	24 (51.1)	71 (44.1)	27 (49.1)	
	1	85 (24.5)	11 (23.4)	38 (23.6)	14 (25.5)	
	2	49 (14.1)	3 (6.4)	22 (13.7)	8 (14.5)	
	3	20 (5.8)	5 (10.6)	12 (7.5)	4 (7.3)	
	4+	41 (11.8)	4 (8.5)	18 (11.2)	2 (3.6)	

Table 36: Acute asthma treatment (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
Active eczema diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.9185
	Yes	11 (3.2)	2 (4.3)	7 (4.3)	2 (3.6)	
Active rhinitis diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.2383
	Yes	99 (28.5)	10 (21.3)	52 (32.3)	21 (38.2)	
Eczema diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.1637
	Yes	93 (26.8)	13 (27.7)	57 (35.4)	20 (36.4)	
Rhinitis diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0422
	Yes	130 (37.5)	13 (27.7)	74 (46.0)	27 (49.1)	
Cardiovascular diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.2003
	Yes	49 (14.1)	2 (4.3)	18 (11.2)	5 (9.1)	
IHD diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.6704
	Yes	17 (4.9)	1 (2.1)	10 (6.2)	2 (3.6)	
Heart failure diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.4487
	Yes	1 (0.3)	0 (0.0)	2 (1.2)	0 (0.0)	
Hypertension diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.2151
	Yes	92 (26.5)	11 (23.4)	32 (19.9)	9 (16.4)	

Table 37: Comorbidities 1 (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value
Diabetes diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.5974
	Yes	30 (8.6)	2 (4.3)	15 (9.3)	3 (5.5)	
Osteoporosis diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.6659
	Yes	8 (2.3)	0 (0.0)	4 (2.5)	2 (3.6)	
GERD diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.1537
	Yes	62 (17.9)	3 (6.4)	25 (15.5)	6 (10.9)	
GERD active diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.2007

	Yes	53 (15.3)	3 (6.4)	18 (11.2)	5 (9.1)	
Anxiety or depression	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.3038
	Yes	139 (40.1)	20 (42.6)	61 (37.9)	15 (27.3)	
Chronic Kidney Disease	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.1357
	Yes	70 (20.2)	6 (12.8)	20 (12.4)	11 (20.0)	
Cerebrovascular disease	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.4449
	Yes	13 (3.7)	1 (2.1)	4 (2.5)	0 (0.0)	
Myocardial infarct	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.7010
	Yes	4 (1.2)	1 (2.1)	3 (1.9)	0 (0.0)	

Table 38: Comorbidities 2 (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
Current peak flow	N (% non-missing)	195 (56.2)	33 (70.2)	79 (49.1)	40 (72.7)	0.1043
	Mean (SD)	403.7 (106.1)	407.7 (111.8)	444.2 (128.9)	422.8 (127.7)	
	Median (IQR)	400.0 (120.0)	380.0 (120.0)	440.0 (200.0)	400.0 (110.0)	
Predicted peak flow	N (% non-missing)	193 (55.6)	33 (70.2)	79 (49.1)	40 (72.7)	0.0038
	Mean (SD)	498.0 (73.8)	520.8 (67.3)	533.5 (78.8)	511.6 (70.0)	
	Median (IQR)	473.8 (123.4)	498.2 (114.6)	541.5 (138.8)	481.2 (127.6)	
Percentage predicted peak flow	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0418
	Mean (SD)	-66.7 (2103.7)	84.5 (17.5)	91.6 (16.0)	86.8 (17.9)	
	Median (IQR)	99.9 (19.6)	88.8 (28.6)	100.0 (17.3)	89.9 (25.6)	
% predicted PF groups	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.1016
	<=33%	9 (2.6)	1 (2.1)	3 (1.9)	2 (3.6)	
	>33% to <50%	75 (21.6)	19 (40.4)	32 (19.9)	15 (27.3)	
	>=50%	263 (75.8)	27 (57.4)	126 (78.3)	38 (69.1)	

Table 39: Peak flow (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value
FeV ₁	N (% non-missing)	53 (15.3)	8 (17.0)	32 (19.9)	11 (20.0)	0.3280
	Mean (SD)	2.3 (1.0)	2.4 (0.6)	2.3 (0.8)	3.0 (1.1)	
	Median (IQR)	2.3 (0.9)	2.5 (1.0)	2.4 (1.2)	3.4 (2.1)	
FVC	N (% non-missing)	95 (27.4)	11 (23.4)	49 (30.4)	13 (23.6)	0.2414
	Mean (SD)	3.3 (0.9)	3.6 (0.6)	3.5 (1.0)	3.9 (1.3)	
	Median (IQR)	3.2 (1.2)	3.8 (0.9)	3.3 (1.2)	4.1 (1.5)	
FEV ₁ /FVC ratio	N (% non-missing)	45 (13.0)	8 (17.0)	21 (13.0)	10 (18.2)	0.0386
	Mean (SD)	0.8 (0.1)	0.7 (0.1)	0.7 (0.1)	0.8 (0.1)	
	Median (IQR)	0.8 (0.1)	0.7 (0.1)	0.7 (0.1)	0.8 (0.1)	
FEV ₁ Percent Predicted	N (% non-missing)	50 (14.4)	7 (14.9)	23 (14.3)	5 (9.1)	0.2930
	Mean (SD)	88.0 (22.8)	73.0 (16.6)	86.5 (21.5)	87.8 (15.3)	
	Median (IQR)	88.0 (31.0)	74.0 (28.0)	91.0 (31.0)	91.0 (13.0)	
FEV1 % predicted groups	N (% non-missing)	50 (14.4)	7 (14.9)	23 (14.3)	5 (9.1)	0.5247
	50% or less	2 (4.0)	0 (0.0)	2 (8.7)	0 (0.0)	
	>50% to <80%	14 (28.0)	4 (57.1)	8 (34.8)	1 (20.0)	
	80% to <100%	18 (36.0)	3 (42.9)	5 (21.7)	3 (60.0)	
	100%+	16 (32.0)	0 (0.0)	8 (34.8)	1 (20.0)	

Table 40: Lung function (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value
Asthma consultations	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.1156
	Mean (SD)	1.9 (1.6)	2.5 (2.3)	1.7 (1.3)	2.4 (2.2)	

	Median (IQR)	2.0 (1.0)	2.0 (3.0)	1.0 (1.0)	2.0 (2.0)	
Asthma consultations	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.8844
	0	40 (11.5)	4 (8.5)	23 (14.3)	6 (10.9)	
	1	126 (36.3)	18 (38.3)	58 (36.0)	17 (30.9)	
	2+	181 (52.2)	25 (53.2)	80 (49.7)	32 (58.2)	
Asthma related accident and emergency attendance	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0177
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	
Asthma related accident and emergency attendance	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0177
	1	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	
Asthma related unplanned inpatient attendance	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0002
	1	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	
Asthma related unplanned inpatient attendance	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0002
	1	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	

Table 41: Healthcare Resource Utilisation (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value
LAMA prescriptions per patient	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.8785
	Mean (SD)	0.1 (0.4)	0.1 (0.9)	0.2 (1.3)	0.1 (0.5)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	
ICS/LABA prescriptions per patient	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0056
	Mean (SD)	4.1 (4.0)	2.6 (3.1)	4.7 (3.9)	3.9 (4.0)	
	Median (IQR)	3.0 (6.0)	2.0 (4.0)	4.0 (5.0)	3.0 (5.0)	
Mono ICS prescriptions per patient	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0777
	Mean (SD)	1.2 (2.4)	0.9 (2.2)	0.6 (1.5)	0.8 (1.7)	
	Median (IQR)	0.0 (1.0)	0.0 (1.0)	0.0 (0.0)	0.0 (1.0)	
LTRA prescriptions per patient	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.9242
	Mean (SD)	0.7 (2.1)	0.6 (2.3)	0.9 (2.8)	0.6 (1.9)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	

THEO prescriptions per patient	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.3897
	Mean (SD)	0.1 (1.0)	0.0 (0.0)	0.2 (1.6)	0.0 (0.0)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	

Table 42: Asthma prescriptions per patient (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
LABA prescription (yes/no)	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.7232
	Yes	8 (2.3)	1 (2.1)	3 (1.9)	0 (0.0)	
LAMA prescription (yes/no)	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.8843
	Yes	7 (2.0)	1 (2.1)	5 (3.1)	1 (1.8)	
SAMA prescription (yes/no)	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.2636
	Yes	8 (2.3)	0 (0.0)	1 (0.6)	0 (0.0)	
LTRA prescription (yes/no)	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.9174
	Yes	43 (12.4)	5 (10.6)	22 (13.7)	8 (14.5)	
Theophylline prescription (yes/no)	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.3909
	Yes	8 (2.3)	0 (0.0)	5 (3.1)	0 (0.0)	

Table 43: Asthma prescriptions yes/no (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
SABA prescriptions	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.5701
	Mean (SD)	3.1 (3.4)	2.7 (3.3)	3.2 (3.8)	3.8 (4.3)	
	Median (IQR)	2.0 (4.0)	1.0 (3.0)	2.0 (3.0)	2.0 (4.0)	
SABA inhalers	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.5650
	Mean (SD)	3.7 (4.4)	3.4 (4.5)	3.5 (4.1)	4.7 (6.1)	

	Median (IQR)	2.0 (4.0)	2.0 (4.0)	2.0 (4.0)	2.0 (5.0)	
SABA daily dose	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.5450
	Mean (SD)	1.0 (1.2)	0.9 (1.2)	0.9 (1.1)	1.3 (1.7)	
	Median (IQR)	0.6 (1.1)	0.5 (1.1)	0.6 (1.1)	0.6 (1.4)	
SABA dosage	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.5450
	Mean (SD)	201.3 (243.9)	184.7 (246.0)	189.7 (222.6)	256.3 (336.4)	
	Median (IQR)	109.6 (219.2)	98.6 (219.2)	109.6 (219.2)	109.6 (274.0)	

Table 44: SABA usage (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Kruskal Wallis test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Kruskal Wallis test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
Number of SABA prescriptions	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.9701
	0	79 (22.8)	11 (23.4)	36 (22.4)	10 (18.2)	
	1-3	159 (45.8)	24 (51.1)	75 (46.6)	25 (45.5)	
	4-6	62 (17.9)	6 (12.8)	24 (14.9)	11 (20.0)	
	>=7	47 (13.5)	6 (12.8)	26 (16.1)	9 (16.4)	
Number of SABA inhalers	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.9865
	0	79 (22.8)	11 (23.4)	36 (22.4)	10 (18.2)	
	1-3	140 (40.3)	22 (46.8)	68 (42.2)	22 (40.0)	
	4-6	65 (18.7)	7 (14.9)	27 (16.8)	12 (21.8)	
	>=7	63 (18.2)	7 (14.9)	30 (18.6)	11 (20.0)	
Mean daily SABA dosage (mcg)	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.8149
	<100	128 (36.9)	24 (51.1)	64 (39.8)	17 (30.9)	
	100-200	93 (26.8)	9 (19.1)	41 (25.5)	15 (27.3)	
	201-400	77 (22.2)	9 (19.1)	35 (21.7)	14 (25.5)	
	>400	49 (14.1)	5 (10.6)	21 (13.0)	9 (16.4)	

Table 45: Categorised SABA usage (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Kruskal Wallis test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Kruskal Wallis test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
ICS daily dose	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0153
	Mean (SD)	587.2 (498.6)	399.9 (411.7)	601.5 (498.1)	555.9 (472.0)	
	Median (IQR)	416.4 (602.7)	246.6 (356.2)	493.1 (602.7)	394.5 (465.7)	
ICS inhalers	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0219
	Mean (SD)	6.9 (5.1)	4.9 (4.0)	6.7 (4.5)	6.4 (5.3)	
	Median (IQR)	6.0 (7.0)	3.0 (6.0)	6.0 (7.0)	5.0 (5.0)	
ICS prescriptions	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0100
	Mean (SD)	5.4 (3.7)	3.8 (3.3)	5.4 (3.6)	4.9 (3.6)	
	Median (IQR)	5.0 (6.0)	3.0 (4.0)	4.0 (6.0)	4.0 (4.0)	
ICS adherence	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.2964
	Mean (SD)	69.9 (66.0)	60.2 (61.2)	63.6 (42.7)	68.2 (71.6)	
	Median (IQR)	57.5 (71.2)	41.1 (49.3)	57.5 (60.3)	49.3 (57.5)	

Table 46: ICS usage (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Kruskal Wallis test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Kruskal Wallis test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
Number of ICS containing inhalers	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0573
	1-3	107 (30.8)	24 (51.1)	47 (29.2)	19 (34.5)	
	4-6	94 (27.1)	11 (23.4)	39 (24.2)	18 (32.7)	
	>=7	146 (42.1)	12 (25.5)	75 (46.6)	18 (32.7)	
Mean daily ICS dosage (mcg)	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0133
	<250	103 (29.7)	24 (51.1)	44 (27.3)	15 (27.3)	

	250-<500	91 (26.2)	11 (23.4)	43 (26.7)	22 (40.0)	
	>=500	153 (44.1)	12 (25.5)	74 (46.0)	18 (32.7)	
ICS adherence (%)	N (% non-missing)	346 (99.7)	47 (100.0)	161 (100.0)	55 (100.0)	0.6197
	<40	111 (32.1)	21 (44.7)	55 (34.2)	16 (29.1)	
	40-79	109 (31.5)	16 (34.0)	52 (32.3)	22 (40.0)	
	80-120	87 (25.1)	6 (12.8)	40 (24.8)	12 (21.8)	
	>120	39 (11.3)	4 (8.5)	14 (8.7)	5 (9.1)	

Table 47: Categorised ICS usage (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Kruskal Wallis test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Kruskal Wallis test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
Asthma ATS exacerbations	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.1541
	0	254 (73.2)	35 (74.5)	121 (75.2)	31 (56.4)	
	1	65 (18.7)	10 (21.3)	20 (12.4)	14 (25.5)	
	2	24 (6.9)	2 (4.3)	15 (9.3)	8 (14.5)	
	3	3 (0.9)	0 (0.0)	4 (2.5)	2 (3.6)	
	4	1 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	
Asthma ATS exacerbations	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0403
	Mean (SD)	0.4 (0.7)	0.3 (0.5)	0.4 (0.8)	0.7 (0.9)	
Acute respiratory event	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.9442
	0	138 (39.8)	20 (42.6)	63 (39.1)	22 (40.0)	
	1	95 (27.4)	14 (29.8)	40 (24.8)	14 (25.5)	
	2	53 (15.3)	4 (8.5)	29 (18.0)	12 (21.8)	
	3	24 (6.9)	4 (8.5)	12 (7.5)	4 (7.3)	
	4+	37 (10.7)	5 (10.6)	17 (10.6)	3 (5.5)	
Acute respiratory event	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.9357
	Mean (SD)	1.3 (1.7)	1.3 (1.6)	1.3 (1.6)	1.1 (1.2)	

Table 48: Exacerbations (categorisation 2)

*P-value computed from chi-squared test for categorical variables, or Kruskal Wallis test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Kruskal Wallis test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
Medication cost without ICS	N (% non-missing)	340 (98.0)	45 (95.7)	158 (98.1)	55 (100.0)	0.6512
	Mean (SD)	34.6 (70.3)	37.1 (93.7)	38.1 (96.1)	37.4 (76.6)	
	Median (IQR)	9.5 (23.0)	8.0 (10.0)	9.0 (20.0)	13.0 (34.0)	
Medication cost	N (% non-missing)	340 (98.0)	45 (95.7)	158 (98.1)	55 (100.0)	0.0062
	Mean (SD)	268.5 (228.1)	189.6 (222.1)	285.6 (238.2)	251.6 (231.6)	
	Median (IQR)	198.5 (287.0)	104.0 (155.0)	216.0 (285.0)	176.0 (266.0)	
Healthcare resource cost	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0807
	Mean (SD)	91.7 (86.4)	126.0 (146.9)	79.9 (73.5)	138.0 (192.8)	
	Median (IQR)	84.0 (84.0)	84.0 (126.0)	84.0 (42.0)	84.0 (126.0)	
Total cost without ICS	N (% non-missing)	340 (98.0)	45 (95.7)	158 (98.1)	55 (100.0)	0.3044
	Mean (SD)	126.2 (120.9)	162.2 (177.9)	117.6 (117.6)	175.5 (209.8)	
	Median (IQR)	89.0 (103.0)	90.0 (162.0)	87.5 (93.0)	97.0 (149.0)	
Total cost	N (% non-missing)	340 (98.0)	45 (95.7)	158 (98.1)	55 (100.0)	0.1055
	Mean (SD)	360.1 (253.7)	314.6 (291.9)	365.1 (242.5)	389.6 (319.6)	
	Median (IQR)	296.0 (288.5)	203.0 (274.0)	322.0 (329.0)	262.0 (256.0)	

Table 49: Total healthcare resource utilisation costs for categorisation 2.

P values computed using Kruskal Wallis. Summary statistics presented as counts and percentages.

15.2.1 Statistically significant difference between unmatched patient groups (categorisation 2)

		Low eosinophil, low FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, high FeNO	P value*
Gender	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0177
	Male	113 (32.6)	19 (40.4)	74 (46.0)	25 (45.5)	

Smoking status	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0115
	Non-smoker	138 (39.8)	23 (48.9)	45 (28.0)	31 (56.4)	
	Ex-smoker	40 (11.5)	5 (10.6)	32 (19.9)	5 (9.1)	
	Current smoker	111 (32.0)	12 (25.5)	58 (36.0)	12 (21.8)	
BMI	N (% non-missing)	331 (95.4)	43 (91.5)	155 (96.3)	51 (92.7)	0.0005
	Mean (SD)	29.9 (6.5)	27.8 (6.9)	30.4 (7.8)	26.7 (5.6)	
	Median (IQR)	29.0 (8.4)	25.9 (8.9)	28.8 (9.0)	25.6 (7.2)	
BMI	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0411
	Underweight	1 (0.3)	0 (0.0)	2 (1.2)	1 (1.8)	
	Normal	81 (23.3)	19 (40.4)	36 (22.4)	20 (36.4)	
	Overweight	102 (29.4)	8 (17.0)	48 (29.8)	18 (32.7)	
Mean daily ICS dosage (mcg)	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0133
	<250	103 (29.7)	24 (51.1)	44 (27.3)	15 (27.3)	
	250-<500	91 (26.2)	11 (23.4)	43 (26.7)	22 (40.0)	
	>=500	153 (44.1)	12 (25.5)	74 (46.0)	18 (32.7)	
Asthma ATS exacerbations	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0403
	Mean (SD)	0.4 (0.7)	0.3 (0.5)	0.4 (0.8)	0.7 (0.9)	
Medication cost	N (% non-missing)	340 (98.0)	45 (95.7)	158 (98.1)	55 (100.0)	0.0062
	Mean (SD)	268.5 (228.1)	189.6 (222.1)	285.6 (238.2)	251.6 (231.6)	
	Median (IQR)	198.5 (287.0)	104.0 (155.0)	216.0 (285.0)	176.0 (266.0)	
ICS daily dose	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0153
	Mean (SD)	587.2 (498.6)	399.9 (411.7)	601.5 (498.1)	555.9 (472.0)	
	Median (IQR)	416.4 (602.7)	246.6 (356.2)	493.1 (602.7)	394.5 (465.7)	
ICS inhalers	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0219
	Mean (SD)	6.9 (5.1)	4.9 (4.0)	6.7 (4.5)	6.4 (5.3)	
	Median (IQR)	6.0 (7.0)	3.0 (6.0)	6.0 (7.0)	5.0 (5.0)	
ICS prescriptions	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0100
	Mean (SD)	5.4 (3.7)	3.8 (3.3)	5.4 (3.6)	4.9 (3.6)	
	Median (IQR)	5.0 (6.0)	3.0 (4.0)	4.0 (6.0)	4.0 (4.0)	
	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0056
	Mean (SD)	4.1 (4.0)	2.6 (3.1)	4.7 (3.9)	3.9 (4.0)	

ICS/LABA prescriptions per patient	Median (IQR)	3.0 (6.0)	2.0 (4.0)	4.0 (5.0)	3.0 (5.0)	
Asthma related accident and emergency attendance	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0177
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	
Asthma related unplanned inpatient attendance	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0002
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	
FEV1/FVC ratio	N (% non-missing)	45 (13.0)	8 (17.0)	21 (13.0)	10 (18.2)	0.0386
	Mean (SD)	0.8 (0.1)	0.7 (0.1)	0.7 (0.1)	0.8 (0.1)	
	Median (IQR)	0.8 (0.1)	0.7 (0.1)	0.7 (0.1)	0.8 (0.1)	
Predicted peak flow	N (% non-missing)	193 (55.6)	33 (70.2)	79 (49.1)	40 (72.7)	0.0038
	Mean (SD)	498.0 (73.8)	520.8 (67.3)	533.5 (78.8)	511.6 (70.0)	
	Median (IQR)	473.8 (123.4)	498.2 (114.6)	541.5 (138.8)	481.2 (127.6)	
Percentage predicted peak flow	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0418
	Mean (SD)	-66.7 (2103.7)	84.5 (17.5)	91.6 (16.0)	86.8 (17.9)	
	Median (IQR)	99.9 (19.6)	88.8 (28.6)	100.0 (17.3)	89.9 (25.6)	
Rhinitis diagnosis	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0422
	Yes	130 (37.5)	13 (27.7)	74 (46.0)	27 (49.1)	
Acute OCS use (yes/no)	N (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0486
	Yes	93 (26.8)	12 (25.5)	40 (24.8)	24 (43.6)	

Table 50: Unmatched comparison using categorisation 2, with significant differences between covariates illustrated. Comparison is based on non-missing data. Unmatched pair analysis

15.3 Unmatched comparison between low BEC and low FeNO vs high BEC and high FeNO patients (categorisation 1)

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
Gender	N (% non-missing)	296 (100.0)	27 (100.0)	0.5487	11.9
	Male	93 (31.4)	10 (37.0)		

Age	N (% non-missing)	296 (100.0)	27 (100.0)	0.0131	59.2
	Mean (SD)	52.9 (12.8)	43.3 (19.0)		
	Median (IQR)	55.0 (17.0)	41.0 (37.0)		
Age group	N (% non-missing)	296 (100.0)	27 (100.0)	<0.0001	103.9
	Under 35	28 (9.5)	12 (44.4)		
	35-65	229 (77.4)	9 (33.3)		
	66-80	39 (13.2)	6 (22.2)		
Smoking status	N (% non-missing)	245 (82.8)	22 (81.5)	0.2403	38.3
	Non-smoker	110 (44.9)	14 (63.6)		
	Ex-smoker	35 (14.3)	2 (9.1)		
	Current smoker	100 (40.8)	6 (27.3)		
Height	N (% non-missing)	285 (96.3)	27 (100.0)	0.2469	18.0
	Mean (SD)	1.66 (0.09)	1.67 (0.09)		
	Median (IQR)	1.64 (0.14)	1.67 (0.13)		
Weight	N (% non-missing)	282 (95.3)	26 (96.3)	0.0602	33.4
	Mean (SD)	82.4 (18.9)	75.8 (20.8)		
	Median (IQR)	80.4 (26.5)	71.8 (23.2)		

Table 51: Demographic summary

*P-value computed from chi-squared test for categorical variables, or Kruskal Wallis test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Kruskal Wallis test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
BMI	N (% non-missing)	280 (94.6)	26 (96.3)	0.0098	47.3
	Mean (SD)	30.0 (6.7)	26.9 (6.4)		
	Median (IQR)	29.0 (9.1)	25.5 (8.4)		
BMI	N (% non-missing)	280 (94.6)	26 (96.3)	0.0486	46.0
	Underweight	1 (0.4)	1 (3.8)		
	Normal	68 (24.3)	10 (38.5)		
	Overweight	89 (31.8)	8 (30.8)		
	Obese	122 (43.6)	7 (26.9)		

FENO value	N (% non-missing)	296 (100.0)	27 (100.0)	<0.0001	288.1
	Mean (SD)	14.1 (5.7)	73.1 (28.4)		
	Median (IQR)	14.0 (10.0)	65.0 (22.0)		
Eosinophil count	N (% non-missing)	296 (100.0)	27 (100.0)	<0.0001	278.9
	Mean (SD)	0.2 (0.1)	0.5 (0.2)		
	Median (IQR)	0.2 (0.1)	0.5 (0.2)		
COPD diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.0508	27.7
	Yes	5 (1.7)	2 (7.4)		

Table 52: Clinical measurements

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
Acute oral corticosteroid prescriptions	N (% non-missing)	296 (100.0)	27 (100.0)	0.0406	55.7
	0	213 (72.0)	13 (48.1)		
	1	60 (20.3)	8 (29.6)		
	2	20 (6.8)	5 (18.5)		
	3	2 (0.7)	1 (3.7)		
	4	1 (0.3)	0 (0.0)		
Acute oral corticosteroid prescriptions >14 days apart	N (% non-missing)	296 (100.0)	27 (100.0)	0.0557	55.9
	0	213 (72.0)	13 (48.1)		
	1	53 (17.9)	8 (29.6)		
	2	25 (8.4)	5 (18.5)		
	3	3 (1.0)	0 (0.0)		
	4	2 (0.7)	1 (3.7)		
Acute oral corticosteroid use (yes/no)	N (% non-missing)	296 (100.0)	27 (100.0)	0.0098	50.1
	Yes	83 (28.0)	14 (51.9)		
Antibiotics	N (% non-missing)	296 (100.0)	27 (100.0)	0.3142	21.6
	Mean (SD)	1.3 (1.8)	1.0 (1.4)		

	Median (IQR)	1.0 (2.0)	0.0 (2.0)		
Antibiotic courses	N (% non-missing)	296 (100.0)	27 (100.0)	0.5335	39.7
	0	131 (44.3)	15 (55.6)		
	1	70 (23.6)	4 (14.8)		
	2	43 (14.5)	5 (18.5)		
	3	19 (6.4)	2 (7.4)		
	4+	33 (11.1)	1 (3.7)		

Table 53: Acute asthma treatment

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
Active eczema diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.2311	19.7
	Yes	9 (3.0)	2 (7.4)		
Active rhinitis diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.1906	25.5
	Yes	85 (28.7)	11 (40.7)		
Eczema diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.1092	30.8
	Yes	78 (26.4)	11 (40.7)		
Rhinitis diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.3265	19.5
	Yes	114 (38.5)	13 (48.1)		
Cardiovascular diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.1247	37.4
	Yes	42 (14.2)	1 (3.7)		
IHD diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.7545	6.7
	Yes	15 (5.1)	1 (3.7)		
Heart failure diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.7623	8.2
	Yes	1 (0.3)	0 (0.0)		
Hypertension diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.0750	40.6
	Yes	79 (26.7)	3 (11.1)		

Table 54: Comorbidities 1

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
Diabetes diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.1011	44.8
	Yes	27 (9.1)	0 (0.0)		
Osteoporosis diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.1767	21.6
	Yes	8 (2.7)	2 (7.4)		
GERD diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.0408	51.1
	Yes	58 (19.6)	1 (3.7)		
GERD active diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.0202	63.8
	Yes	50 (16.9)	0 (0.0)		
Anxiety or depression	N (% non-missing)	296 (100.0)	27 (100.0)	0.1367	31.4
	Yes	120 (40.5)	7 (25.9)		
Chronic Kidney Disease	N (% non-missing)	296 (100.0)	27 (100.0)	0.7966	5.3
	Yes	61 (20.6)	5 (18.5)		
Cerebrovascular disease	N (% non-missing)	296 (100.0)	27 (100.0)	0.3081	27.8
	Yes	11 (3.7)	0 (0.0)		
Myocardial infarct	N (% non-missing)	296 (100.0)	27 (100.0)	0.5992	14.3
	Yes	3 (1.0)	0 (0.0)		

Table 55: Comorbidities 2

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
Current peak flow	N (% non-missing)	160 (54.1)	20 (74.1)	0.7758	3.8
	Mean (SD)	401.3 (102.9)	406.0 (142.4)		
	Median (IQR)	392.5 (115.0)	400.0 (92.5)		

Predicted peak flow	N (% non-missing)	158 (53.4)	20 (74.1)	0.4500	13.8
	Mean (SD)	495.7 (71.4)	505.8 (74.9)		
	Median (IQR)	472.5 (121.1)	478.3 (127.7)		
Percentage predicted peak flow	N (% non-missing)	158 (53.4)	20 (74.1)	0.7787	8.4
	Mean (SD)	81.1 (15.9)	79.5 (22.4)		
	Median (IQR)	81.9 (22.1)	82.3 (25.5)		
% predicted PF groups	N (% non-missing)	158 (53.4)	20 (74.1)	0.1384	.
	33-50	5 (3.2)	2 (10)		
	>=50	153 (96.8)	18 (90.0)		

Table 56: Peak flow

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
FeV ₁	N (% non-missing)	53 (17.9)	4 (14.8)	0.5117	49.3
	Mean (SD)	11.1 (25.0)	2.4 (1.1)		
	Median (IQR)	2.3 (1.2)	2.0 (1.5)		
FVC	N (% non-missing)	87 (29.4)	4 (14.8)	0.8999	3.9
	Mean (SD)	3.3 (0.9)	3.2 (1.3)		
	Median (IQR)	3.2 (1.2)	3.3 (1.7)		
FEV ₁ /FVC_ratio	N (% non-missing)	40 (13.5)	4 (14.8)	0.9511	7.4
	Mean (SD)	0.8 (0.1)	0.8 (0.1)		
	Median (IQR)	0.8 (0.1)	0.8 (0.2)		
FEV ₁ Percent Predicted	N (% non-missing)	55 (18.6)	5 (18.5)	0.6199	13.8
	Mean (SD)	71.8 (40.1)	66.4 (38.7)		
	Median (IQR)	83.0 (44.0)	81.0 (25.0)		
FEV1 % predicted groups	N (% non-missing)	55 (18.6)	5 (18.5)	0.3866	99.9
	50% or less	12 (21.8)	1 (20.0)		
	>50% to <80%	13 (23.6)	1 (20.0)		
	80% to <100%	15 (27.3)	3 (60.0)		

	100%+	15 (27.3)	0 (0.0)		
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Table 57: Lung function

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
Asthma consultations	N (% non-missing)	296 (100.0)	27 (100.0)	0.0363	29.7
	Mean (SD)	1.8 (1.5)	2.3 (1.4)		
	Median (IQR)	1.5 (1.0)	2.0 (2.0)		
Asthma consultations	N (% non-missing)	296 (100.0)	27 (100.0)	0.0966	47.0
	0	34 (11.5)	3 (11.1)		
	1	114 (38.5)	5 (18.5)		
	2+	148 (50.0)	19 (70.4)		
Asthma related accident and emergency	N (% non-missing)	296 (100.0)	27 (100.0)	0.2683	9.1
	1	0 (0.0)	0 (0.0)		
Asthma related unplanned inpatient admission	N (% non-missing)	296 (100.0)	27 (100.0)	0.0009	27.7
	1	0 (0.0)	1 (3.7)		

Table 58: Healthcare Resource Utilisation

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
LAMA prescriptions per patient	N (% non-missing)	296 (100.0)	27 (100.0)	0.4561	16.1
	Mean (SD)	0.0 (0.4)	0.1 (0.8)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
	N (% non-missing)	296 (100.0)	27 (100.0)	0.6179	28.8
	Mean (SD)	4.2 (4.1)	3.2 (2.5)		

ICS/LABA prescriptions per patient	Median (IQR)	3.0 (6.0)	3.0 (5.0)		
Mono ICS prescriptions per patient	N (% non-missing)	296 (100.0)	27 (100.0)	0.8528	9.5
	Mean (SD)	1.2 (2.5)	1.0 (2.2)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
LTRA prescriptions per patient	N (% non-missing)	296 (100.0)	27 (100.0)	0.4255	8.6
	Mean (SD)	0.7 (2.3)	0.9 (2.4)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
THEO prescriptions per patient	N (% non-missing)	296 (100.0)	27 (100.0)	0.4561	16.0
	Mean (SD)	0.1 (1.0)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
SAMA prescriptions per patient	N (% non-missing)	296 (100.0)	27 (100.0)	0.4198	14.5
	Mean (SD)	0.0 (0.4)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		

Table 59: Asthma prescriptions per patient

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
LABA prescription (yes/no)	N (% non-missing)	296 (100.0)	27 (100.0)	0.3870	23.6
	Yes	8 (2.7)	0 (0.0)		
LAMA prescription (yes/no)	N (% non-missing)	296 (100.0)	27 (100.0)	0.4580	12.5
	Yes	5 (1.7)	1 (3.7)		
SAMA prescription (yes/no)	N (% non-missing)	296 (100.0)	27 (100.0)	0.4192	22.0
	Yes	7 (2.4)	0 (0.0)		
LTRA prescription (yes/no)	N (% non-missing)	296 (100.0)	27 (100.0)	0.4055	15.7
	Yes	38 (12.8)	5 (18.5)		
Theophylline prescription (yes/no)	N (% non-missing)	296 (100.0)	27 (100.0)	0.4552	20.3
	Yes	6 (2.0)	0 (0.0)		

Table 60: Asthma prescriptions yes/no

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
SABA prescriptions	N (% non-missing)	296 (100.0)	27 (100.0)	0.1054	32.5
	Mean (SD)	3.0 (3.2)	4.3 (4.4)		
	Median (IQR)	2.0 (3.5)	3.0 (4.0)		
SABA inhalers	N (% non-missing)	296 (100.0)	27 (100.0)	0.1317	27.5
	Mean (SD)	3.6 (4.3)	5.0 (5.6)		
	Median (IQR)	2.0 (4.0)	3.0 (3.0)		
Daily SABA dosage	N (% non-missing)	296 (100.0)	27 (100.0)	0.1216	27.3
	Mean (SD)	1.0 (1.2)	1.4 (1.5)		
	Median (IQR)	0.6 (1.1)	0.8 (0.8)		

Table 61: SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
Number of SABA prescriptions	N (% non-missing)	296 (100.0)	27 (100.0)	0.2883	45.3
	0	68 (23.0)	2 (7.4)		
	1-3	136 (45.9)	14 (51.9)		
	4-6	54 (18.2)	6 (22.2)		
	>=7	38 (12.8)	5 (18.5)		
Number of SABA inhalers	N (% non-missing)	296 (100.0)	27 (100.0)	0.2489	46.6
	1	68 (23.0)	2 (7.4)		
	2	119 (40.2)	12 (44.4)		
	3	58 (19.6)	8 (29.6)		

	4	51 (17.2)	5 (18.5)		
Mean daily SABA dosage (mcg)	N (% non-missing)	296 (100.0)	27 (100.0)	0.4703	33.5
	<100	109 (36.8)	6 (22.2)		
	100-200	80 (27.0)	8 (29.6)		
	201-400	68 (23.0)	8 (29.6)		
	>400	39 (13.2)	5 (18.5)		

Table 62: Categorized SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
ICS daily dose	N (% non-missing)	296 (100.0)	27 (100.0)	0.2595	33.3
	Mean (SD)	586.9 (503.5)	443.6 (342.1)		
	Median (IQR)	427.4 (602.7)	350.7 (252.0)		
ICS/LABA or mono ICS inhalers	N (% non-missing)	296 (100.0)	27 (100.0)	0.1642	43.7
	Mean (SD)	7.0 (5.2)	5.1 (2.8)		
	Median (IQR)	6.0 (7.0)	5.0 (3.0)		
ICS/LABA or mono ICS prescriptions	N (% non-missing)	296 (100.0)	27 (100.0)	0.2926	36.6
	Mean (SD)	5.6 (3.8)	4.4 (2.3)		
	Median (IQR)	5.0 (6.0)	5.0 (4.0)		
ICS adherence	N (% non-missing)	296 (100.0)	27 (100.0)	0.1469	34.3
	Mean (SD)	70.1 (65.8)	52.3 (32.9)		
	Median (IQR)	64.4 (69.9)	49.3 (35.7)		

Table 63: ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
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Number of ICS/LABA or mono ICS prescriptions	N (% non-missing)	296 (100.0)	27 (100.0)	0.0870	47.8
	1-3	113 (38.2)	11 (40.7)		
	4-6	84 (28.4)	12 (44.4)		
	>=7	99 (33.4)	4 (14.8)		
Number of ICS/LABA or mono ICS inhalers	N (% non-missing)	296 (100.0)	27 (100.0)	0.0110	59.6
	2	90 (30.4)	7 (25.9)		
	3	76 (25.7)	14 (51.9)		
	4	130 (43.9)	6 (22.2)		
Mean daily ICS dosage (mcg)	N (% non-missing)	296 (100.0)	27 (100.0)	0.0050	67.4
	<250	89 (30.1)	8 (29.6)		
	250-<500	74 (25.0)	14 (51.9)		
	>=500	133 (44.9)	5 (18.5)		
Mean daily ICS dosage (mcg)	N (% non-missing)	296 (100.0)	27 (100.0)	0.0050	67.4
	<250	89 (30.1)	8 (29.6)		
	250-<500	74 (25.0)	14 (51.9)		
	>=500	133 (44.9)	5 (18.5)		

Table 64: Categorized ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/ low FeNO (n=296)	High eosinophil /high FeNO (n=27)	P value*	SDD
Asthma ATS exacerbations	N (% non-missing)	296 (100.0)	27 (100.0)	0.0063	57.8
	0	213 (72.0)	13 (48.1)		
	1	60 (20.3)	8 (29.6)		
	2	20 (6.8)	4 (14.8)		
	3	2 (0.7)	2 (7.4)		
	4	1 (0.3)	0 (0.0)		
	Mean (SD)	1.4 (0.7)	1.8 (1.0)	0.0049	53.4

Asthma ATS exacerbations	Median (IQR)	1.0 (1.0)	2.0 (1.0)		
Acute respiratory event	N (% non-missing)	117 (39.5)	12 (44.4)	0.0703	59.9
	0	83 (28.0)	3 (11.1)		
	1	44 (14.9)	9 (33.3)		
	2	23 (7.8)	1 (3.7)		
	3	29 (9.8)	2 (7.4)		
	4+	117 (39.5)	12 (44.4)		
Acute respiratory event	Mean (SD)	1.3 (1.6)	1.3 (1.5)	0.8850	0.5
	Median (IQR)	1.0 (2.0)	1.0 (2.0)		

Table 65: Exacerbations

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

15.3.1 Statistically significant difference between unmatched patient groups – high BEC and high FeNO vs low BEC and low FeNO (categorisation 1)

		Low BEC, low FeNO	High BEC, high FeNO	P value
Age	N (% non-missing)	296 (100.0)	27 (100.0)	0.0131
	Mean (SD)	52.9 (12.8)	43.3 (19.0)	
	Median (IQR)	55.0 (17.0)	41.0 (37.0)	
Age categorised	N (% non-missing)	296 (100.0)	27 (100.0)	<0.0001
	Under 35	28 (9.5)	12 (44.4)	
	35-65	229 (77.4)	9 (33.3)	
	44-80	39 (13.2)	6 (22.2)	
	Median (IQR)	80.4 (26.5)	71.8 (23.2)	
BMI	N (% non-missing)	280 (94.6)	26 (96.3)	0.0098
	Mean (SD)	30.0 (6.7)	26.9 (6.4)	
	Median (IQR)	29.0 (9.1)	25.5 (8.4)	
Acute oral corticosteroid courses	N (% non-missing)	296 (100.0)	27 (100.0)	0.0406
	0	213 (72.0)	13 (48.1)	
	1	60 (20.3)	8 (29.6)	
	2	20 (6.8)	5 (18.5)	

	3	2 (0.7)	1 (3.7)	
	4	1 (0.3)	0 (0.0)	
Acute oral corticosteroid use	N (% non-missing)	296 (100.0)	27 (100.0)	0.0098
	Yes	83 (28.0)	14 (51.9)	
GERD diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.0408
	Yes	58 (19.6)	1 (3.7)	
GERD active diagnosis	N (% non-missing)	296 (100.0)	27 (100.0)	0.0202
	Yes	50 (16.9)	0 (0.0)	
Asthma consultations	N (% non-missing)	296 (100.0)	27 (100.0)	0.0363
	Mean (SD)	1.8 (1.5)	2.3 (1.4)	
	Median (IQR)	1.5 (1.0)	2.0 (2.0)	
Asthma related unplanned inpatient admissions	N (% non-missing)	296 (100.0)	27 (100.0)	0.0009
	Yes	0 (0.0)	1 (3.7)	
ICS or ICS/LABA inhalers	N (% non-missing)	296 (100.0)	27 (100.0)	0.0110
	2	90 (30.4)	7 (25.9)	
	3	76 (25.7)	14 (51.9)	
	4	130 (43.9)	6 (22.2)	
Mean daily ICS dosage (mcg)	N (% non-missing)	296 (100.0)	27 (100.0)	0.0050
	<250	89 (30.1)	8 (29.6)	
	250-<500	74 (25.0)	14 (51.9)	
	>=500	133 (44.9)	5 (18.5)	
Asthma ATS exacerbations	N (% non-missing)	296 (100.0)	27 (100.0)	0.0063
	0	213 (72.0)	13 (48.1)	
	1	60 (20.3)	8 (29.6)	
	2	20 (6.8)	4 (14.8)	
	3	2 (0.7)	2 (7.4)	
	4	1 (0.3)	0 (0.0)	
Asthma ATS exacerbations	N (% non-missing)	296 (100.0)	27 (100.0)	0.0049
	Mean (SD)	1.4 (0.7)	1.8 (1.0)	
	Median (IQR)	1.0 (1.0)	2.0 (1.0)	

Table 66: Unmatched comparison using categorisation 1, with significant differences between covariates illustrated. Comparison is based on non-missing data

15.4 Characterisation of high BEC OR high FeNO vs unmatched low BEC and low FeNO

		Low eosinophil, low FeNO (N=296)	High eosinophil or high FeNO (N=242)	P value*	SDD
Gender	N (% non-missing)	296 (100.0)	242 (100.0)	0.0003	31.7

	Male	93 (31.4)	113 (46.7)		
Age	N (% non-missing)	296 (100.0)	242 (100.0)	0.1238	16.6
	Mean (SD)	52.9 (12.8)	50.7 (14.2)		
	Median (IQR)	55.0 (17.0)	52.0 (22.0)		
Age group	N (% non-missing)	296 (100.0)	242 (100.0)	0.0163	24.9
	Under 35	28 (9.5)	38 (15.7)		
	35-65	229 (77.4)	161 (66.5)		
	66-80	39 (13.2)	43 (17.8)		
Smoking status	N (% non-missing)	245 (82.8)	205 (84.7)	0.2896	14.9
	Non-smoker	110 (44.9)	91 (44.4)		
	Ex-smoker	35 (14.3)	40 (19.5)		
	Current smoker	100 (40.8)	74 (36.1)		
Height	N (% non-missing)	285 (96.3)	234 (96.7)	0.0006	27.4
	Mean (SD)	1.66 (0.09)	1.68 (0.09)		
	Median (IQR)	1.64 (0.14)	1.67 (0.12)		
Weight	N (% non-missing)	282 (95.3)	232 (95.9)	0.8505	1.1
	Mean (SD)	82.4 (18.9)	82.6 (21.4)		
	Median (IQR)	80.4 (26.5)	79.8 (27.6)		

Table 67: Demographic summary

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (N=296)	High eosinophil or high FeNO (N=242)	P value*	SDD
BMI	N (% non-missing)	280 (94.6)	231 (95.5)	0.0607	11.8
	Mean (SD)	30.0 (6.7)	29.2 (7.3)		
	Median (IQR)	29.0 (9.1)	27.8 (8.4)		
BMI	N (% non-missing)	280 (94.6)	231 (95.5)	0.3182	16.5
	Underweight	1 (0.4)	3 (1.3)		
	Normal	68 (24.3)	68 (29.4)		
	Overweight	89 (31.8)	71 (30.7)		

	Obese	122 (43.6)	89 (38.5)		
FENO value	N (% non-missing)	296 (100.0)	242 (100.0)	<0.0001	89.4
	Mean (SD)	14.1 (5.7)	33.4 (30.0)		
	Median (IQR)	14.0 (10.0)	24.0 (33.0)		
Eosinophil count	N (% non-missing)	296 (100.0)	242 (100.0)	<0.0001	177.1
	Mean (SD)	0.2 (0.1)	0.4 (0.2)		
	Median (IQR)	0.2 (0.1)	0.4 (0.2)		
COPD diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.5194	5.5
	Yes	5 (1.7)	6 (2.5)		

Table 68: Clinical measurements

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
Acute oral corticosteroid prescriptions	N (% non-missing)	296 (100.0)	242 (100.0)	0.3260	18.5
	0	213 (72.0)	172 (71.1)		
	1	60 (20.3)	40 (16.5)		
	2	20 (6.8)	24 (9.9)		
	3	2 (0.7)	5 (2.1)		
	4	1 (0.3)	1 (0.4)		
Acute oral corticosteroid prescriptions >14 days apart	N (% non-missing)	296 (100.0)	242 (100.0)	0.5176	15.5
	0	213 (72.0)	172 (71.1)		
	1	53 (17.9)	36 (14.9)		
	2	25 (8.4)	26 (10.7)		
	3	3 (1.0)	6 (2.5)		
	4	2 (0.7)	2 (0.8)		
Acute oral corticosteroid use (yes/no)	N (% non-missing)	296 (100.0)	242 (100.0)	0.8209	2.0
	Yes	83 (28.0)	70 (28.9)		

Antibiotics	N (% non-missing)	296 (100.0)	242 (100.0)	0.7055	3.2
	Mean (SD)	1.3 (1.8)	1.3 (1.7)		
	Median (IQR)	1.0 (2.0)	1.0 (2.0)		
Antibiotic courses	N (% non-missing)	296 (100.0)	242 (100.0)	0.9409	7.7
	0	131 (44.3)	110 (45.5)		
	1	70 (23.6)	59 (24.4)		
	2	43 (14.5)	32 (13.2)		
	3	19 (6.4)	18 (7.4)		
	4+	33 (11.1)	23 (9.5)		

Table 69: Acute asthma treatment

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
Active eczema diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.3587	7.9
	Yes	9 (3.0)	11 (4.5)		
Active rhinitis diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.4981	5.9
	Yes	85 (28.7)	76 (31.4)		
Eczema diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.0572	16.5
	Yes	78 (26.4)	82 (33.9)		
Rhinitis diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.2146	10.8
	Yes	114 (38.5)	106 (43.8)		
Cardiovascular diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.1330	13.1
	Yes	42 (14.2)	24 (9.9)		
IHD diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.9541	0.5
	Yes	15 (5.1)	12 (5.0)		
Heart failure diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.4490	6.4
	Yes	1 (0.3)	2 (0.8)		
	N (% non-missing)	296 (100.0)	242 (100.0)	0.0266	19.4

Hypertension diagnosis	Yes	79 (26.7)	45 (18.6)		
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Table 70: Comorbidities 1

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
Diabetes diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.6001	4.6
	Yes	27 (9.1)	19 (7.9)		
Osteoporosis diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.8714	1.4
	Yes	8 (2.7)	6 (2.5)		
GERD diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.0489	17.3
	Yes	58 (19.6)	32 (13.2)		
GERD active diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.0195	20.6
	Yes	50 (16.9)	24 (9.9)		
Anxiety or depression	N (% non-missing)	296 (100.0)	242 (100.0)	0.2350	10.3
	Yes	120 (40.5)	86 (35.5)		
Chronic Kidney Disease	N (% non-missing)	296 (100.0)	242 (100.0)	0.0853	15.0
	Yes	61 (20.6)	36 (14.9)		
Cerebrovascular disease	N (% non-missing)	296 (100.0)	242 (100.0)	0.1481	12.8
	Yes	11 (3.7)	4 (1.7)		
Myocardial infarct	N (% non-missing)	296 (100.0)	242 (100.0)	0.8037	2.1
	Yes	3 (1.0)	3 (1.2)		

Table 71: Comorbidities 2

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
Current peak flow	N (% non-missing)	160 (54.1)	138 (57.0)	0.0105	30.1
	Mean (SD)	401.3 (102.9)	436.2 (127.3)		
	Median (IQR)	392.5 (115.0)	430.0 (170.0)		
Predicted peak flow	N (% non-missing)	158 (53.4)	138 (57.0)	0.0001	44.8
	Mean (SD)	495.7 (71.4)	528.4 (74.3)		
	Median (IQR)	472.5 (121.1)	524.7 (131.1)		
Percentage predicted peak flow	N (% non-missing)	158 (53.4)	138 (57.0)	0.7563	4.9
	Mean (SD)	81.1 (15.9)	82.0 (19.0)		
	Median (IQR)	81.9 (22.1)	81.3 (24.7)		
% predicted PF groups	N (% non-missing)	158 (53.4)	138 (57.0)	0.5913	6.2
	33-50%	5 (3.2)	6 (4.3)		
	>=50%	153 (96.8)	132 (95.7)		

Table 72: Peak flow

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
Current peak flow	N (% non-missing)	81 (27.4)	80 (33.1)	0.0160	41.1
	Mean (SD)	389.4 (98.5)	437.3 (132.0)		
	Median (IQR)	380.0 (120.0)	430.0 (175.0)		
Predicted peak flow	N (% non-missing)	158 (53.4)	49 (68.1)	0.0001	44.8
	Mean (SD)	495.7 (71.4)	503.2 (79.3)		
	Median (IQR)	472.5 (121.1)	480.6 (123.5)		
	N (% non-missing)	79 (26.7)	80 (33.1)	0.8336	6.7

Percentage predicted peak flow	Mean (SD)	81.0 (15.1)	82.2 (19.6)		
	Median (IQR)	81.0 (22.3)	80.9 (26.2)		
% predicted PF groups	N (% non-missing)	79 (26.7)	80 (33.1)	0.3173	15.8
	33-50%	1 (1.3)	3 (3.7)		
	>=50%	78 (98.7)	77 (96.3)		

Table 73: Peak flow

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
FEV ₁	N (% non-missing)	53 (17.9)	49 (20.2)	0.7605	26.2
	Mean (SD)	11.1 (25.0)	5.6 (15.8)		
	Median (IQR)	2.3 (1.2)	2.6 (1.4)		
FVC	N (% non-missing)	87 (29.4)	68 (28.1)	0.0734	30.1
	Mean (SD)	3.3 (0.9)	3.6 (1.0)		
	Median (IQR)	3.2 (1.2)	3.5 (1.3)		
FEV ₁ /FVC_ratio	N (% non-missing)	40 (13.5)	35 (14.5)	0.0278	43.9
	Mean (SD)	0.8 (0.1)	0.7 (0.1)		
	Median (IQR)	0.8 (0.1)	0.7 (0.2)		
FEV ₁ Percent Predicted	N (% non-missing)	55 (18.6)	50 (20.7)	0.0448	43.8
	Mean (SD)	71.8 (40.1)	53.3 (44.4)		
	Median (IQR)	83.0 (44.0)	66.5 (94.0)		
FEV1 % predicted groups	N (% non-missing)	55 (18.6)	50 (20.7)	0.1633	45.2
	50% or less	12 (21.8)	21 (42.0)		
	>50% to <80%	13 (23.6)	10 (20.0)		
	80% to <100%	15 (27.3)	10 (20.0)		
	100%+	15 (27.3)	9 (18.0)		

Table 74: Lung function

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
Asthma consultations	N (% non-missing)	296 (100.0)	242 (100.0)	0.7552	5.4
	Mean (SD)	1.8 (1.5)	1.9 (1.7)		
	Median (IQR)	1.5 (1.0)	2.0 (1.0)		
Asthma consultations	N (% non-missing)	296 (100.0)	242 (100.0)	0.6661	7.8
	0	34 (11.5)	32 (13.2)		
	1	114 (38.5)	85 (35.1)		
	2+	148 (50.0)	125 (51.7)		
Asthma related accident and emergency	N (% non-missing)	296 (100.0)	242 (100.0)	0.2683	9.1
	1	0 (0.0)	1 (0.4)		
Asthma related unplanned inpatient admission	N (% non-missing)	296 (100.0)	242 (100.0)	0.1171	12.9
	1	0 (0.0)	2 (0.8)		

Table 75: Healthcare Resource Utilisation

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
LAMA prescriptions per patient	N (% non-missing)	296 (100.0)	27 (100.0)	0.4561	16.1
	Mean (SD)	0.0 (0.4)	0.1 (0.8)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
ICS/LABA prescriptions per patient	N (% non-missing)	296 (100.0)	242 (100.0)	0.5516	1.6
	Mean (SD)	4.2 (4.1)	4.3 (3.9)		
	Median (IQR)	3.0 (6.0)	3.0 (5.0)		

Mono ICS prescriptions per patient	N (% non-missing)	296 (100.0)	242 (100.0)	0.0178	29.1
	Mean (SD)	1.2 (2.5)	0.6 (1.5)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
LTRA prescriptions per patient	N (% non-missing)	296 (100.0)	242 (100.0)	0.8659	0.3
	Mean (SD)	0.7 (2.3)	0.7 (2.4)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
THEO prescriptions per patient	N (% non-missing)	296 (100.0)	242 (100.0)	0.9744	3.6
	Mean (SD)	0.1 (1.0)	0.2 (1.3)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
SAMA prescriptions per patient	N (% non-missing)	296 (100.0)	27 (100.0)	0.4198	14.5
	Mean (SD)	0.0 (0.4)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		

Table 76: Asthma prescriptions per patient

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
LABA prescription (yes/no)	N (% non-missing)	296 (100.0)	242 (100.0)	0.4120	7.2
	Yes	8 (2.7)	4 (1.7)		
LAMA prescription (yes/no)	N (% non-missing)	296 (100.0)	242 (100.0)	0.3471	8.0
	Yes	5 (1.7)	7 (2.9)		
SAMA prescription (yes/no)	N (% non-missing)	296 (100.0)	242 (100.0)	0.0628	16.7
	Yes	7 (2.4)	1 (0.4)		
LTRA prescription (yes/no)	N (% non-missing)	296 (100.0)	242 (100.0)	0.8783	1.3
	Yes	38 (12.8)	30 (12.4)		
Theophylline prescription (yes/no)	N (% non-missing)	296 (100.0)	242 (100.0)	0.9746	0.3
	Yes	6 (2.0)	5 (2.1)		

Table 77: Asthma prescriptions per patient (yes/no)

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
SABA prescriptions	N (% non-missing)	296 (100.0)	242 (100.0)	0.8559	6.5
	Mean (SD)	3.0 (3.2)	3.2 (3.8)		
	Median (IQR)	2.0 (3.5)	2.0 (4.0)		
SABA inhalers	N (% non-missing)	296 (100.0)	242 (100.0)	0.9156	2.1
	Mean (SD)	3.6 (4.3)	3.7 (4.6)		
	Median (IQR)	2.0 (4.0)	2.0 (4.0)		
Daily SABA dosage	N (% non-missing)	296 (100.0)	242 (100.0)	0.9635	2.1
	Mean (SD)	197.6 (238.6)	202.8 (254.3)		
	Median (IQR)	109.6 (219.2)	109.6 (219.2)		

Table 78: SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
Number of SABA prescriptions	N (% non-missing)	296 (100.0)	242 (100.0)	0.7363	9.8
	0	68 (23.0)	52 (21.5)		
	1-3	136 (45.9)	113 (46.7)		
	4-6	54 (18.2)	39 (16.1)		
	>=7	38 (12.8)	38 (15.7)		
Number of SABA inhalers	N (% non-missing)	296 (100.0)	242 (100.0)	0.9269	5.9
	1	68 (23.0)	52 (21.5)		
	2	119 (40.2)	102 (42.1)		

	3	58 (19.6)	44 (18.2)		
	4	51 (17.2)	44 (18.2)		
Mean daily SABA dosage (mcg)	N (% non-missing)	296 (100.0)	242 (100.0)	0.9570	4.9
	<100	109 (36.8)	94 (38.8)		
	100-200	80 (27.0)	61 (25.2)		
	201-400	68 (23.0)	55 (22.7)		
	>400	39 (13.2)	32 (13.2)		

Table 79: Categorized SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
ICS daily dose	N (% non-missing)	296 (100.0)	242 (100.0)	0.6125	4.5
	Mean (SD)	586.9 (503.5)	564.9 (482.6)		
	Median (IQR)	427.4 (602.7)	438.4 (569.9)		
ICS/LABA or mono ICS inhalers	N (% non-missing)	296 (100.0)	242 (100.0)	0.2792	11.8
	Mean (SD)	7.0 (5.2)	6.4 (4.7)		
	Median (IQR)	6.0 (7.0)	5.0 (6.0)		
ICS/LABA or mono ICS prescriptions	N (% non-missing)	296 (100.0)	242 (100.0)	0.1305	13.8
	Mean (SD)	5.6 (3.8)	5.0 (3.6)		
	Median (IQR)	5.0 (6.0)	4.0 (5.0)		
ICS adherence	N (% non-missing)	296 (100.0)	242 (100.0)	0.2110	11.4
	Mean (SD)	70.1 (65.8)	63.4 (51.9)		
	Median (IQR)	64.4 (69.9)	54.8 (63.0)		

Table 80: ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
Number of ICS/LABA or mono ICS prescriptions	N (% non-missing)	296 (100.0)	242 (100.0)	0.2588	14.3
	0	0 (0.0)	0 (0.0)		
	1-3	113 (38.2)	106 (43.8)		
	4-6	84 (28.4)	70 (28.9)		
	>=7	99 (33.4)	66 (27.3)		
Number of ICS/LABA or mono ICS inhalers	N (% non-missing)	296 (100.0)	242 (100.0)	0.6045	8.7
	0	0 (0.0)	0 (0.0)		
	1-3	90 (30.4)	83 (34.3)		
	4-6	76 (25.7)	61 (25.2)		
	>=7	130 (43.9)	98 (40.5)		
Mean daily ICS dosage (mcg)	N (% non-missing)	296 (100.0)	242 (100.0)	0.5311	9.8
	<250	89 (30.1)	75 (31.0)		
	250-<500	74 (25.0)	69 (28.5)		
	>=500	133 (44.9)	98 (40.5)		
Mean daily ICS dosage (mcg)	N (% non-missing)	295 (99.7)	242 (100.0)	0.4665	13.9
	<40	95 (32.2)	84 (34.7)		
	40-79	90 (30.5)	83 (34.3)		
	80-120	76 (25.8)	54 (22.3)		
	>120	34 (11.5)	21 (8.7)		

Table 81: Categorized ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=296)	High eosinophil or high FeNO/eosinophil (n=242)	P value*	SDD
Asthma ATS exacerbations	N (% non-missing)	296 (100.0)	242 (100.0)	0.2128	20.7
	0	213 (72.0)	172 (71.1)		
	1	60 (20.3)	39 (16.1)		

	2	20 (6.8)	24 (9.9)		
	3	2 (0.7)	6 (2.5)		
	4	1 (0.3)	1 (0.4)		
Asthma ATS exacerbations	Mean (SD)	0.4 (0.7)	0.5 (0.8)	0.5586	10.6
	Median (IQR)	0, (0, 1)	0 (0,1)		
	N (% non-missing)	296 (100.0)	242 (100.0)	0.8619	9.9
Acute respiratory event	0	117 (39.5)	96 (39.7)		
	1	83 (28.0)	62 (25.6)		
	2	44 (14.9)	44 (18.2)		
	3	23 (7.8)	17 (7.0)		
	4+	29 (9.8)	23 (9.5)		
Acute respiratory event	Mean (SD)	1.3 (1.6)	1.3 (1.5)	0.8850	0.5
	Median (IQR)	1.0 (2.0)	1.0 (2.0)		

Table 82: Exacerbations

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

15.4.1 Statistically significant difference between unmatched patient groups – high BEC or high FeNO vs low BEC and low FeNO (categorisation 1)

		Low BEC and low FeNO	High BEC or high FeNO	P-value
Gender	N (% non-missing)	296 (100.0)	242 (100.0)	0.0003
	Male	93 (31.4)	113 (46.7)	
Age categorised	N (% non-missing)	296 (100.0)	242 (100.0)	0.0163
	Under 35	28 (9.5)	38 (15.7)	
	35-65	229 (77.4)	161 (66.5)	
	44-80	39 (13.2)	43 (17.8)	
Hypertension diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.0266
	Yes	79 (26.7)	45 (18.6)	
GERD diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.0489

	Yes	58 (19.6)	32 (13.2)	
GERD active diagnosis	N (% non-missing)	296 (100.0)	242 (100.0)	0.0195
	Yes	50 (16.9)	24 (9.9)	
Current peak flow	N (% non-missing)	160 (54.1)	138 (57.0)	0.0105
	Mean (SD)	401.3 (102.9)	436.2 (127.3)	
	Median (IQR)	392.5 (115.0)	430.0 (170.0)	
Predicted peak flow	N (% non-missing)	158 (53.4)	138 (57.0)	0.0001
	Mean (SD)	495.7 (71.4)	528.4 (74.3)	
	Median (IQR)	472.5 (121.1)	524.7 (131.1)	
FEV1/FVC_Ratio	N (% non-missing)	40 (13.5)	35 (14.5)	0.0278
	Mean (SD)	0.8 (0.1)	0.7 (0.1)	
	Median (IQR)	0.8 (0.1)	0.7 (0.2)	
FEV1 Percent Predicted	N (% non-missing)	55 (18.6)	50 (20.7)	0.0448
	Mean (SD)	71.8 (40.1)	53.3 (44.4)	
	Median (IQR)	83.0 (44.0)	66.5 (94.0)	
Standalone ICS treatment	N (% non-missing)	296 (100.0)	242 (100.0)	0.0178
	Mean (SD)	1.2 (2.5)	0.6 (1.5)	
	Median (IQR)	0.0 (1.0)	0.0 (1.0)	

Table 83: Unmatched comparison using categorisation 1, with significant differences between covariates illustrated. Comparison is based on non-missing data

15.5 Unmatched comparison between high BEC and high FeNO vs low BEC and low FeNO (characterisation 2)

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
Gender	N (% non-missing)	347 (100.0)	55 (100.0)	0.0614	26.7
	Male	113 (32.6)	25 (45.5)		
Age	N (% non-missing)	347 (100.0)	55 (100.0)	0.1685	27.1
	Mean (SD)	52.7 (13.0)	48.6 (17.0)		
	Median (IQR)	55.0 (17.0)	53.0 (31.0)		
Age group	N (% non-missing)	347 (100.0)	55 (100.0)	0.0015	48.6
	Under 35	36 (10.4)	14 (25.5)		
	35-65	264 (76.1)	30 (54.5)		
	66-80	47 (13.5)	11 (20.0)		
Smoking status	N (% non-missing)	347 (100.0)	55 (100.0)	0.1427	34.0

	Non-smoker	138 (39.8)	31 (56.4)		
	Ex-smoker	40 (11.5)	5 (9.1)		
	Current smoker	111 (32.0)	12 (21.8)		
Height	N (% non-missing)	336 (96.8)	53 (96.4)	0.1722	6.4
	Mean (SD)	165.9 (9.4)	164.7 (24.5)		
	Median (IQR)	165.0 (13.0)	167.0 (12.0)		
Weight	N (% non-missing)	333 (96.0)	52 (94.5)	0.0156	34.5
	Mean (SD)	82.4 (18.6)	75.9 (18.8)		
	Median (IQR)	80.0 (25.5)	74.9 (21.3)		

Table 84: Demographic summary

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
BMI	N (% non-missing)	341 (98.3)	52 (94.5)	0.0002	54.8
	Mean (SD)	29.8 (6.2)	26.6 (5.6)		
	Median (IQR)	29.1 (8.4)	25.5 (6.9)		
BMI	N (% non-missing)	347 (100.0)	55 (100.0)	0.0051	54.7
	Underweight	1 (0.3)	1 (1.8)		
	Normal	82 (23.6)	21 (38.2)		
	Overweight	106 (30.5)	18 (32.7)		
	Obese	152 (43.8)	12 (21.8)		
FENO	N (% non-missing)	347 (100.0)	55 (100.0)	<0.0001	214.0
	Mean (SD)	16.3 (7.6)	56.8 (25.7)		
	Median (IQR)	15.0 (11.0)	49.0 (25.0)		
eosinophil count	N (% non-missing)	347 (100.0)	55 (100.0)	<0.0001	190.9
	Mean (SD)	0.2 (0.1)	0.5 (0.3)		
	Median (IQR)	0.2 (0.1)	0.5 (0.3)		
COPD diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)	0.1495	39.3
	Yes	0 (0.0)	2 (7.4)		

Table 85: Clinical measurements

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=347)	High eosinophil, high FeNO (n=55)	P-value*	SDD
Acute oral corticosteroid prescriptions	N (% non-missing)	347 (100.0)	55 (100.0)	0.0889	38.3
	0	254 (73.2)	31 (56.4)		
	1	58 (16.7)	13 (23.6)		
	2	27 (7.8)	9 (16.4)		
	3	6 (1.7)	1 (1.8)		
	4	2 (0.6)	1 (1.8)		
Acute oral corticosteroid prescriptions >14 days apart	N (% non-missing)	347 (100.0)	55 (100.0)	0.1031	38.4
	0	254 (73.2)	31 (56.4)		
	1	65 (18.7)	15 (27.3)		
	2	24 (6.9)	8 (14.5)		
	3	3 (0.9)	1 (1.8)		
	4	1 (0.3)	0 (0.0)		
Acute oral corticosteroid use (yes/no)	N (% non-missing)	347 (100.0)	55 (100.0)	0.0107	35.8
	Yes	93 (26.8)	24 (43.6)		
Antibiotics	N (% non-missing)	347 (100.0)	55 (100.0)	0.1977	25.1
	Mean (SD)	0.2 (0.5)	0.3 (0.6)		
	Median (IQR)	0.0 (0.0)	0.0 (1.0)		
Antibiotic courses	N (% non-missing)	347 (100.0)	55 (100.0)	0.3144	25.1
	0	283 (81.6)	41 (74.5)		
	1	52 (15.0)	10 (18.2)		
	2	10 (2.9)	4 (7.3)		
	3	2 (0.6)	0 (0.0)		

Table 86: Acute asthma treatment

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
Active eczema diagnosis	N (% non-missing)	347 (100.0)	55 (100.0)	0.8559	2.6
	Yes	11 (3.2)	2 (3.6)		
Active rhinitis diagnosis	N (% non-missing)	347 (100.0)	55 (100.0)	0.1462	20.6
	Yes	99 (28.5)	21 (38.2)		
Eczema diagnosis	N (% non-missing)	347 (100.0)	55 (100.0)	0.1427	20.7
	Yes	93 (26.8)	20 (36.4)		
Rhinitis diagnosis	N (% non-missing)	347 (100.0)	55 (100.0)	0.1006	23.6
	Yes	130 (37.5)	27 (49.1)		
Cardiovascular diagnosis	N (% non-missing)	347 (100.0)	55 (100.0)	0.3095	15.8
	Yes	49 (14.1)	5 (9.1)		
IHD diagnosis	N (% non-missing)	347 (100.0)	55 (100.0)	0.6818	6.3
	Yes	17 (4.9)	2 (3.6)		
Heart failure diagnosis	N (% non-missing)	347 (100.0)	55 (100.0)	0.6902	7.6
	Yes	1 (0.3)	0 (0.0)		
Hypertension diagnosis	N (% non-missing)	347 (100.0)	55 (100.0)	0.1069	24.9
	Yes	92 (26.5)	9 (16.4)		

Table 87: Comorbidities 1

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. **Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations**

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
Diabetes diagnosis	N (% non-missing)	347 (100.0)	55 (100.0)	0.4232	12.5
	Yes	30 (8.6)	3 (5.5)		
Osteoporosis diagnosis	N (% non-missing)	347 (100.0)	55 (100.0)	0.5560	7.8
	Yes	8 (2.3)	2 (3.6)		

GERD diagnosis	N (% non-missing)	347 (100.0)	55 (100.0)	0.2009	19.9
	Yes	62 (17.9)	6 (10.9)		
GERD active diagnosis	N (% non-missing)	347 (100.0)	55 (100.0)	0.2253	19.0
	Yes	53 (15.3)	5 (9.1)		
Anxiety or depression	N (% non-missing)	347 (100.0)	55 (100.0)	0.0700	27.3
	Yes	139 (40.1)	15 (27.3)		
Chronic Kidney Disease	N (% non-missing)	347 (100.0)	55 (100.0)	0.9763	0.4
	Yes	70 (20.2)	11 (20.0)		
Cerebrovascular disease	N (% non-missing)	347 (100.0)	55 (100.0)	0.1445	27.9
	Yes	13 (3.7)	0 (0.0)		
Myocardial infarct	N (% non-missing)	347 (100.0)	55 (100.0)	0.4236	15.3
	Yes	4 (1.2)	0 (0.0)		

Table 88: Comorbidities 2

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
Current peak flow	N (% non-missing)	195 (56.2)	40 (72.7)	0.3365	16.3
	Mean (SD)	403.7 (106.1)	422.8 (127.7)		
	Median (IQR)	400.0 (120.0)	400.0 (110.0)		
Predicted peak flow	N (% non-missing)	193 (55.6)	40 (72.7)	0.2218	19.0
	Mean (SD)	498.0 (73.8)	511.6 (70.0)		
	Median (IQR)	473.8 (123.4)	481.2 (127.6)		
Percentage predicted peak flow	N (% non-missing)	193 (55.6)	40 (72.7)	0.9005	4.4
	Mean (SD)	81.1 (16.1)	81.9 (18.7)		
	Median (IQR)	82.6 (22.7)	81.3 (21.5)		
% predicted PF groups	N (% non-missing)	14 (51.9)	20 (74.1)	0.9150	7.0
	33-50	1 (7.10)	2 (10.0)		

	>=50	13 (92.9)	18 (90.0)		.
	>=80%	111 (57.5)	23 (57.5)		

Table 89: Peak flow

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
FeV₁	N (% non-missing)	53 (15.3)	11 (20.0)	0.0909	65.9
	Mean (SD)	2.3 (1.0)	3.0 (1.1)		
	Median (IQR)	2.3 (0.9)	3.4 (2.1)		
FVC	N (% non-missing)	95 (27.4)	13 (23.6)	0.0919	49.6
	Mean (SD)	3.3 (0.9)	3.9 (1.3)		
	Median (IQR)	3.2 (1.2)	4.1 (1.5)		
FEV₁/FVC_ratio	N (% non-missing)	45 (13.0)	10 (18.2)	0.9477	12.9
	Mean (SD)	0.8 (0.1)	0.8 (0.1)		
	Median (IQR)	0.8 (0.1)	0.8 (0.1)		
FEV₁ Percent Predicted	N (% non-missing)	50 (14.4)	5 (9.1)	0.9533	1.2
	Mean (SD)	88.0 (22.8)	87.8 (15.3)		
	Median (IQR)	88.0 (31.0)	91.0 (13.0)		
FEV1 % predicted groups	N (% non-missing)	50 (14.4)	5 (9.1)	0.7520	55.1
	50% or less	2 (4.0)	0 (0.0)		
	>50% to <80%	14 (28.0)	1 (20.0)		
	80% to <100%	18 (36.0)	3 (60.0)		
	100%+	16 (32.0)	1 (20.0)		

Table 90: Lung function

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
Asthma consultations	N (% non-missing)	347 (100.0)	55 (100.0)	0.1535	26.2
		1.9 (1.6)	2.4 (2.2)		
		2.0 (1.0)	2.0 (2.0)		
	Mean (SD)	347 (100.0)	55 (100.0)	0.6942	12.5
	Median (IQR)	40 (11.5)	6 (10.9)		
Asthma consultations	N (% non-missing)	126 (36.3)	17 (30.9)		
	0	181 (52.2)	32 (58.2)		
	1	347 (100.0)	55 (100.0)	0.0119	19.2
	2+	0 (0.0)	1 (1.8)		
Asthma related accident and emergency	N (% non-missing)	347 (100.0)	55 (100.0)	0.0119	19.2
	1	0 (0.0)	1 (1.8)		
Asthma related unplanned inpatient admission	N (% non-missing)	347 (100.0)	55 (100.0)	0.0004	27.5
	1	0 (0.0)	2 (3.6)		

Table 91: Healthcare Resource Utilisation

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=27)	P value*	SDD
LAMA prescriptions per patient	N (% non-missing)	347 (100.0)	55 (100.0)	0.9277	4.3
	Mean (SD)	0.1 (0.4)	0.1 (0.5)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
ICS/LABA prescriptions per patient	N (% non-missing)	347 (100.0)	55 (100.0)	0.8104	4.9
	Mean (SD)	4.1 (4.0)	3.9 (4.0)		
	Median (IQR)	3.0 (6.0)	3.0 (5.0)		
Mono ICS prescriptions per patient	N (% non-missing)	347 (100.0)	55 (100.0)	0.8843	16.1
	Mean (SD)	1.2 (2.4)	0.8 (1.7)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
	N (% non-missing)	347 (100.0)	55 (100.0)	0.7119	2.8

LTRA prescriptions per patient	Mean (SD)	0.7 (2.1)	0.6 (1.9)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
THEO prescriptions per patient	N (% non-missing)	347 (100.0)	55 (100.0)	0.2560	17.1
	Mean (SD)	0.1 (1.0)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
SAMA prescriptions per patient	N (% non-missing)	347 (100.0)	55 (100.0)	0.2560	.
	Mean (SD)	0.1 (0.5)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		

Table 92: Asthma prescriptions per patient

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
LABA prescription (yes/no)	N (% non-missing)	347 (100.0)	55 (100.0)	0.2554	21.7
	Yes	8 (2.3)	0 (0.0)		
LAMA prescription (yes/no)	N (% non-missing)	347 (100.0)	55 (100.0)	0.9217	1.5
	Yes	7 (2.0)	1 (1.8)		
SAMA prescription (yes/no)	N (% non-missing)	347 (100.0)	55 (100.0)	0.2554	21.7
	Yes	8 (2.3)	0 (0.0)		
LTRA prescription (yes/no)	N (% non-missing)	347 (100.0)	55 (100.0)	0.6557	6.3
	Yes	43 (12.4)	8 (14.5)		
Theophylline prescription (yes/no)	N (% non-missing)	347 (100.0)	55 (100.0)	0.2554	21.7
	Yes	8 (2.3)	0 (0.0)		

Table 93: Asthma prescriptions yes/no

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
SABA prescriptions	N (% non-missing)	347 (100.0)	55 (100.0)	0.3391	18.2
	Mean (SD)	3.1 (3.4)	3.8 (4.3)		
	Median (IQR)	2.0 (4.0)	2.0 (4.0)		
SABA inhalers	N (% non-missing)	347 (100.0)	55 (100.0)	0.3799	19.6
	Mean (SD)	3.7 (4.4)	4.7 (6.1)		
	Median (IQR)	2.0 (4.0)	2.0 (5.0)		
Daily SABA dosage	N (% non-missing)	347 (100.0)	55 (100.0)	0.3888	18.7
	Mean (SD)	201.3 (243.9)	256.3 (336.4)		
	Median (IQR)	109.6 (219.2)	109.6 (274.0)		

Table 94: SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
Number of SABA prescriptions	N (% non-missing)	347 (100.0)	55 (100.0)	0.8394	13.5
	0	79 (22.8)	10 (18.2)		
	1-3	159 (45.8)	25 (45.5)		
	4-6	62 (17.9)	11 (20.0)		
	>=7	47 (13.5)	9 (16.4)		
Number of SABA inhalers	N (% non-missing)	347 (100.0)	55 (100.0)	0.8552	13.0
	0	79 (22.8)	10 (18.2)		
	1-3	140 (40.3)	22 (40.0)		
	4-6	65 (18.7)	12 (21.8)		
	>=7	63 (18.2)	11 (20.0)		
Mean daily SABA dosage (mcg)	N (% non-missing)	347 (100.0)	55 (100.0)	0.8343	13.6
	<100	128 (36.9)	17 (30.9)		
	100-200	93 (26.8)	15 (27.3)		
	201-400	77 (22.2)	14 (25.5)		
	>400	49 (14.1)	9 (16.4)		

Table 95: Categorized SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
ICS daily dose	N (% non-missing)	347 (100.0)	55 (100.0)	0.7320	6.5
	Mean (SD)	587.2 (498.6)	555.9 (472.0)		
	Median (IQR)	416.4 (602.7)	394.5 (465.7)		
ICS/LABA or mono ICS inhalers	N (% non-missing)	347 (100.0)	55 (100.0)	0.5161	8.3
	Mean (SD)	6.9 (5.1)	6.4 (5.3)		
	Median (IQR)	6.0 (7.0)	5.0 (5.0)		
ICS/LABA or mono ICS prescriptions	N (% non-missing)	347 (100.0)	55 (100.0)	0.4032	12.5
	Mean (SD)	5.4 (3.7)	4.9 (3.6)		
	Median (IQR)	5.0 (6.0)	4.0 (4.0)		
ICS adherence	N (% non-missing)	347 (100.0)	55 (100.0)	0.7451	2.4
	Mean (SD)	69.9 (66.0)	68.2 (71.6)		
	Median (IQR)	57.5 (71.2)	49.3 (57.5)		

Table 96: ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
Number of ICS/LABA or mono ICS prescriptions	N (% non-missing)	347 (100.0)	55 (100.0)	0.2425	25.8
	1-3	138 (39.8)	25 (45.5)		
	4-6	101 (29.1)	19 (34.5)		
	>=7	108 (31.1)	11 (20.0)		

Number of ICS/LABA or mono ICS inhalers	N (% non-missing)	347 (100.0)	55 (100.0)	0.4133	19.6
	1-3, n (%)	107 (30.8)	19 (34.5)		
	4-6, n (%)	94 (27.1)	18 (32.7)		
	>=7, n (%)	146 (42.1)	18 (32.7)		
Mean daily ICS dosage (mcg)	N (% non-missing)	347 (100.0)	55 (100.0)	0.0935	30.9
	<250	103 (29.7)	15 (27.3)		
	250-<500	91 (26.2)	22 (40.0)		
	>=500	153 (44.1)	18 (32.7)		
ICS adherence(%)	N (% non-missing)	346 (99.7)	55 (100.0)	0.6591	18.1
	<40, n (%)	111 (32.1)	16 (29.1)		
	40-79, n (%)	109 (31.5)	22 (40.0)		
	80-120, n (%)	87 (25.1)	12 (21.8)		
	>120, n (%)	39 (11.3)	5 (9.1)		

Table 97: Categorized ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil/high FeNO (n=55)	P value*	SDD
Asthma ATS exacerbations	N (% non-missing)	347 (100.0)	55 (100.0)	0.0487	40.6
	0, n (%)	254 (73.2)	31 (56.4)		
	1, n (%)	65 (18.7)	14 (25.5)		
	2, n (%)	24 (6.9)	8 (14.5)		
	3, n (%)	3 (0.9)	2 (3.6)		
	4, n (%)	1 (0.3)	0 (0.0)		
Asthma ATS exacerbations	Mean (SD)	0.4 (0.7)	0.7 (0.9)	0.0063	40.6
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
Acute respiratory event	N (% non-missing)	347 (100.0)	55 (100.0)	0.0761	40,5
	0, n (%)	233 (67.1)	27 (49.1)		
	1, n (%)	74 (21.3)	16 (29.1)		
	2, n (%)	32 (9.2)	9 (16.4)		

	3, n (%)	7 (2.0)	3 (5.5)		
	4+, n (%)	1 (0.3)	0 (0.0)		
Acute respiratory event	N (% non-missing)	347 (100.0)	55 (100.0)	0.0061	.
	Mean (SD)	0.5 (0.8)	0.8 (0.9)		
	Median (IQR)	0.0 (1.0)	1.0 (1.0)		

Table 98: Exacerbations

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n = 347)	High eosinophil, high FeNO (n=55)	P value*	SDD
Medication cost without ICS	N (% non-missing)	340 (98.0)	55 (100.0)	0.2514	3.9
	Mean (SD)	34.6 (70.3)	37.4 (76.6)		
	Median (IQR)	9.5 (23.0)	13.0 (34.0)		
Medication cost	N (% non-missing)	340 (98.0)	55 (100.0)	0.4987	7.4
	Mean (SD)	268.5 (228.1)	251.6 (231.6)		
	Median (IQR)	198.5 (287.0)	176.0 (266.0)		
Healthcare resource cost	N (% non-missing)	347 (100.0)	55 (100.0)	0.1511	31.0
	Mean (SD)	91.7 (86.4)	138.0 (192.8)		
	Median (IQR)	84.0 (84.0)	84.0 (126.0)		
Total cost without ICS	N (% non-missing)	340 (98.0)	55 (100.0)	0.2116	28.8
	Mean (SD)	126.2 (120.9)	175.5 (209.8)		
	Median (IQR)	89.0 (103.0)	97.0 (149.0)		
Total cost	N (% non-missing)	340 (98.0)	55 (100.0)	0.9815	10.2
	Mean (SD)	360.1 (253.7)	389.6 (319.6)		
	Median (IQR)	296.0 (288.5)	262.0 (256.0)		

Table 99: Healthcare costs.

*P-value computed from Mann Whitney test. Where data is missing, percentages are given as a percentage of the non-missing variables

15.5.1 Statistically significant difference between unmatched patient groups – high BEC and high FeNO vs low BEC and low FeNO
(categorisation 2)

		Low BEC, low FeNO	High BEC, high FeNO	P-value
Categorised age	N (% non-missing)	347 (100.0)	55 (100.0)	0.0015
	Under 35	36 (10.4)	14 (25.5)	
	35-65	264 (76.1)	30 (54.5)	
	44-80	47 (13.5)	11 (20.0)	
BMI	N (% non-missing)	341 (98.3)	52 (94.5)	0.0002
	Mean (SD)	29.8 (6.2)	26.6 (5.6)	
	Median (IQR)	29.1 (8.4)	25.5 (6.9)	
BMI	N (% non-missing)	347 (100.0)	55 (100.0)	0.0051
	Underweight	1 (0.3)	1 (1.8)	
	Normal	82 (23.6)	21 (38.2)	
	Overweight	106 (30.5)	18 (32.7)	
	Obese	152 (43.8)	12 (21.8)	
	missing	6 (1.7)	3 (5.5)	
Acute oral corticosteroid use	N (% non-missing)	347 (100.0)	55 (100.0)	0.0107
	Yes	93 (26.8)	24 (43.6)	
Asthma related accident and emergency attendance	N (% non-missing)	347 (100.0)	55 (100.0)	0.0119
	Yes	0 (0.0)	1 (1.8)	
Asthma related unplanned inpatient admission	N (% non-missing)	347 (100.0)	55 (100.0)	0.0004
	Yes	0 (0.0)	2 (3.6)	
Asthma ATS exacerbations	N (% non-missing)	347 (100.0)	55 (100.0)	0.0063
	Mean (SD)	0.4 (0.7)	0.7 (0.9)	
	Median (IQR)	0.0 (1.0)	0.0 (1.0)	
Asthma ATS exacerbations	N (% non-missing)	347 (100.0)	55 (100.0)	0.0487
	0	254 (73.2)	31 (56.4)	
	1	65 (18.7)	14 (25.5)	
	2	24 (6.9)	8 (14.5)	
	3	3 (0.9)	2 (3.6)	
	4+	1 (0.3)	0 (0.0)	
	Missing	0 (0.0)	0 (0.0)	
Asthma respiratory event	N (% non-missing)	347 (100.0)	55 (100.0)	0.0061
	Mean (SD)	0.5 (0.8)	0.8 (0.9)	
	Median (IQR)	0.0 (1.0)	1.0 (1.0)	

Table 100: High BEC and high FeNO vs reference – significant differences of covariates between groups

15.6 Unmatched characterisation of high BEC vs low BEC and low FeNO patients (categorisation 2)

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
Gender	N (% non-missing)	347 (100.0)	218 (100.0)	0.0015	27.5
	Male	113 (32.6)	100 (45.9)		
Age	N (% non-missing)	347 (100.0)	218 (100.0)	0.2644	12.2
	Mean (SD)	52.7 (13.0)	51.0 (14.2)		
	Median (IQR)	55.0 (17.0)	53.0 (21.0)		
Age group	N (% non-missing)	347 (100.0)	218 (100.0)	0.0799	19.3
	Under 35	36 (10.4)	31 (14.2)		
	35-65	264 (76.1)	147 (67.4)		
	66-80	47 (13.5)	40 (18.3)		
Smoking status	N (% non-missing)	347 (100.0)	218 (100.0)	0.2804	16.7
	Non smoker	138 (39.8)	77 (35.3)		
	Ex-smoker	40 (11.5)	37 (17.0)		
	Current smoker	111 (32.0)	71 (32.6)		
Height	N (% non-missing)	336 (96.8)	211 (96.8)	0.0100	9.5
	Mean (SD)	165.9 (9.4)	167.1 (14.5)		
	Median (IQR)	165.0 (13.0)	167.0 (13.0)		
Weight	N (% non-missing)	333 (96.0)	210 (96.3)	0.9011	3.8
	Mean (SD)	82.4 (18.6)	83.2 (21.5)		
	Median (IQR)	80.0 (25.5)	80.7 (27.3)		

Table 101: Demographic summary

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
BMI	N (% non-missing)	341 (98.3)	212 (97.2)	0.0612	13.7
	Mean (SD)	29.8 (6.2)	29.0 (6.5)		
	Median (IQR)	29.1 (8.4)	27.8 (8.0)		
BMI	N (% non-missing)	347 (100.0)	218 (100.0)	0.2328	19.9
	Underweight	1 (0.3)	3 (1.4)		
	Normal	82 (23.6)	59 (27.1)		
	Overweight	106 (30.5)	71 (32.6)		
FENO	N (% non-missing)	347 (100.0)	218 (100.0)	<0.0001	68.0
	Mean (SD)	16.3 (7.6)	27.9 (22.8)		
	Median (IQR)	15.0 (11.0)	22.0 (22.0)		
eosinophil count	N (% non-missing)	347 (100.0)	216 (99.1)	<0.0001	200.2
	Mean (SD)	0.2 (0.1)	0.4 (0.2)		
	Median (IQR)	0.2 (0.1)	0.4 (0.2)		
COPD diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.4543	6.3
	Yes	5 (1.4)	5 (2.3)		

Table 102: Clinical measurements

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=347)	High eosinophil, (n=218)	P-value*	SDD
Acute oral corticosteroid prescriptions	N (% non-missing)	347 (100.0)	218 (100.0)	0.5755	14.5
	0	254 (73.2)	154 (70.6)		
	1	58 (16.7)	32 (14.7)		
	2	27 (7.8)	24 (11.0)		
	3	6 (1.7)	6 (2.8)		
	4	2 (0.6)	2 (0.9)		

Acute oral corticosteroid prescriptions >14 days apart	N (% non-missing)	347 (100.0)	218 (100.0)	0.3052	18.5
	0	254 (73.2)	154 (70.6)		
	1	65 (18.7)	35 (16.1)		
	2	24 (6.9)	23 (10.6)		
	3	3 (0.9)	5 (2.3)		
	4	1 (0.3)	1 (0.5)		
Acute oral corticosteroid use (yes/no)	N (% non-missing)	347 (100.0)	218 (100.0)	0.5090	5.7
	Yes	93 (26.8)	64 (29.4)		
Antibiotics	N (% non-missing)	347 (100.0)	218 (100.0)	0.6725	16.8
	Mean (SD)	0.2 (0.5)	0.3 (0.6)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
Antibiotic courses	N (% non-missing)	347 (100.0)	218 (100.0)	0.2624	16.8
	0	283 (81.6)	176 (80.7)		
	1	52 (15.0)	27 (12.4)		
	2	10 (2.9)	12 (5.5)		
	3	2 (0.6)	3 (1.4)		

Table 103: Acute asthma treatment

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
Active eczema diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.3861	7.3
	Yes	11 (3.2)	10 (4.6)		
Active rhinitis diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.2127	10.7
	Yes	99 (28.5)	73 (33.5)		
Eczema diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.0237	19.5
	Yes	93 (26.8)	78 (35.8)		
Rhinitis diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.0369	18.0
	Yes	130 (37.5)	101 (46.3)		
	N (% non-missing)	347 (100.0)	218 (100.0)	0.2154	10.9

Cardiovascular diagnosis	Yes	49 (14.1)	23 (10.6)		
IHD diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.7509	2.7
	Yes	17 (4.9)	12 (5.5)		
Heart failure diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.3164	8.1
	Yes	1 (0.3)	2 (0.9)		
Hypertension diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.0487	17.3
	Yes	92 (26.5)	42 (19.3)		

Table 104: Comorbidities 1

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
Diabetes diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.8719	1.4
	Yes	30 (8.6)	18 (8.3)		
Osteoporosis diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.7394	2.8
	Yes	8 (2.3)	6 (2.8)		
GERD diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.3218	8.6
	Yes	62 (17.9)	32 (14.7)		
GERD active diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.1504	12.6
	Yes	53 (15.3)	24 (11.0)		
Anxiety or depression	N (% non-missing)	347 (100.0)	218 (100.0)	0.2594	9.8
	Yes	139 (40.1)	77 (35.3)		
Chronic Kidney Disease	N (% non-missing)	347 (100.0)	218 (100.0)	0.0722	15.8
	Yes	70 (20.2)	31 (14.2)		
Cerebrovascular disease	N (% non-missing)	347 (100.0)	218 (100.0)	0.1954	11.6
	Yes	13 (3.7)	4 (1.8)		
Myocardial infarct	N (% non-missing)	347 (100.0)	218 (100.0)	0.8152	2.0
	Yes	4 (1.2)	3 (1.4)		

Table 105: Comorbidities 2

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
Current peak flow	N (% non-missing)	195 (56.2)	120 (55.0)	0.0213	28.1
	Mean (SD)	403.7 (106.1)	436.7 (127.9)		
	Median (IQR)	400.0 (120.0)	430.0 (170.0)		
Predicted peak flow	N (% non-missing)	193 (55.6)	120 (55.0)	0.0015	37.8
	Mean (SD)	498.0 (73.8)	526.3 (76.0)		
	Median (IQR)	473.8 (123.4)	504.2 (133.6)		
Percentage predicted peak flow	N (% non-missing)	193 (55.6)	120 (55.0)	0.6502	7.5
	Mean (SD)	81.1 (16.1)	82.4 (19.0)		
	Median (IQR)	82.6 (22.7)	82.1 (26.7)		
% predicted PF groups	N (% non-missing)	193 (55.6)	120 (55.0)	0.9430	4.0
	33-50	7 (3.6)	5 (4.2)		
	>=50	75 (38.9)	48 (40.0)		
	>=80%	111 (57.5)	67 (55.8)		

Table 106: Peak flow

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
FeV ₁	N (% non-missing)	53 (15.3)	43 (19.7)	0.3418	19.0
	Mean (SD)	2.3 (1.0)	2.5 (1.0)		
	Median (IQR)	2.3 (0.9)	2.5 (1.5)		
FVC	N (% non-missing)	95 (27.4)	62 (28.4)	0.2221	20.9
	Mean (SD)	3.3 (0.9)	3.5 (1.1)		
	Median (IQR)	3.2 (1.2)	3.4 (1.4)		
	N (% non-missing)	45 (13.0)	31 (14.2)	0.1137	28.3

FEV ₁ /FVC_ratio	Mean (SD)	0.8 (0.1)	0.7 (0.1)		
	Median (IQR)	0.8 (0.1)	0.7 (0.2)		
FEV ₁ Percent Predicted	N (% non-missing)	50 (14.4)	28 (12.8)	0.7665	6.0
	Mean (SD)	88.0 (22.8)	86.7 (20.3)		
	Median (IQR)	88.0 (31.0)	91.0 (28.0)		
FEV1 % predicted groups	N (% non-missing)	50 (14.4)	28 (12.8)	0.8620	20.2
	50% or less	2 (4.0)	2 (7.1)		
	>50% to <80%	14 (28.0)	9 (32.1)		
	80% to <100%	18 (36.0)	8 (28.6)		
	100%+	16 (32.0)	9 (32.1)		

Table 107: Lung function

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=241)	P value*	SDD
Asthma consultations	N (% non-missing)	347 (100.0)	218 (100.0)	0.6626	3.2
		1.9 (1.6)	1.8 (1.6)		
		2.0 (1.0)	2.0 (1.0)		
		347 (100.0)	218 (100.0)	0.8195	5.4
		40 (11.5)	29 (13.3)		
	Mean (SD)	126 (36.3)	77 (35.3)		
	Median (IQR)	181 (52.2)	112 (51.4)		
Asthma consultations	N (% non-missing)	347 (100.0)	218 (100.0)	0.2067	9.6
	0	0 (0.0)	1 (0.5)		
	1	347 (100.0)	218 (100.0)	0.2067	9.6
	2+	0 (0.0)	1 (0.5)		
Asthma related accident and emergency	N (% non-missing)	347 (100.0)	218 (100.0)	0.0739	13.6
	1	0 (0.0)	2 (0.9)		
	N (% non-missing)	347 (100.0)	218 (100.0)	0.0739	13.6

Asthma related unplanned inpatient admission	1	0 (0.0)	2 (0.9)		
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Table 108: Healthcare Resource Utilisation

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
LAMA prescriptions per patient	N (% non-missing)	347 (100.0)	218 (100.0)	0.5586	12.2
	Mean (SD)	0.1 (0.4)	0.2 (1.2)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
ICS/LABA prescriptions per patient	N (% non-missing)	347 (100.0)	218 (100.0)	0.1418	9.2
	Mean (SD)	4.1 (4.0)	4.4 (3.9)		
	Median (IQR)	3.0 (6.0)	4.0 (5.0)		
Mono ICS prescriptions per patient	N (% non-missing)	347 (100.0)	218 (100.0)	0.0380	25.8
	Mean (SD)	1.2 (2.4)	0.7 (1.6)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
LTRA prescriptions per patient	N (% non-missing)	347 (100.0)	218 (100.0)	0.5269	6.8
	Mean (SD)	0.7 (2.1)	0.8 (2.6)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
THEO prescriptions per patient	N (% non-missing)	347 (100.0)	218 (100.0)	1.0000	4.7
	Mean (SD)	0.1 (1.0)	0.2 (1.4)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
SAMA prescriptions per patient	N (% non-missing)	347 (100.0)	218 (100.0)	0.0896	23.8
	Mean (SD)	0.1 (0.5)	0.0 (0.4)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		

Table 109: Asthma prescriptions per patient

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
LABA prescription (yes/no)	N (% non-missing)	347 (100.0)	218 (100.0)	0.4364	6.9
	Yes	8 (2.3)	3 (1.4)		
LAMA prescription (yes/no)	N (% non-missing)	347 (100.0)	218 (100.0)	0.5706	4.8
	Yes	7 (2.0)	6 (2.8)		
SAMA prescription (yes/no)	N (% non-missing)	347 (100.0)	218 (100.0)	0.0879	15.9
	Yes	8 (2.3)	1 (0.5)		
LTRA prescription (yes/no)	N (% non-missing)	347 (100.0)	218 (100.0)	0.5306	5.4
	Yes	43 (12.4)	31 (14.2)		
Theophylline prescription (yes/no)	N (% non-missing)	347 (100.0)	218 (100.0)	0.9927	0.1
	Yes	8 (2.3)	5 (2.3)		

Table 110: Asthma prescriptions yes/no

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
SABA prescriptions	N (% non-missing)	347 (100.0)	218 (100.0)	0.6349	7.4
	Mean (SD)	3.1 (3.4)	3.3 (3.9)		
	Median (IQR)	2.0 (4.0)	2.0 (4.0)		
SABA inhalers	N (% non-missing)	347 (100.0)	218 (100.0)	0.8738	2.5
	Mean (SD)	3.7 (4.4)	3.8 (4.7)		
	Median (IQR)	2.0 (4.0)	2.0 (4.0)		
Daily SABA dosage	N (% non-missing)	347 (100.0)	218 (100.0)	0.8346	2.4
	Mean (SD)	201.3 (243.9)	207.3 (256.1)		
	Median (IQR)	109.6 (219.2)	109.6 (219.2)		

Table 111: SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
Number of SABA prescriptions	N (% non-missing)	347 (100.0)	218 (100.0)	0.8259	8.2
	0	79 (22.8)	46 (21.1)		
	1-3	159 (45.8)	101 (46.3)		
	4-6	62 (17.9)	36 (16.5)		
	>=7	47 (13.5)	35 (16.1)		
Number of SABA inhalers	N (% non-missing)	347 (100.0)	218 (100.0)	0.9729	4.1
	0	79 (22.8)	46 (21.1)		
	1-3	140 (40.3)	90 (41.3)		
	4-6	65 (18.7)	41 (18.8)		
	>=7	63 (18.2)	41 (18.8)		
Mean daily SABA dosage (mcg)	N (% non-missing)	347 (100.0)	218 (100.0)	0.9832	3.5
	<100	128 (36.9)	81 (37.2)		
	100-200	93 (26.8)	56 (25.7)		
	201-400	77 (22.2)	51 (23.4)		
	>400	49 (14.1)	30 (13.8)		

Table 112: Categorized SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
ICS daily dose	N (% non-missing)	347 (100.0)	218 (100.0)	0.9325	0.0
	Mean (SD)	587.2 (498.6)	587.3 (489.8)		
	Median (IQR)	416.4 (602.7)	479.4 (569.9)		
ICS/LABA or mono ICS inhalers	N (% non-missing)	347 (100.0)	218 (100.0)	0.8590	4.8
	Mean (SD)	6.9 (5.1)	6.6 (4.7)		
	Median (IQR)	6.0 (7.0)	6.0 (7.0)		

ICS/LABA or mono ICS prescriptions	N (% non-missing)	347 (100.0)	218 (100.0)	0.6941	4.8
	Mean (SD)	5.4 (3.7)	5.2 (3.6)		
	Median (IQR)	5.0 (6.0)	4.0 (5.0)		
ICS adherence	N (% non-missing)	347 (100.0)	218 (100.0)	0.4749	9.3
	Mean (SD)	69.9 (66.0)	64.4 (51.4)		
	Median (IQR)	57.5 (71.2)	54.8 (60.3)		

Table 113: ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
Number of ICS/LABA or mono ICS prescriptions	N (% non-missing)	347 (100.0)	218 (100.0)	0.7951	5.9
	1-3	138 (39.8)	90 (41.3)		
	4-6	101 (29.1)	66 (30.3)		
	>=7	108 (31.1)	62 (28.4)		
Number of ICS/LABA or mono ICS inhalers	N (% non-missing)	347 (100.0)	218 (100.0)	0.9700	2.1
	1-3, n (%)	107 (30.8)	68 (31.2)		
	4-6, n (%)	94 (27.1)	57 (26.1)		
	>=7, n (%)	146 (42.1)	93 (42.7)		
Mean daily ICS dosage (mcg)	N (% non-missing)	347 (100.0)	218 (100.0)	0.5720	9.1
	<250	103 (29.7)	60 (27.5)		
	250-<500	91 (26.2)	66 (30.3)		
	>=500	153 (44.1)	92 (42.2)		
ICS adherence(%)	N (% non-missing)	346 (99.7)	218 (100.0)	0.7370	9.8
	<40, n (%)	111 (32.1)	73 (33.5)		
	40-79, n (%)	109 (31.5)	74 (33.9)		
	80-120, n (%)	87 (25.1)	52 (23.9)		
	>120, n (%)	39 (11.3)	19 (8.7)		

Table 114: Categorised ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High eosinophil (n=218)	P value*	SDD
Asthma ATS exacerbations	N (% non-missing)	347 (100.0)	218 (100.0)	0.1916	20.7
	0, n (%)	254 (73.2)	154 (70.6)		
	1, n (%)	65 (18.7)	34 (15.6)		
	2, n (%)	24 (6.9)	23 (10.6)		
	3, n (%)	3 (0.9)	6 (2.8)		
	4, n (%)	1 (0.3)	1 (0.5)		
Asthma ATS exacerbations	Mean (SD)	0.4 (0.7)	0.5 (0.8)	0.3114	20.7
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
Acute respiratory event	N (% non-missing)	347 (100.0)	218 (100.0)	0.3339	18.0
	0, n (%)	233 (67.1)	137 (62.8)		
	1, n (%)	74 (21.3)	43 (19.7)		
	2, n (%)	32 (9.2)	28 (12.8)		
	3, n (%)	7 (2.0)	8 (3.7)		
	4+, n (%)	1 (0.3)	2 (0.9)		
Acute respiratory event	N (% non-missing)	347 (100.0)	218 (100.0)	0.1619	18.9
	Mean (SD)	0.5 (0.8)	0.6 (0.9)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		

Table 115: Exacerbations

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n = 347)	High eosinophil (n=218)	P value*	SDD
Medication cost without ICS	N (% non-missing)	340 (98.0)	215 (98.6)	0.6466	4.4
	Mean (SD)	34.6 (70.3)	38.1 (91.0)		

	Median (IQR)	9.5 (23.0)	11.0 (20.0)		
Medication cost	N (% non-missing)	340 (98.0)	215 (98.6)	0.7669	3.1
	Mean (SD)	268.5 (228.1)	275.7 (235.9)		
	Median (IQR)	198.5 (287.0)	211.0 (285.0)		
Healthcare resource cost	N (% non-missing)	347 (100.0)	218 (100.0)	0.4589	2.4
	Mean (SD)	91.7 (86.4)	94.2 (117.9)		
	Median (IQR)	84.0 (84.0)	84.0 (84.0)		
Total cost without ICS	N (% non-missing)	340 (98.0)	215 (98.6)	0.7642	4.5
	Mean (SD)	126.2 (120.9)	132.3 (148.1)		
	Median (IQR)	89.0 (103.0)	88.0 (122.0)		
Total cost	N (% non-missing)	340 (98.0)	215 (98.6)	0.7827	3.8
	Mean (SD)	360.1 (253.7)	369.9 (263.5)		
	Median (IQR)	296.0 (288.5)	297.0 (321.0)		

Table 116: Healthcare costs.

*P-value computed from Mann Whitney test. Where data is missing, percentages are given as a percentage of the non-missing variables

15.6.1 Statistically significant difference between unmatched patient groups – high BEC vs low BEC and low FeNO (categorisation 2)

		Low BEC, low FeNO	High BEC	P
Gender	N (% non-missing)	347 (100.0)	218 (100.0)	0.0015
	Male	113 (32.6)	100 (45.9)	
Eczema diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.0237
	Yes	93 (26.8)	78 (35.8)	
Rhinitis diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.0369
	Yes	130 (37.5)	101 (46.3)	
Hypertension diagnosis	N (% non-missing)	347 (100.0)	218 (100.0)	0.0487
	Yes	92 (26.5)	42 (19.3)	
Current peak flow	N (% non-missing)	195 (56.2)	120 (55.0)	0.0213
	Mean (SD)	403.7 (106.1)	436.7 (127.9)	
	Median (IQR)	400.0 (120.0)	430.0 (170.0)	
Predicted peak flow	N (% non-missing)	193 (55.6)	120 (55.0)	0.0015
	Mean (SD)	498.0 (73.8)	526.3 (76.0)	
	Median (IQR)	473.8 (123.4)	504.2 (133.6)	
Standalone ICS prescriptions	N (% non-missing)	347 (100.0)	218 (100.0)	0.0380

	Mean (SD)	1.2 (2.4)	0.7 (1.6)
	Median (IQR)	0.0 (1.0)	0.0 (1.0)

Table 117: High BEC vs reference – significant differences of covariates between groups Unmatched characterisation of high FeNO vs low BEC and low FeNO

15.7 Unmatched characterisation of high BEC vs low BEC and low FeNO patients (categorisation 2)

		Low eosinophil, low FeNO (n = 347)	High eosinophil (n=103)	P value*	SDD
Gender	N (% non-missing)	347 (100.0)	103 (100.0)	0.0378	23.1
	Male	113 (32.6)	45 (43.7)		
Age	N (% non-missing)	347 (100.0)	103 (100.0)	0.0236	31.8
	Mean (SD)	52.7 (13.0)	48.0 (16.2)		
	Median (IQR)	55.0 (17.0)	53.0 (30.0)		
Age group	N (% non-missing)	347 (100.0)	103 (100.0)	0.0001	46.6
	Under 35	36 (10.4)	27 (26.2)		
	35-65	264 (76.1)	58 (56.3)		
	66-80	47 (13.5)	18 (17.5)		
Smoking status	N (% non-missing)	347 (100.0)	103 (100.0)	0.1042	28.0
	Non-smoker	138 (39.8)	55 (53.4)		
	Ex-smoker	40 (11.5)	10 (9.7)		
	Current smoker	111 (32.0)	24 (23.3)		
Height	N (% non-missing)	336 (96.8)	98 (95.1)	0.0022	9.4
	Mean (SD)	165.9 (9.4)	167.3 (19.2)		
	Median (IQR)	165.0 (13.0)	168.0 (12.0)		
Weight	N (% non-missing)	333 (96.0)	97 (94.2)	0.0222	19.5
	Mean (SD)	82.4 (18.6)	78.5 (21.6)		
	Median (IQR)	80.0 (25.5)	75.0 (23.0)		

Table 118: Demographic summary

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
BMI	N (% non-missing)	341 (98.3)	98 (95.1)	<0.0001	50.7
	Mean (SD)	29.8 (6.2)	26.8 (5.7)		
	Median (IQR)	29.1 (8.4)	25.7 (7.7)		
BMI	N (% non-missing)	347 (100.0)	103 (100.0)	0.0008	47.1
	Underweight	1 (0.3)	2 (1.9)		
	Normal	82 (23.6)	40 (38.8)		
	Overweight	106 (30.5)	28 (27.2)		
	Obese	152 (43.8)	28 (27.2)		
FENO	N (% non-missing)	347 (100.0)	103 (100.0)	<0.0001	192.4
	Mean (SD)	16.3 (7.6)	59.9 (31.1)		
	Median (IQR)	15.0 (11.0)	51.0 (24.0)		
eosinophil count	N (% non-missing)	347 (100.0)	102 (99.0)	<0.0001	106.1
	Mean (SD)	0.2 (0.1)	0.4 (0.3)		
	Median (IQR)	0.2 (0.1)	0.3 (0.3)		
COPD diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.1200	15.2
	Yes	5 (1.4)	4 (3.9)		

Table 119: Clinical measurements

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
Acute oral corticosteroid prescriptions	N (% non-missing)	347 (100.0)	103 (100.0)	0.6093	18.0
	0	254 (73.2)	67 (65.0)		
	1	58 (16.7)	22 (21.4)		
	2	27 (7.8)	11 (10.7)		
	3	6 (1.7)	2 (1.9)		
	4	2 (0.6)	1 (1.0)		
	N (% non-missing)	347 (100.0)	103 (100.0)	0.5437	19.9

Acute oral corticosteroid prescriptions >14 days apart	0	254 (73.2)	67 (65.0)		
	1	65 (18.7)	25 (24.3)		
	2	24 (6.9)	10 (9.7)		
	3	3 (0.9)	1 (1.0)		
	4	1 (0.3)	0 (0.0)		
Acute oral corticosteroid use (yes/no)	N (% non-missing)	347 (100.0)	103 (100.0)	0.1082	17.7
	Yes	93 (26.8)	36 (35.0)		
Antibiotics	N (% non-missing)	347 (100.0)	103 (100.0)	0.3508	18.7
	Mean (SD)	0.2 (0.5)	0.3 (0.6)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
Antibiotic courses	N (% non-missing)	347 (100.0)	103 (100.0)	0.4240	18.7
	0	283 (81.6)	80 (77.7)		
	1	52 (15.0)	17 (16.5)		
	2	10 (2.9)	6 (5.8)		
	3	2 (0.6)	0 (0.0)		

Table 120: Acute asthma treatment

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
Active eczema diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.7232	3.9
	Yes	11 (3.2)	4 (3.9)		
Active rhinitis diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.7580	3.4
	Yes	99 (28.5)	31 (30.1)		
Eczema diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.2985	11.5
	Yes	93 (26.8)	33 (32.0)		
Rhinitis diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.8010	2.8
	Yes	130 (37.5)	40 (38.8)		
Cardiovascular diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.0480	24.1
	Yes	49 (14.1)	7 (6.8)		

IHD diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.3903	10.3
	Yes	17 (4.9)	3 (2.9)		
Heart failure diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.5855	7.6
	Yes	1 (0.3)	0 (0.0)		
Hypertension diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.1436	16.9
	Yes	92 (26.5)	20 (19.4)		

Table 121: Comorbidities 1

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
Diabetes diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.2071	15.2
	Yes	30 (8.6)	5 (4.9)		
Osteoporosis diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.8259	2.5
	Yes	8 (2.3)	2 (1.9)		
GERD diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.0256	27.1
	Yes	62 (17.9)	9 (8.7)		
GERD active diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.0507	23.7
	Yes	53 (15.3)	8 (7.8)		
Anxiety or depression	N (% non-missing)	347 (100.0)	103 (100.0)	0.2661	12.6
	Yes	139 (40.1)	35 (34.0)		
Chronic Kidney Disease	N (% non-missing)	347 (100.0)	103 (100.0)	0.4078	9.5
	Yes	70 (20.2)	17 (16.5)		
Cerebrovascular disease	N (% non-missing)	347 (100.0)	103 (100.0)	0.1542	18.4
	Yes	13 (3.7)	1 (1.0)		
Myocardial infarct	N (% non-missing)	347 (100.0)	103 (100.0)	0.8771	1.8
	Yes	4 (1.2)	1 (1.0)		

Table 122: Comorbidities 2

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
Current peak flow	N (% non-missing)	195 (56.2)	74 (71.8)	0.5225	10.7
	Mean (SD)	403.7 (106.1)	415.8 (119.4)		
	Median (IQR)	400.0 (120.0)	400.0 (120.0)		
Predicted peak flow	N (% non-missing)	193 (55.6)	74 (71.8)	0.0327	25.6
	Mean (SD)	498.0 (73.8)	516.1 (68.1)		
	Median (IQR)	473.8 (123.4)	494.0 (123.7)		
Percentage predicted peak flow	N (% non-missing)	193 (55.6)	74 (71.8)	0.4625	6.5
	Mean (SD)	81.1 (16.1)	80.0 (17.9)		
	Median (IQR)	82.6 (22.7)	78.9 (21.5)		
% predicted PF groups	N (% non-missing)	193 (55.6)	74 (71.8)	0.4245	17.9
	33-50	7 (3.6)	3 (4.1)		
	>=50	75 (38.9)	35 (47.3)		
	>=80%	111 (57.5)	36 (48.6)		

Table 123: Peak flow

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
FeV ₁	N (% non-missing)	53 (15.3)	19 (18.4)	0.1776	42.9
	Mean (SD)	2.3 (1.0)	2.7 (1.0)		
	Median (IQR)	2.3 (0.9)	2.8 (1.6)		
FVC	N (% non-missing)	95 (27.4)	24 (23.3)	0.0424	43.6
	Mean (SD)	3.3 (0.9)	3.8 (1.0)		
	Median (IQR)	3.2 (1.2)	3.8 (1.3)		
FEV ₁ /FVC_ratio	N (% non-missing)	45 (13.0)	18 (17.5)	0.1826	26.9
	Mean (SD)	0.8 (0.1)	0.7 (0.1)		

	Median (IQR)	0.8 (0.1)	0.7 (0.1)		
FEV ₁ Percent Predicted	N (% non-missing)	50 (14.4)	12 (11.7)	0.1415	44.0
	Mean (SD)	88.0 (22.8)	79.2 (17.1)		
	Median (IQR)	88.0 (31.0)	80.5 (26.0)		
FEV1 % predicted groups	N (% non-missing)	50 (14.4)	12 (11.7)	0.3160	71.8
	50% or less	2 (4.0)	0 (0.0)		
	>50% to <80%	14 (28.0)	5 (41.7)		
	80% to <100%	18 (36.0)	6 (50.0)		
	100%+	16 (32.0)	1 (8.3)		

Table 124: Lung function

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
Asthma consultations	N (% non-missing)	347 (100.0)	103 (100.0)	0.0924	27.2
	Mean (SD)	1.9 (1.6)	2.4 (2.2)		
	Median (IQR)	2.0 (1.0)	2.0 (2.0)		
Asthma consultations	N (% non-missing)	347 (100.0)	103 (100.0)	0.8070	7.4
	0	40 (11.5)	10 (9.7)		
	1	126 (36.3)	36 (35.0)		
	2+	181 (52.2)	57 (55.3)		
Asthma related accident and emergency	N (% non-missing)	347 (100.0)	103 (100.0)	0.0661	14.0
	1	0 (0.0)	1 (1.0)		
Asthma related unplanned inpatient admission	N (% non-missing)	347 (100.0)	103 (100.0)	0.0093	19.9
	1	0 (0.0)	2 (1.9)		

Table 125: Healthcare Resource Utilisation

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
LAMA prescriptions per patient	N (% non-missing)	347 (100.0)	103 (100.0)	0.9690	7.7
	Mean (SD)	0.1 (0.4)	0.1 (0.7)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
ICS/LABA prescriptions per patient	N (% non-missing)	347 (100.0)	103 (100.0)	0.0797	21.5
	Mean (SD)	4.1 (4.0)	3.3 (3.6)		
	Median (IQR)	3.0 (6.0)	2.0 (5.0)		
Mono ICS prescriptions per patient	N (% non-missing)	347 (100.0)	103 (100.0)	0.5174	13.8
	Mean (SD)	1.2 (2.4)	0.9 (1.9)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
LTRA prescriptions per patient	N (% non-missing)	347 (100.0)	103 (100.0)	0.9869	2.6
	Mean (SD)	0.7 (2.1)	0.6 (2.1)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
THEO prescriptions per patient	N (% non-missing)	347 (100.0)	103 (100.0)	0.1204	17.1
	Mean (SD)	0.1 (1.0)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
SAMA prescriptions per patient	N (% non-missing)	347 (100.0)	103 (100.0)	0.1204	.
	Mean (SD)	0.1 (0.5)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		

Table 126: Asthma prescriptions per patient

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
LABA prescription (yes/no)	N (% non-missing)	347 (100.0)	103 (100.0)	0.3956	10.5
	Yes	8 (2.3)	1 (1.0)		
LAMA prescription (yes/no)	N (% non-missing)	347 (100.0)	103 (100.0)	0.9616	0.5
	Yes	7 (2.0)	2 (1.9)		
	N (% non-missing)	347 (100.0)	103 (100.0)	0.1200	21.7

SAMA prescription (yes/no)	Yes	8 (2.3)	0 (0.0)		
LTRA prescription (yes/no)	N (% non-missing)	347 (100.0)	103 (100.0)	0.9506	0.7
	Yes	43 (12.4)	13 (12.6)		
Theophylline prescription (yes/no)	N (% non-missing)	347 (100.0)	103 (100.0)	0.1200	21.7
	Yes	8 (2.3)	0 (0.0)		

Table 127: Asthma prescriptions yes/no

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
SABA prescriptions	N (% non-missing)	347 (100.0)	103 (100.0)	0.9041	5.7
	Mean (SD)	3.1 (3.4)	3.3 (3.9)		
	Median (IQR)	2.0 (4.0)	2.0 (4.0)		
SABA inhalers	N (% non-missing)	347 (100.0)	103 (100.0)	0.9223	8.9
	Mean (SD)	3.7 (4.4)	4.1 (5.4)		
	Median (IQR)	2.0 (4.0)	2.0 (4.0)		
Daily SABA dosage	N (% non-missing)	347 (100.0)	103 (100.0)	0.9756	8.3
	Mean (SD)	201.3 (243.9)	223.8 (297.5)		
	Median (IQR)	109.6 (219.2)	109.6 (219.2)		

Table 128: SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
Number of SABA prescriptions	N (% non-missing)	347 (100.0)	103 (100.0)	0.9249	7.8
	0	79 (22.8)	21 (20.4)		
	1-3	159 (45.8)	50 (48.5)		

	4-6	62 (17.9)	17 (16.5)		
	>=7	47 (13.5)	15 (14.6)		
Number of SABA inhalers	N (% non-missing)	347 (100.0)	103 (100.0)	0.9500	6.7
	0	79 (22.8)	21 (20.4)		
	1-3	140 (40.3)	44 (42.7)		
	4-6	65 (18.7)	20 (19.4)		
	>=7	63 (18.2)	18 (17.5)		
Mean daily SABA dosage (mcg)	N (% non-missing)	347 (100.0)	103 (100.0)	0.8932	8.9
	<100	128 (36.9)	41 (39.8)		
	100-200	93 (26.8)	24 (23.3)		
	201-400	77 (22.2)	24 (23.3)		
	>400	49 (14.1)	14 (13.6)		

Table 129: Categorized SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
ICS daily dose	N (% non-missing)	347 (100.0)	103 (100.0)	0.0226	22.5
	Mean (SD)	587.2 (498.6)	480.4 (449.2)		
	Median (IQR)	416.4 (602.7)	328.8 (427.4)		
ICS/LABA or mono ICS inhalers	N (% non-missing)	347 (100.0)	103 (100.0)	0.0159	24.0
	Mean (SD)	6.9 (5.1)	5.7 (4.8)		
	Median (IQR)	6.0 (7.0)	4.0 (6.0)		
ICS/LABA or mono ICS prescriptions	N (% non-missing)	347 (100.0)	103 (100.0)	0.0065	27.9
	Mean (SD)	5.4 (3.7)	4.4 (3.5)		
	Median (IQR)	5.0 (6.0)	3.0 (4.0)		
ICS adherence	N (% non-missing)	347 (100.0)	103 (100.0)	0.1364	8.6
	Mean (SD)	69.9 (66.0)	64.2 (66.6)		
	Median (IQR)	57.5 (71.2)	49.3 (54.8)		

Table 130: ICS usage

* P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
Number of ICS/LABA or mono ICS prescriptions	N (% non-missing)	347 (100.0)	103 (100.0)	0.0139	33.9
	1-3	138 (39.8)	56 (54.4)		
	4-6	101 (29.1)	28 (27.2)		
	>=7	108 (31.1)	19 (18.4)		
Number of ICS/LABA or mono ICS inhalers	N (% non-missing)	347 (100.0)	103 (100.0)	0.0337	29.6
	1-3, n (%)	107 (30.8)	44 (42.7)		
	4-6, n (%)	94 (27.1)	29 (28.2)		
	>=7, n (%)	146 (42.1)	30 (29.1)		
Mean daily ICS dosage (mcg)	N (% non-missing)	347 (100.0)	103 (100.0)	0.0242	31.6
	<250	103 (29.7)	40 (38.8)		
	250-<500	91 (26.2)	33 (32.0)		
	>=500	153 (44.1)	30 (29.1)		
ICS adherence(%)	N (% non-missing)	346 (99.7)	103 (100.0)	0.2920	22.3
	<40, n (%)	111 (32.1)	38 (36.9)		
	40-79, n (%)	109 (31.5)	38 (36.9)		
	80-120, n (%)	87 (25.1)	18 (17.5)		
	>120, n (%)	39 (11.3)	9 (8.7)		

Table 131: Categorized ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
Asthma ATS exacerbations	N (% non-missing)	347 (100.0)	103 (100.0)	0.4743	20.8
	0, n (%)	254 (73.2)	67 (65.0)		
	1, n (%)	65 (18.7)	24 (23.3)		

	2, n (%)	24 (6.9)	10 (9.7)		
	3, n (%)	3 (0.9)	2 (1.9)		
	4, n (%)	1 (0.3)	0 (0.0)		
Asthma ATS exacerbations	Mean (SD)	0.4 (0.7)	0.5 (0.8)	0.0996	20.8
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
Acute respiratory event	N (% non-missing)	347 (100.0)	103 (100.0)	0.2906	24.9
	0, n (%)	233 (67.1)	58 (56.3)		
	1, n (%)	74 (21.3)	29 (28.2)		
	2, n (%)	32 (9.2)	12 (11.7)		
	3, n (%)	7 (2.0)	4 (3.9)		
	4+, n (%)	1 (0.3)	0 (0.0)		
Acute respiratory event	N (% non-missing)	347 (100.0)	103 (100.0)	0.0455	.
	Mean (SD)	0.5 (0.8)	0.6 (0.8)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		

Table 132: Exacerbations

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=347)	High FeNO (n=103)	P value*	SDD
Medication cost without ICS	N (% non-missing)	340 (98.0)	101 (98.1)	0.5101	3.2
	Mean (SD)	34.6 (70.3)	37.0 (83.8)		
	Median (IQR)	9.5 (23.0)	11.0 (19.0)		
Medication cost	N (% non-missing)	340 (98.0)	101 (98.1)	0.0093	20.5
	Mean (SD)	268.5 (228.1)	221.8 (228.0)		
	Median (IQR)	198.5 (287.0)	144.0 (228.0)		
Healthcare resource cost	N (% non-missing)	347 (100.0)	103 (100.0)	0.1138	29.4
	Mean (SD)	91.7 (86.4)	131.6 (171.8)		
	Median (IQR)	84.0 (84.0)	84.0 (126.0)		
Total cost without ICS	N (% non-missing)	340 (98.0)	101 (98.1)	0.2388	26.0
	Mean (SD)	126.2 (120.9)	168.4 (194.6)		

	Median (IQR)	89.0 (103.0)	95.0 (151.0)		
Total cost	N (% non-missing)	340 (98.0)	101 (98.1)	0.1111	2.5
	Mean (SD)	360.1 (253.7)	353.1 (307.9)		
	Median (IQR)	296.0 (288.5)	233.0 (253.0)		

Table 133: Healthcare costs.

*P-value computed from Mann Whitney test. Where data is missing, percentages are given as a percentage of the non-missing variables

15.7.1 Statistically significant difference between unmatched patient groups – high FeNO vs low BEC and low FeNO (categorisation 2)

		Low BEC and low FeNO	High FeNO	P-value
Gender	N (% non-missing)	347 (100.0)	103 (100.0)	0.0378
	Male	113 (32.6)	45 (43.7)	
Age	N (% non-missing)	347 (100.0)	103 (100.0)	0.0236
	Mean (SD)	52.7 (13.0)	48.0 (16.2)	
	Median (IQR)	55.0 (17.0)	53.0 (30.0)	
Age categorised	N (% non-missing)	347 (100.0)	103 (100.0)	0.0001
	Under 35	36 (10.4)	27 (26.2)	
	35-65	264 (76.1)	58 (56.3)	
	44-80	47 (13.5)	18 (17.5)	
BMI	N (% non-missing)	341 (98.3)	98 (95.1)	<0.0001
	Mean (SD)	29.8 (6.2)	26.8 (5.7)	
	Median (IQR)	29.1 (8.4)	25.7 (7.7)	
BMI	N (% non-missing)	347 (100.0)	103 (100.0)	0.0008
	Underweight	1 (0.3)	2 (1.9)	
	Normal	82 (23.6)	40 (38.8)	
	Overweight	106 (30.5)	28 (27.2)	
	Obese	152 (43.8)	28 (27.2)	
	missing	6 (1.7)	5 (4.9)	
Cardiovascular diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.0480
	Yes	49 (14.1)	7 (6.8)	
GERD diagnosis	N (% non-missing)	347 (100.0)	103 (100.0)	0.0256
	Yes	62 (17.9)	9 (8.7)	
Predicted peak flow	N (% non-missing)	193 (55.6)	74 (71.8)	0.0327
	Mean (SD)	498.0 (73.8)	516.1 (68.1)	
	Median (IQR)	473.8 (123.4)	494.0 (123.7)	

FVC	N (% non-missing)	95 (27.4)	24 (23.3)	0.0424
	Mean (SD)	3.3 (0.9)	3.8 (1.0)	
	Median (IQR)	3.2 (1.2)	3.8 (1.3)	
Asthma related unplanned inpatient admission	N (% non-missing)	347 (100.0)	103 (100.0)	0.0093
	Yes	0 (0.0)	2 (1.9)	
ICS daily dose	N (% non-missing)	347 (100.0)	103 (100.0)	0.0226
	Mean (SD)	587.2 (498.6)	480.4 (449.2)	
	Median (IQR)	416.4 (602.7)	328.8 (427.4)	
ICS inhalers	N (% non-missing)	347 (100.0)	103 (100.0)	0.0159
	Mean (SD)	6.9 (5.1)	5.7 (4.8)	
	Median (IQR)	6.0 (7.0)	4.0 (6.0)	
ICS prescriptions	N (% non-missing)	347 (100.0)	103 (100.0)	0.0065
	Mean (SD)	5.4 (3.7)	4.4 (3.5)	
	Median (IQR)	5.0 (6.0)	3.0 (4.0)	
ICS prescriptions	N (% non-missing)	347 (100.0)	103 (100.0)	0.0139
	1-3	138 (39.8)	56 (54.4)	
	4-6	101 (29.1)	28 (27.2)	
	>=7	108 (31.1)	19 (18.4)	
ICS inhalers	N (% non-missing)	347 (100.0)	103 (100.0)	0.0337
	2	107 (30.8)	44 (42.7)	
	3	94 (27.1)	29 (28.2)	
	4	146 (42.1)	30 (29.1)	
Mean daily ICS dosage (mcg)	N (% non-missing)	347 (100.0)	103 (100.0)	0.0242
	<250	103 (29.7)	40 (38.8)	
	250-<500	91 (26.2)	33 (32.0)	
	>=500	153 (44.1)	30 (29.1)	
Asthma respiratory event	N (% non-missing)	347 (100.0)	103 (100.0)	0.0455
	Mean (SD)	0.5 (0.8)	0.6 (0.8)	
	Median (IQR)	0.0 (1.0)	0.0 (1.0)	
Medication costs inc ICS	N (% non-missing)	340 (98.0)	101 (98.1)	0.0093
	Mean (SD)	268.5 (228.1)	221.8 (228.0)	
	Median (IQR)	198.5 (287.0)	144.0 (228.0)	

Table 134: High FeNO vs unmatched reference statistically significant differences between patient groups

15.8 Matched comparison of high BEC and high FeNO vs low BEC and low FeNO (categorisation 1)

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
Gender	N (% non-missing)	27 (100.0)	27 (100.0)	1.0000	0.0
	Male	10 (37.0)	10 (37.0)		
Age	N (% non-missing)	27 (100.0)	27 (100.0)	0.9379	0.8
	Mean (SD)	43.5 (18.8)	43.3 (19.0)		
	Median (IQR)	41.0 (37.0)	41.0 (37.0)		
Age group	N (% non-missing)	27 (100.0)	27 (100.0)	1.0000	0.0
	Under 35	12 (44.4)	12 (44.4)		
	35-65	9 (33.3)	9 (33.3)		
	66-80	6 (22.2)	6 (22.2)		
Smoking status	N (% non-missing)	27 (100.0)	27 (100.0)	0.7645	11.3
	Non-smoker	13 (48.1)	14 (51.9)		
	Ex-smoker	1 (3.7)	2 (7.4)		
	Current smoker	13 (48.1)	11 (40.7)		
Height	N (% non-missing)	23 (85.2)	27 (100.0)	0.4649	12.9
	Mean (SD)	1.66 (0.10)	1.67 (0.09)		
	Median (IQR)	1.64 (0.16)	1.67 (0.13)		
Weight	N (% non-missing)	24 (88.9)	26 (96.3)	0.6480	6.7
	Mean (SD)	77.0 (16.6)	75.8 (20.8)		
	Median (IQR)	76.0 (18.9)	71.8 (23.2)		

Table 135: Demographic summary

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
BMI	N (% non-missing)	23 (85.2)	26 (96.3)	0.4346	12.0
	Mean (SD)	27.7 (7.2)	26.9 (6.4)		

	Median (IQR)	26.8 (5.5)	25.5 (8.4)		
BMI	N (% non-missing)	27 (100.0)	27 (100.0)	0.2927	30.0
	Underweight	0 (0.0)	1 (3.7)		
	Normal	7 (25.9)	10 (37.0)		
	Overweight	12 (44.4)	8 (29.6)		
	Obese	4 (14.8)	7 (25.9)		
COPD diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)	0.1495	39.3
	Yes	0 (0.0)	2 (7.4)		

Table 136: Clinical measurements

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
Acute oral corticosteroid prescriptions	N (% non-missing)	27 (100.0)	27 (100.0)	0.0427	79.6
	0	21 (77.8)	13 (48.1)		
	1	6 (22.2)	8 (29.6)		
	2	0 (0.0)	5 (18.5)		
	3+	0 (0.0)	1 (3.7)		
Acute oral corticosteroid prescriptions >14 days apart	N (% non-missing)	27 (100.0)	27 (100.0)	0.0427	77.1
	0	21 (77.8)	13 (48.1)		
	1	6 (22.2)	8 (29.6)		
	2	0 (0.0)	5 (18.5)		
	3+	0 (0.0)	1 (3.7)		
Acute oral corticosteroid use (yes/no)	N (% non-missing)	27 (100.0)	27 (100.0)	0.0242	63.3
	Yes	6 (22.2)	14 (51.9)		
Antibiotics	N (% non-missing)	27 (100.0)	27 (100.0)	0.7016	2.3
	Mean (SD)	0.9 (1.8)	1.0 (1.4)		
	Median (IQR)	0.0 (1.0)	0.0 (2.0)		
Antibiotic courses	N (% non-missing)	27 (100.0)	27 (100.0)	0.2922	12.8
	0	15 (55.6)	15 (55.6)		

	1	8 (29.6)	4 (14.8)		
	2	2 (7.4)	5 (18.5)		
	3	0 (0.0)	2 (7.4)		
	4	2 (7.4)	1 (3.7)		

Table 137: Acute asthma treatment

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
Active eczema diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)	0.6387	12.6
	Yes	3 (11.1)	2 (7.4)		
Active rhinitis diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)	0.2482	31.2
	Yes	7 (25.9)	11 (40.7)		
Eczema diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)	0.7801	7.5
	Yes	10 (37.0)	11 (40.7)		
Rhinitis diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)	0.1628	38.0
	Yes	8 (29.6)	13 (48.1)		
Cardiovascular diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)	0.2987	28.0
	Yes	3 (11.1)	1 (3.7)		
IHD diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)	0.5525	15.9
	Yes	2 (7.4)	1 (3.7)		
Heart failure diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)		0.0
	Yes	0 (0.0)	0 (0.0)		
Hypertension diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)	0.4436	20.6
	Yes	5 (18.5)	3 (11.1)		

Table 138: Comorbidities 1

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
Diabetes diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)		0.0
	Yes	0 (0.0)	0 (0.0)		
Osteoporosis diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)	0.1495	39.3
	Yes	0 (0.0)	2 (7.4)		
GERD diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)	0.2987	28.0
	Yes	3 (11.1)	1 (3.7)		
GERD active diagnosis	N (% non-missing)	27 (100.0)	27 (100.0)	0.3128	27.2
	Yes	1 (3.7)	0 (0.0)		
Anxiety or depression	N (% non-missing)	27 (100.0)	27 (100.0)	0.7613	8.1
	Yes	8 (29.6)	7 (25.9)		
Chronic Kidney Disease	N (% non-missing)	27 (100.0)	27 (100.0)	1.0000	0.0
	Yes	5 (18.5)	5 (18.5)		
Cerebrovascular disease	N (% non-missing)	27 (100.0)	27 (100.0)	0.3128	27.2
	Yes	1 (3.7)	0 (0.0)		
Myocardial infarct	N (% non-missing)	27 (100.0)	27 (100.0)		0.0
	Yes	0 (0.0)	0 (0.0)		

Table 139: Comorbidities 2

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
Current peak flow	N (% non-missing)	14 (51.9)	20 (74.1)	0.4819	16.6
	Mean (SD)	386.9 (80.0)	406.0 (142.4)		
	Median (IQR)	390.0 (80.0)	400.0 (92.5)		
Predicted peak flow	N (% non-missing)	14 (51.9)	20 (74.1)	0.9721	26.1
	Mean (SD)	488.9 (53.4)	505.8 (74.9)		
	Median (IQR)	482.7 (47.2)	478.3 (127.7)		
Percentage predicted peak flow	N (% non-missing)	14 (51.9)	20 (74.1)	0.9164	1.0
	Mean (SD)	79.7 (16.1)	79.5 (22.4)		
	Median (IQR)	79.8 (10.8)	82.3 (25.5)		

% predicted PF groups	N (% non-missing)	14 (51.9)	20 (74.1)	0.7725	9.9
	33-50	1 (7.10)	2 (10.0)		
	>=50	13 (92.9)	18 (90.0)		.

Table 140: Peak flow

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
FeV ₁	N (% non-missing)	5 (18.5)	4 (14.8)	0.6242	20.9
	Mean (SD)	2.6 (0.9)	2.4 (1.1)		
	Median (IQR)	2.2 (0.1)	2.0 (1.5)		
FVC	N (% non-missing)	9 (33.3)	4 (14.8)	0.7576	21.7
	Mean (SD)	3.5 (1.2)	3.2 (1.3)		
	Median (IQR)	3.2 (1.4)	3.3 (1.7)		
FEV ₁ /FVC_ratio	N (% non-missing)	5 (18.5)	4 (14.8)	0.6213	44.4
	Mean (SD)	0.7 (0.1)	0.8 (0.1)		
	Median (IQR)	0.7 (0.1)	0.8 (0.2)		
FEV ₁ Percent Predicted	N (% non-missing)	5 (18.5)	5 (18.5)	0.2506	93.3
	Mean (SD)	97.4 (26.6)	66.4 (38.7)		
	Median (IQR)	92.0 (40.0)	81.0 (25.0)		
FEV1 % predicted groups	N (% non-missing)	5 (18.5)	5 (18.5)	0.2276	63.2
	50% or less	0 (0.0)	1 (20.0)		
	>50% to <80%	2 (40.0)	1 (20.0)		
	80% to <100%	1 (20.0)	3 (60.0)		
	100%+	2 (40.0)	0 (0.0)		

Table 141: Lung function

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
Asthma consultations	N (% non-missing)	27 (100.0)	27 (100.0)	0.2110	10.6
	Mean (SD)	2.1 (2.0)	2.3 (1.4)		
	Median (IQR)	2.0 (1.0)	2.0 (2.0)		
Asthma consultations	N (% non-missing)	27 (100.0)	27 (100.0)	0.3600	30.9
	0	4 (14.8)	3 (11.1)		
	1	9 (33.3)	5 (18.5)		
	2+	14 (51.9)	19 (70.4)		
Asthma related accident and emergency	N (% non-missing)	27 (100.0)	27 (100.0)		0.0
	1	0 (0.0)	0 (0.0)		
Asthma related unplanned inpatient admission	N (% non-missing)	27 (100.0)	27 (100.0)	0.3128	27.2
	1	0 (0.0)	1 (3.7)		

Table 142: Healthcare Resource Utilisation

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
LAMA prescriptions per patient	N (% non-missing)	27 (100.0)	27 (100.0)	0.3173	27.2
	Mean (SD)	0.0 (0.0)	0.1 (0.8)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
ICS/LABA prescriptions per patient	N (% non-missing)	27 (100.0)	27 (100.0)	0.6546	10.5
	Mean (SD)	3.6 (4.3)	3.2 (2.5)		
	Median (IQR)	1.0 (7.0)	3.0 (5.0)		
Mono ICS prescriptions per patient	N (% non-missing)	27 (100.0)	27 (100.0)	0.4898	8.9
	Mean (SD)	1.2 (1.9)	1.0 (2.2)		
	Median (IQR)	0.0 (2.0)	0.0 (1.0)		

LTRA prescriptions per patient	N (% non-missing)	27 (100.0)	27 (100.0)	0.2243	30.7
	Mean (SD)	0.3 (1.2)	0.9 (2.4)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
THEO prescriptions per patient	N (% non-missing)	27 (100.0)	27 (100.0)		0.0
	Mean (SD)	0.0 (0.0)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
SAMA prescriptions per patient	N (% non-missing)	27 (100.0)	27 (100.0)	0.3173	27.2
	Mean (SD)	0.0 (0.2)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		

Table 143: Asthma prescriptions per patient

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
LABA prescription (yes/no)	N (% non-missing)	27 (100.0)	27 (100.0)		0.0
	Yes	0 (0.0)	0 (0.0)		
LAMA prescription (yes/no)	N (% non-missing)	27 (100.0)	27 (100.0)	0.3128	27.2
	Yes	0 (0.0)	1 (3.7)		
SAMA prescription (yes/no)	N (% non-missing)	27 (100.0)	27 (100.0)	0.3128	27.2
	Yes	1 (3.7)	0 (0.0)		
LTRA prescription (yes/no)	N (% non-missing)	27 (100.0)	27 (100.0)	0.2242	32.9
	Yes	2 (7.4)	5 (18.5)		
Theophylline prescription (yes/no)	N (% non-missing)	27 (100.0)	27 (100.0)		0.0
	Yes	0 (0.0)	0 (0.0)		

Table 144: Asthma prescriptions yes/no

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
SABA prescriptions	N (% non-missing)	27 (100.0)	27 (100.0)	0.2986	38.9

SABA inhalers	Mean (SD)	2.9 (2.6)	4.3 (4.4)		
	Median (IQR)	2.0 (4.0)	3.0 (4.0)		
	N (% non-missing)	27 (100.0)	27 (100.0)	0.3506	38.8
Daily SABA dosage	Mean (SD)	3.3 (3.0)	5.0 (5.6)		
	Median (IQR)	3.0 (4.0)	3.0 (3.0)		
	N (% non-missing)	27 (100.0)	27 (100.0)	0.2681	43.6
Daily SABA dosage	Mean (SD)	0.8 (0.8)	1.4 (1.5)		
	Median (IQR)	0.8 (0.9)	0.8 (0.8)		
	N (% non-missing)	27 (100.0)	27 (100.0)		

Table 145: SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
Number of SABA prescriptions	N (% non-missing)	27 (100.0)	27 (100.0)	0.4526	36.7
	0	6 (22.2)	2 (7.4)		
	1-3	13 (48.1)	14 (51.9)		
	4-6	5 (18.5)	6 (22.2)		
	>=7	3 (11.1)	5 (18.5)		
Number of SABA inhalers	N (% non-missing)	27 (100.0)	27 (100.0)	0.4229	35.6
	0	6 (22.2)	2 (7.4)		
	1-3	12 (44.4)	12 (44.4)		
	4-6	5 (18.5)	8 (29.6)		
	>=7	4 (14.8)	5 (18.5)		
Mean daily SABA dosage (mcg)	N (% non-missing)	27 (100.0)	27 (100.0)	0.5066	37.6
	<100	8 (29.6)	6 (22.2)		
	100-200	11 (40.7)	8 (29.6)		
	201-400	6 (22.2)	8 (29.6)		
	>400	2 (7.4)	5 (18.5)		

Table 146: Categorised SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
ICS daily dose	N (% non-missing)	27 (100.0)	27 (100.0)	0.6339	2.0
	Mean (SD)	436.5 (372.1)	443.6 (342.1)		
	Median (IQR)	328.8 (520.5)	350.7 (252.0)		
ICS/LABA or mono ICS inhalers	N (% non-missing)	27 (100.0)	27 (100.0)	0.8345	14.7
	Mean (SD)	5.7 (4.1)	5.1 (2.8)		
	Median (IQR)	4.0 (7.0)	5.0 (3.0)		
ICS/LABA or mono ICS prescriptions	N (% non-missing)	23 (100.0)	23 (100.0)	0.6024	9.5
	Mean (SD)	5.0 (3.8)	4.7 (2.4)		
	Median (IQR)	4.0 (4.0)	5.0 (4.0)		
ICS adherence	N (% non-missing)	27 (100.0)	27 (100.0)	0.7158	13.4
	Mean (SD)	57.1 (39.3)	52.3 (32.9)		
	Median (IQR)	54.8 (54.8)	49.3 (35.7)		

Table 147: ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
Number of ICS/LABA or mono ICS prescriptions	N (% non-missing)	27 (100.0)	27 (100.0)	0.0259	26.7
	1-3	12 (44.4)	11 (40.7)		
	4-6	4 (14.8)	12 (44.4)		
	>=7	11 (40.7)	4 (14.8)		
Number of ICS/LABA or mono ICS inhalers	N (% non-missing)	27 (100.0)	27 (100.0)	0.0147	8.9
	1-3, n (%)	11 (40.7)	7 (25.9)		
	4-6, n (%)	4 (14.8)	14 (51.9)		
	>=7, n (%)	12 (44.4)	6 (22.2)		

Mean daily ICS dosage (mcg)	N (% non-missing)	27 (100.0)	27 (100.0)	0.1388	4.7
	<250	11 (40.7)	8 (29.6)		
	250-<500	7 (25.9)	14 (51.9)		
	>=500	9 (33.3)	5 (18.5)		
ICS adherence(%)	N (% non-missing)	27 (100.0)	27 (100.0)	0.5095	4.2
	<40, n (%)	12 (44.4)	10 (37.0)		
	40-79, n (%)	7 (25.9)	12 (44.4)		
	80-120, n (%)	7 (25.9)	4 (14.8)		
	>120, n (%)	1 (3.7)	1 (3.7)		

Table 148: Categorical ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=27)	High eosinophil/high FeNO (n=27)	P value*	SDD
Asthma ATS exacerbations	N (% non-missing)	27 (100.0)	27 (100.0)	0.0427	79.7
	0, n (%)	21 (77.8)	13 (48.1)		
	1, n (%)	6 (22.2)	8 (29.6)		
	2, n (%)	0 (0.0)	4 (14.8)		
	3, n (%)	0 (0.0)	2 (7.4)		
Asthma ATS exacerbations	Mean (SD)	0.2 (0.4)	0.8 (1.0)	0.0109	79.7
	Median (IQR)	0.0 (0.0)	1.0 (1.0)		
Acute respiratory event	N (% non-missing)	27 (100.0)	27 (100.0)	0.0370	27.3
	0, n (%)	13 (48.1)	12 (44.4)		
	1, n (%)	10 (37.0)	3 (11.1)		
	2, n (%)	1 (3.7)	9 (33.3)		
	3, n (%)	1 (3.7)	1 (3.7)		
	4+, n (%)	2 (7.4)	2 (7.4)		
Acute respiratory event	N (% non-missing)	27 (100.0)	27 (100.0)	0.3106	14.4
	Mean (SD)	1.0 (1.7)	1.2 (1.4)		
	Median (IQR)	1.0 (1.0)	1.0 (2.0)		

Table 149: Exacerbations

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observation

15.9 Matched comparison of high BEC or high FeNO vs low BEC and low FeNO (categorisation 1)

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
Gender	N (% non-missing)	200 (100.0)	200 (100.0)	1.0000	0.0
	Male	84 (42.0)	84 (42.0)		
Age	N (% non-missing)	200 (100.0)	200 (100.0)	0.9223	1.1
	Mean (SD)	51.7 (13.1)	51.6 (13.2)		
	Median (IQR)	54.0 (18.5)	53.0 (19.5)		
Age group	N (% non-missing)	200 (100.0)	200 (100.0)	0.4289	7.6
	Under 35	24 (12.0)	25 (12.5)		
	35-65	150 (75.0)	140 (70.0)		
Smoking status	66-80	26 (13.0)	35 (17.5)		
	N (% non-missing)	200 (100.0)	200 (100.0)	1.0000	0.0
	Non-smoker	73 (36.5)	73 (36.5)		
Height	Ex-smoker	23 (11.5)	23 (11.5)		
	Current smoker	71 (35.5)	71 (35.5)		
	N (% non-missing)	192 (96.0)	193 (96.5)	0.5696	2.6
Weight	Mean (SD)	1.67 (0.10)	1.68 (0.09)		
	Median (IQR)	1.66 (0.14)	1.67 (0.11)		
	N (% non-missing)	191 (95.5)	192 (96.0)	0.1488	11.5
Weight	Mean (SD)	84.3 (19.1)	82.0 (20.9)		
	Median (IQR)	83.0 (26.5)	79.4 (25.0)		

Table 150: Demographic summary

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
BMI	N (% non-missing)	189 (94.5)	191 (95.5)	0.1025	13.4
	Mean (SD)	30.0 (6.9)	29.1 (7.0)		
	Median (IQR)	28.7 (8.1)	27.8 (7.9)		
BMI	N (% non-missing)	189 (94.5)	191 (95.5)	0.5752	16.1
	Underweight	1 (0.5)	2 (1.0)		
	Normal	44 (22.0)	57 (28.5)		
	Overweight	63 (31.5)	61 (30.5)		
	Obese	81 (40.5)	71 (35.5)		
COPD diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	1.0000	0.0
	Yes	5 (2.5)	5 (2.5)		

Table 151: Clinical measurements

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P-value*	SDD
Acute oral corticosteroid prescriptions	N (% non-missing)	200 (100.0)	200 (100.0)	0.1661	14.9
	0	143 (71.5)	137 (68.5)		
	1	39 (19.5)	36 (18.0)		
	2	18 (9.0)	21 (10.5)		
	3	0 (0.0)	5 (2.5)		
	4	0 (0.0)	1 (0.5)		
Acute oral corticosteroid prescriptions >14 days apart	N (% non-missing)	200 (100.0)	200 (100.0)	0.3964	12.3
	0	143 (71.5)	137 (68.5)		
	1	34 (17.0)	33 (16.5)		

	2	21 (10.5)	22 (11.0)		
	3	1 (0.5)	6 (3.0)		
	4	1 (0.5)	2 (1.0)		
Acute oral corticosteroid use (yes/no)	N (% non-missing)	200 (100.0)	200 (100.0)	0.5127	6.5
	Yes	57 (28.5)	63 (31.5)		
Antibiotics	N (% non-missing)	200 (100.0)	200 (100.0)	0.5578	6.2
	Mean (SD)	1.4 (1.8)	1.3 (1.8)		
	Median (IQR)	1.0 (2.0)	1.0 (2.0)		
Antibiotic courses	N (% non-missing)	200 (100.0)	200 (100.0)	0.8297	8.9
	0	88 (44.0)	90 (45.0)		
	1	44 (22.0)	49 (24.5)		
	2	28 (14.0)	29 (14.5)		
	3	15 (7.5)	14 (7.0)		
	4	25 (12.5)	18 (9.0)		

Table 152: Acute asthma treatment

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
Active eczema diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	0.3347	9.6
	Yes	7 (3.5)	11 (5.5)		
Active rhinitis diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	0.1056	16.2
	Yes	55 (27.5)	70 (35.0)		
Eczema diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	0.1284	15.2
	Yes	54 (27.0)	68 (34.0)		
Rhinitis diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	0.0858	17.2
	Yes	77 (38.5)	94 (47.0)		
Cardiovascular diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	0.0696	18.2
	Yes	31 (15.5)	19 (9.5)		
IHD diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	1.0000	0.0

	Yes	9 (4.5)	9 (4.5)		
Heart failure diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	0.3167	10.0
	Yes	0 (0.0)	1 (0.5)		
Hypertension diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	0.0592	18.9
	Yes	55 (27.5)	39 (19.5)		

Table 153: Comorbidities 1

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
Diabetes diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	0.8630	1.7
	Yes	19 (9.5)	18 (9.0)		
Osteoporosis diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	0.5218	6.4
	Yes	4 (2.0)	6 (3.0)		
GERD diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	0.1882	13.2
	Yes	40 (20.0)	30 (15.0)		
GERD active diagnosis	N (% non-missing)	200 (100.0)	200 (100.0)	0.0630	18.6
	Yes	35 (17.5)	22 (11.0)		
Anxiety or depression	N (% non-missing)	200 (100.0)	200 (100.0)	0.6795	4.1
	Yes	77 (38.5)	73 (36.5)		
Chronic Kidney Disease	N (% non-missing)	200 (100.0)	200 (100.0)	0.1614	14.0
	Yes	35 (17.5)	25 (12.5)		
Cerebrovascular disease	N (% non-missing)	200 (100.0)	200 (100.0)	0.2002	12.8
	Yes	7 (3.5)	3 (1.5)		
Myocardial infarct	N (% non-missing)	200 (100.0)	200 (100.0)	0.3149	10.0
	Yes	3 (1.5)	1 (0.5)		

Table 154: Comorbidities 2

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
Current peak flow	N (% non-missing)	95 (54.9)	100 (57.8)	0.6984	5.8
	Mean (SD)	428.2 (111.6)	435.4 (135.8)		
	Median (IQR)	400.0 (140.0)	430.0 (170.0)		
Predicted peak flow	N (% non-missing)	105 (52.5)	110 (55.0)	0.7422	4.5
	Mean (SD)	516.0 (73.2)	519.4 (75.8)		
	Median (IQR)	485.8 (134.7)	487.6 (137.8)		
Percentage predicted peak flow	N (% non-missing)	105 (52.5)	110 (55.0)	0.6294	4.7
	Mean (SD)	82.2 (16.1)	83.0 (19.5)		
	Median (IQR)	81.8 (23.1)	82.5 (23.5)		
% predicted PF groups	N (% non-missing)	105 (52.5)	110 (55.0)	0.3418	13.0
	33-50	3 (2.9)	6 (5.5)		
	>=50%	102 (97.1)	104 (94.5)		

Table 155: Peak flow

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
FeV ₁	N (% non-missing)	28 (16.2)	33 (19.1)	0.0799	45.5
	Mean (SD)	16.8 (31.0)	5.4 (17.0)		
	Median (IQR)	2.8 (1.9)	2.5 (1.2)		
FVC	N (% non-missing)	48 (27.7)	45 (26.0)	1.0000	1.1
	Mean (SD)	3.4 (0.9)	3.4 (1.0)		
	Median (IQR)	3.3 (1.2)	3.3 (1.2)		
	N (% non-missing)	24 (13.9)	24 (13.9)	0.0523	46.1

FEV ₁ /FVC_ratio	Mean (SD)	0.8 (0.1)	0.7 (0.1)		
	Median (IQR)	0.8 (0.1)	0.7 (0.1)		
FEV ₁ Percent Predicted	N (% non-missing)	31 (17.9)	34 (19.7)	0.2215	33.4
	Mean (SD)	70.8 (41.9)	56.0 (46.5)		
	Median (IQR)	84.4 (60.0)	73.5 (95.0)		
FEV1 % predicted groups	N (% non-missing)	37 (18.5)	43 (21.5)	0.3501	24.5
	50% or less	8 (21.6)	17 (39.5)		
	>50% to <80%	11 (29.7)	8 (18.6)		
	80% to <100%	9 (24.3)	9 (20.9)		
	100%+	9 (24.3)	9 (20.9)		

Table 156: Lung function

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
Asthma consultations	N (% non-missing)	200 (100.0)	200 (100.0)	0.7248	6.7
	Mean (SD)	1.8 (1.6)	2.0 (1.8)		
	Median (IQR)	1.5 (1.0)	2.0 (1.0)		
Asthma consultations	N (% non-missing)	200 (100.0)	200 (100.0)	0.7434	1.4
	0	22 (11.0)	26 (13.0)		
	1	78 (39.0)	72 (36.0)		
	2+	100 (50.0)	102 (51.0)		
Asthma related accident and emergency	N (% non-missing)	200 (100.0)	200 (100.0)	0.3167	10.0
	1	0 (0.0)	1 (0.5)		
Asthma related unplanned inpatient admission	N (% non-missing)	200 (100.0)	200 (100.0)	0.3167	10.0
	1	0 (0.0)	1 (0.5)		

Table 157: Healthcare Resource Utilisation

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
LAMA prescriptions per patient	N (% non-missing)	200 (100.0)	200 (100.0)	0.3469	16.6
	Mean (SD)	0.0 (0.4)	0.2 (1.3)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
ICS/LABA prescriptions per patient	N (% non-missing)	200 (100.0)	200 (100.0)	0.4736	2.1
	Mean (SD)	4.1 (4.0)	4.1 (3.7)		
	Median (IQR)	3.0 (5.0)	3.5 (5.0)		
Mono ICS prescriptions per patient	N (% non-missing)	200 (100.0)	200 (100.0)	0.0112	32.7
	Mean (SD)	1.4 (2.7)	0.6 (1.6)		
	Median (IQR)	0.0 (1.0)	0.0 (0.0)		
LTRA prescriptions per patient	N (% non-missing)	200 (100.0)	200 (100.0)	0.7507	4.8
	Mean (SD)	0.5 (1.9)	0.6 (2.3)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
THEO prescriptions per patient	N (% non-missing)	173 (100.0)	173 (100.0)	0.6473	9.0
	Mean (SD)	0.0 (0.5)	0.1 (1.2)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
SAMA prescriptions per patient	N (% non-missing)	200 (100.0)	200 (100.0)	0.0137	16.4
	Mean (SD)	0.1 (0.5)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		

Table 158: Asthma prescriptions per patient

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
LABA prescription (yes/no)	N (% non-missing)	200 (100.0)	200 (100.0)	0.5218	6.4
	Yes	6 (3.0)	4 (2.0)		

LAMA prescription (yes/no)	N (% non-missing)	173 (100.0)	173 (100.0)	0.1525	15.4
	Yes	2 (1.2)	6 (3.5)		
SAMA prescription (yes/no)	N (% non-missing)	200 (100.0)	200 (100.0)	0.0136	24.8
	Yes	6 (3.0)	0 (0.0)		
LTRA prescription (yes/no)	N (% non-missing)	200 (100.0)	200 (100.0)	0.7539	3.1
	Yes	22 (11.0)	24 (12.0)		
Theophylline prescription (yes/no)	N (% non-missing)	200 (100.0)	200 (100.0)	0.7360	3.4
	Yes	5 (2.5)	4 (2.0)		

Table 159: Asthma prescriptions yes/no

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
SABA prescriptions	N (% non-missing)	200 (100.0)	200 (100.0)	0.3017	2.4
	Mean (SD)	3.2 (3.2)	3.1 (3.7)		
	Median (IQR)	2.0 (4.0)	2.0 (3.0)		
SABA inhalers	N (% non-missing)	200 (100.0)	200 (100.0)	0.1804	5.6
	Mean (SD)	3.8 (4.3)	3.6 (4.7)		
	Median (IQR)	2.5 (4.0)	2.0 (4.0)		
Daily SABA dosage	N (% non-missing)	200 (100.0)	200 (100.0)	0.1912	6.4
	Mean (SD)	1.1 (1.2)	1.0 (1.3)		
	Median (IQR)	0.7 (1.1)	0.6 (1.1)		

Table 160: SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
Number of SABA prescriptions	N (% non-missing)	200 (100.0)	200 (100.0)	0.8218	4.8
	0	38 (19.0)	45 (22.5)		
	1-3	97 (48.5)	93 (46.5)		
	4-6	38 (19.0)	34 (17.0)		
	>=7	27 (13.5)	28 (14.0)		
Number of SABA inhalers	N (% non-missing)	200 (100.0)	200 (100.0)	0.8299	8.6
	1	38 (19.0)	45 (22.5)		
	2	85 (42.5)	84 (42.0)		
	3	41 (20.5)	39 (19.5)		
	4	36 (18.0)	32 (16.0)		
Mean daily SABA dosage (mcg)	N (% non-missing)	200 (100.0)	200 (100.0)	0.2808	13.2
	<100	67 (33.5)	83 (41.5)		
	100-200	58 (29.0)	47 (23.5)		
	201-400	45 (22.5)	47 (23.5)		
	>400	30 (15.0)	23 (11.5)		

Table 161: Categorized SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
ICS daily dose	N (% non-missing)	200 (100.0)	200 (100.0)	0.3202	12.4
	Mean (SD)	599.6 (509.8)	540.5 (441.6)		
	Median (IQR)	438.4 (602.7)	411.0 (550.7)		
ICS/LABA or mono ICS inhalers	N (% non-missing)	200 (100.0)	200 (100.0)	0.2432	13.1
	Mean (SD)	7.0 (5.2)	6.4 (4.8)		
	Median (IQR)	6.0 (7.0)	5.0 (6.0)		

ICS/LABA or mono ICS prescriptions	N (% non-missing)	200 (100.0)	200 (100.0)	0.0973	17.9
	Mean (SD)	5.6 (3.7)	4.9 (3.4)		
	Median (IQR)	5.0 (5.5)	4.0 (4.5)		
ICS adherence	N (% non-missing)	200 (100.0)	200 (100.0)	0.1931	13.9
	Mean (SD)	72.2 (72.7)	63.3 (53.3)		
	Median (IQR)	61.7 (64.4)	52.0 (61.7)		

Table 162: ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
Number of ICS/LABA or mono ICS prescriptions	N (% non-missing)	200 (100.0)	200 (100.0)	0.1410	16.3
	1-3	76 (38.0)	85 (42.5)		
	4-6	56 (28.0)	65 (32.5)		
	>=7	68 (34.0)	50 (25.0)		
Number of ICS/LABA or mono ICS inhalers	N (% non-missing)	200 (100.0)	200 (100.0)	0.4884	11.2
	1-3	57 (28.5)	68 (34.0)		
	4-6	55 (27.5)	52 (26.0)		
	>=7	88 (44.0)	80 (40.0)		
Mean daily ICS dosage (mcg)	N (% non-missing)	200 (100.0)	200 (100.0)	0.2118	11.3
	<250	58 (29.0)	61 (30.5)		
	250-<500	49 (24.5)	62 (31.0)		
	>=500	93 (46.5)	77 (38.5)		
ICS adherence (%)	N (% non-missing)	199 (99.5)	200 (100.0)	0.3289	16.0
	<40, n (%)	64 (32.2)	72 (36.0)		
	40-79, n (%)	58 (29.1)	68 (34.0)		
	80-120, n (%)	51 (25.6)	41 (20.5)		
	>120, n (%)	26 (13.1)	19 (9.5)		

Table 163: Categorised ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil, low FeNO (n=200)	High eosinophil or high FeNO (n=200)	P value*	SDD
Asthma ATS exacerbations	N (% non-missing)	173 (100.0)	173 (100.0)	0.0481	13.7
	0, n (%)	120 (69.4)	120 (69.4)		
	1, n (%)	41 (23.7)	28 (16.2)		
	2, n (%)	11 (6.4)	19 (11.0)		
	3, n (%)	0 (0.0)	5 (2.9)		
	4+, n (%)	1 (0.6)	1 (0.6)		
Asthma ATS exacerbations	Mean (SD)	0.4 (0.6)	0.5 (0.8)	0.3423	15.5
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
Acute respiratory event	N (% non-missing)	200 (100.0)	200 (100.0)	0.7267	1.5
	0, n (%)	80 (40.0)	78 (39.0)		
	1, n (%)	52 (26.0)	50 (25.0)		
	2, n (%)	29 (14.5)	39 (19.5)		
	3, n (%)	16 (8.0)	14 (7.0)		
	4+, n (%)	23 (11.5)	19 (9.5)		
Acute respiratory event	N (% non-missing)	200 (100.0)	200 (100.0)	0.9090	1.0
	Mean (SD)	1.3 (1.6)	1.3 (1.5)		
	Median (IQR)	1.0 (2.0)	1.0 (2.0)		

Table 164: Exacerbations

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. ‡Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

15.10 Matched comparison of high BEC and high FeNO vs low BEC and low FeNO (categorisation 2)

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
Gender	N (% non-missing)	53 (100.0)	53 (100.0)	0.9647	0.9
	Male	48.4 (16.7)	48.2 (16.9)		
Age	N (% non-missing)	53.0 (32.0)	53.0 (31.0)	0.8655	5.7
	Mean (SD)	53 (100.0)	53 (100.0)		
	Median (IQR)	14 (26.4)	14 (26.4)		
Age group	N (% non-missing)	31 (58.5)	29 (54.7)	1.0000	0.0
	Under 35	8 (15.1)	10 (18.9)		
	35-65	53 (100.0)	53 (100.0)		
	66-80	31 (58.5)	31 (58.5)		
Smoking status	N (% non-missing)	4 (7.5)	4 (7.5)		
	Non-smoker	11 (20.8)	11 (20.8)		
	Ex-smoker	4 (7.5)	4 (7.5)		
	Current smoker	11 (20.8)	11 (20.8)		
Height	N (% non-missing)	52 (98.1)	52 (98.1)	0.9017	15.7
	Mean (SD)	167.80 (9.83)	164.84 (24.85)		
	Median (IQR)	167.30 (16.50)	166.50 (14.00)		
Weight	N (% non-missing)	52 (98.1)	52 (98.1)	0.1462	28.4
	Mean (SD)	81.5 (17.2)	76.4 (18.9)		
	Median (IQR)	78.8 (27.3)	75.0 (21.8)		

Table 165: Demographic summary

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
BMI	N (% non-missing)	52 (98.1)	51 (96.2)	0.0386	38.1

	Mean (SD)	29.0 (5.9)	26.8 (5.6)		
	Median (IQR)	28.4 (8.3)	25.6 (7.1)		
BMI	N (% non-missing)	53 (100.0)	53 (100.0)	0.4334	25.1
	Underweight	1 (1.9)	1 (1.9)		
	Normal	14 (26.4)	19 (35.8)		
	Overweight	16 (30.2)	19 (35.8)		
	Obese	21 (39.6)	12 (22.6)		
COPD diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)	0.3150	19.4
	Yes	0 (0.0)	1 (1.9)		
FeNO reading	N (% non-missing)	53 (100.0)	53 (100.0)	<0.0001	201.8
	Mean (SD)	18.6 (7.7)	57.8 (26.4)		
	Median (IQR)	20.0 (10.0)	49.0 (28.0)		
Blood eosinophil reading	N (% non-missing)	53 (100.0)	52 (98.1)	<0.0001	189.2
	Mean (SD)	0.1 (0.1)	0.5 (0.3)		
	Median (IQR)	0.1 (0.1)	0.5 (0.2)		

Table 166: Clinical measurements

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
Acute oral corticosteroid prescriptions	N (% non-missing)	53 (100.0)	53 (100.0)	0.5843	24.9
	0	36 (67.9)	29 (54.7)		
	1	11 (20.8)	13 (24.5)		
	2	4 (7.5)	9 (17.0)		
	3	1 (1.9)	1 (1.9)		
	4+	1 (1.9)	1 (1.9)		
Acute oral corticosteroid prescriptions >14 days apart	N (% non-missing)	53 (100.0)	53 (100.0)	0.4269	30.6
	0	36 (67.9)	29 (54.7)		
	1	12 (22.6)	15 (28.3)		
	2	5 (9.4)	8 (15.1)		

	3	0 (0.0)	1 (1.9)		
	4+	0 (0.0)	0 (0.0)		
Acute oral corticosteroid use (yes/no)	N (% non-missing)	53 (100.0)	53 (100.0)	0.1627	27.1
	Yes	17 (32.1)	24 (45.3)		
Antibiotics	N (% non-missing)	53 (100.0)	53 (100.0)	0.9215	3.1
	Mean (SD)	0.3 (0.6)	0.3 (0.6)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
Antibiotic courses	N (% non-missing)	53 (100.0)	53 (100.0)	0.3944	3.1
	0	39 (73.6)	39 (73.6)		
	1	12 (22.6)	10 (18.9)		
	2	1 (1.9)	4 (7.5)		
	3	1 (1.9)	0 (0.0)		
	4+	0 (0)	0 (0)		

Table 167: Acute asthma treatment

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
Active eczema diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)	1.0000	0.0
	Yes	2 (3.8)	2 (3.8)		
Active rhinitis diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)	0.4052	16.1
	Yes	15 (28.3)	19 (35.8)		
Eczema diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)	0.5355	11.9
	Yes	16 (30.2)	19 (35.8)		
Rhinitis diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)	0.0451	39.3
	Yes	15 (28.3)	25 (47.2)		
Cardiovascular diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)	0.7275	6.7
	Yes	4 (7.5)	5 (9.4)		

IHD diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)	0.5581	11.3
	Yes	1 (1.9)	2 (3.8)		
Heart failure diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)		0.0
	Yes	0 (0.0)	0 (0.0)		
Hypertension diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)	0.0990	32.2
	Yes	15 (28.3)	8 (15.1)		

Table 168: Comorbidities 1

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
Diabetes diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)	1.0000	0.0
	Yes	3 (5.7)	3 (5.7)		
Osteoporosis diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)	1.0000	0.0
	Yes	2 (3.8)	2 (3.8)		
GERD diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)	0.7501	6.1
	Yes	6 (11.3)	5 (9.4)		
GERD active diagnosis	N (% non-missing)	53 (100.0)	53 (100.0)	0.5063	12.8
	Yes	6 (11.3)	4 (7.5)		
Anxiety or depression	N (% non-missing)	53 (100.0)	53 (100.0)	0.2943	20.3
	Yes	19 (35.8)	14 (26.4)		
Chronic Kidney Disease	N (% non-missing)	53 (100.0)	53 (100.0)	0.4925	13.2
	Yes	14 (26.4)	11 (20.8)		
Cerebrovascular disease	N (% non-missing)	53 (100.0)	53 (100.0)	0.3150	19.4
	Yes	1 (1.9)	0 (0.0)		

Myocardial infarct	N (% non-missing)	53 (100.0)	53 (100.0)		0.0
	Yes	0 (0.0)	0 (0.0)		

Table 169: Comorbidities 2

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
Current peak flow	N (% non-missing)	35 (66.0)	39 (73.6)	0.7162	14.4
	Mean (SD)	441.1 (98.2)	424.7 (128.8)		
	Median (IQR)	400.0 (170.0)	400.0 (120.0)		
	N (% non-missing)	35 (66.0)	39 (73.6)	0.8838	3.9
Predicted peak flow	Mean (SD)	513.0 (66.7)	510.3 (69.9)		
	Median (IQR)	487.5 (122.0)	481.2 (128.0)		
	N (% non-missing)	35 (66.0)	39 (73.6)	0.3326	20.8
Percentage predicted peak flow	Mean (SD)	85.8 (13.6)	82.4 (18.7)		
	Median (IQR)	86.8 (16.5)	81.5 (18.9)		
	N (% non-missing)	35 (66.0)	39 (73.6)	0.3377	14.8
% predicted PF groups	<=50%, n (%)	24 (68.6)	23 (59.0)		
	>50% to <80%, n (%)	0 (0.0)	2 (5.1)		
	>=80%, n (%)	11 (31.4)	14 (35.9)		

Table 170: Peak flow

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
	N (% non-missing)	5 (9.4)	10 (18.9)	0.9024	8.3

FeV ₁	Mean (SD)	3.0 (1.1)	3.1 (1.1)		
	Median (IQR)	2.3 (1.9)	3.4 (1.4)		
FVC	N (% non-missing)	9 (17.0)	11 (20.8)	0.7324	8.5
	Mean (SD)	4.0 (1.3)	3.9 (1.4)		
	Median (IQR)	3.5 (1.6)	4.1 (1.9)		
FEV ₁ /FVC_ratio	N (% non-missing)	5 (9.4)	9 (17.0)	0.5045	29.6
	Mean (SD)	0.8 (0.1)	0.8 (0.1)		
	Median (IQR)	0.7 (0.1)	0.8 (0.1)		
FEV ₁ Percent Predicted	N (% non-missing)	4 (7.5)	4 (7.5)	0.7728	14.9
	Mean (SD)	95.8 (21.1)	93.3 (10.7)		
	Median (IQR)	90.0 (26.5)	92.5 (14.5)		
FEV1 % predicted groups	N (% non-missing)	4 (7.5)	4 (7.5)	0.5488	36.9
	50% or less	0 (0.0)	0 (0.0)		
	>50% to <80%	1 (25.0)	0 (0.0)		
	80% to <100%	2 (50.0)	3 (75.0)		
	100%+	1 (25.0)	1 (25.0)		

Table 171: Lung function

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
Asthma consultations	N (% non-missing)	53 (100.0)	53 (100.0)	0.8964	12.8
	Mean (SD)	2.1 (1.6)	2.3 (2.2)		
	Median (IQR)	2.0 (1.0)	2.0 (2.0)		
Asthma consultations	N (% non-missing)	53 (100.0)	53 (100.0)	0.7293	13.8
	0	5 (9.4)	6 (11.3)		
	1	14 (26.4)	17 (32.1)		
	2+	34 (64.2)	30 (56.6)		
	N (% non-missing)	53 (100.0)	53 (100.0)	0.3150	19.4

Asthma related accident and emergency	1	0 (0.0)	1 (1.9)		
Asthma related unplanned inpatient admission	N (% non-missing)	53 (100.0)	53 (100.0)	0.1534	27.7
	1	0 (0.0)	2 (3.8)		

Table 172: Healthcare Resource Utilisation

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
LAMA prescriptions per patient	N (% non-missing)	53 (100.0)	53 (100.0)	0.3173	19.4
	Mean (SD)	0.0 (0.0)	0.1 (0.5)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
ICS/LABA prescriptions per patient	N (% non-missing)	53 (100.0)	53 (100.0)	0.2204	18.6
	Mean (SD)	3.3 (3.9)	4.0 (4.0)		
	Median (IQR)	2.0 (5.0)	3.0 (5.0)		
Mono ICS prescriptions per patient	N (% non-missing)	53 (100.0)	53 (100.0)	0.1944	23.3
	Mean (SD)	1.3 (2.3)	0.8 (1.7)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
LTRA prescriptions per patient	N (% non-missing)	53 (100.0)	53 (100.0)	0.7743	6.4
	Mean (SD)	0.5 (1.6)	0.6 (1.9)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
THEO prescriptions per patient	N (% non-missing)	53 (100.0)	53 (100.0)	0.3173	19.4
	Mean (SD)	0.0 (0.3)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
SAMA prescriptions per patient	N (% non-missing)	53 (100.0)	53 (100.0)	0.1553	22.9
	Mean (SD)	0.1 (0.7)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		

Table 173: Asthma prescriptions per patient

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
LABA prescription (yes/no)	N (% non-missing)	53 (100.0)	53 (100.0)	0.3150	19.4
	Yes	1 (1.9)	0 (0.0)		
LAMA prescription (yes/no)	N (% non-missing)	53 (100.0)	53 (100.0)	0.3150	19.4
	Yes	0 (0.0)	1 (1.9)		
SAMA prescription (yes/no)	N (% non-missing)	53 (100.0)	53 (100.0)	0.1534	27.7
	Yes	2 (3.8)	0 (0.0)		
LTRA prescription (yes/no)	N (% non-missing)	53 (100.0)	53 (100.0)	0.7805	5.4
	Yes	7 (13.2)	8 (15.1)		
Theophylline prescription (yes/no)	N (% non-missing)	53 (100.0)	53 (100.0)	0.3150	19.4
	Yes	1 (1.9)	0 (0.0)		

Table 174: Asthma prescriptions yes/no

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
SABA prescriptions	N (% non-missing)	53 (100.0)	53 (100.0)	0.8381	8.8
	Mean (SD)	3.5 (3.8)	3.8 (4.3)		
	Median (IQR)	2.0 (4.0)	2.0 (4.0)		
SABA inhalers	N (% non-missing)	53 (100.0)	53 (100.0)	0.8133	8.3
	Mean (SD)	4.4 (5.6)	4.9 (6.2)		
	Median (IQR)	2.0 (4.0)	2.0 (5.0)		
Daily SABA dosage	N (% non-missing)	53 (100.0)	53 (100.0)	0.8432	7.3
	Mean (SD)	239.0 (309.0)	262.8 (341.0)		
	Median (IQR)	109.6 (219.2)	109.6 (274.0)		

Table 175: SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
Number of SABA prescriptions	N (% non-missing)	53 (100.0)	53 (100.0)	0.9942	3.9
	0	10 (18.9)	10 (18.9)		
	1-3	25 (47.2)	24 (45.3)		
	4-6	10 (18.9)	10 (18.9)		
	>=7	8 (15.1)	9 (17.0)		
Number of SABA inhalers	N (% non-missing)	53 (100.0)	53 (100.0)	0.8877	5.5
	0	10 (18.9)	10 (18.9)		
	1-3	23 (43.4)	20 (37.7)		
	4-6	9 (17.0)	12 (22.6)		
	>=7	11 (20.8)	11 (20.8)		
Mean daily SABA dosage (mcg)	N (% non-missing)	53 (100.0)	53 (100.0)	0.6923	5.3
	<100	15 (28.3)	16 (30.2)		
	100-200	19 (35.8)	14 (26.4)		
	201-400	10 (18.9)	14 (26.4)		
	>400	9 (17.0)	9 (17.0)		

Table 176: Categorical SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
ICS daily dose	N (% non-missing)	53 (100.0)	53 (100.0)	0.6834	4.1
	Mean (SD)	542.3 (445.1)	561.4 (477.6)		
	Median (IQR)	339.7 (646.6)	394.5 (465.7)		
ICS/LABA or mono ICS inhalers	N (% non-missing)	53 (100.0)	53 (100.0)	0.6406	5.1
	Mean (SD)	6.3 (5.1)	6.5 (5.3)		

	Median (IQR)	5.0 (8.0)	6.0 (5.0)		
ICS/LABA or mono ICS prescriptions	N (% non-missing)	53 (100.0)	53 (100.0)	0.4653	8.7
	Mean (SD)	4.7 (3.7)	5.0 (3.7)		
	Median (IQR)	4.0 (4.0)	4.0 (4.0)		
ICS adherence	N (% non-missing)	53 (100.0)	53 (100.0)	0.8149	7.6
	Mean (SD)	64.1 (45.3)	68.6 (72.5)		
	Median (IQR)	54.8 (54.8)	49.3 (49.3)		

Table 177: ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
Number of ICS/LABA or mono ICS prescriptions	N (% non-missing)	53 (100.0)	53 (100.0)	1.0000	0.0
	1-3	24 (45.3)	24 (45.3)		
	4-6	18 (34.0)	18 (34.0)		
	>=7	11 (20.8)	11 (20.8)		
Number of ICS/LABA or mono ICS inhalers	N (% non-missing)	53 (100.0)	53 (100.0)	0.8095	2.2
	1-3, n (%)	19 (35.8)	18 (34.0)		
	4-6, n (%)	14 (26.4)	17 (32.1)		
	>=7, n (%)	20 (37.7)	18 (34.0)		
Mean daily ICS dosage (mcg)	N (% non-missing)	53 (100.0)	53 (100.0)	0.0396	0.0
	<250	20 (37.7)	14 (26.4)		
	250-<500	10 (18.9)	22 (41.5)		
	>=500	23 (43.4)	17 (32.1)		
ICS adherence(%)	N (% non-missing)	53 (100.0)	53 (100.0)	0.4989	1.9
	<40, n (%)	20 (37.7)	15 (28.3)		
	40-79, n (%)	15 (28.3)	22 (41.5)		
	80-120, n (%)	11 (20.8)	11 (20.8)		
	>120, n (%)	7 (13.2)	5 (9.4)		

Table 178: Categorised ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
Asthma ATS exacerbations	N (% non-missing)	53 (100.0)	53 (100.0)	0.3080	34.1
	0, n (%)	36 (67.9)	29 (54.7)		
	1, n (%)	12 (22.6)	14 (26.4)		
	2, n (%)	5 (9.4)	8 (15.1)		
	3, n (%)	0 (0.0)	2 (3.8)		
Asthma ATS exacerbations	N (% non-missing)	53 (100.0)	53 (100.0)	0.1166	34.1
	Mean (SD)	0.4 (0.7)	0.7 (0.9)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
Acute respiratory event	N (% non-missing)	53 (100.0)	53 (100.0)	0.5670	26.3
	0, n (%)	31 (58.5)	25 (47.2)		
	1, n (%)	14 (26.4)	16 (30.2)		
	2, n (%)	7 (13.2)	9 (17.0)		
	3, n (%)	1 (1.9)	3 (5.7)		
	4+, n (%)	0 (0.0)	0 (0.0)		
Acute respiratory event	N (% non-missing)	53 (100.0)	53 (100.0)	0.1985	26.3
	Mean (SD)	0.6 (0.8)	0.8 (0.9)		
	Median (IQR)	0.0 (1.0)	1.0 (1.0)		

Table 179: Exacerbations

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=53)	High eosinophil/high FeNO (n=53)	P value*	SDD
Medication costs not inc ICS	N (% non-missing)	52 (98.1)	53 (100.0)	0.8573	9.2
	Mean (SD)	32.3 (55.8)	38.6 (77.8)		
	Median (IQR)	12.0 (27.0)	13.0 (34.0)		

Medication costs inc ICS	N (% non-missing)	52 (98.1)	53 (100.0)	0.7317	6.7
	Mean (SD)	240.8 (209.9)	255.7 (234.7)		
	Median (IQR)	174.0 (293.0)	176.0 (258.0)		
Physician costs	N (% non-missing)	53 (100.0)	53 (100.0)	0.8819	17.5
	Mean (SD)	110.6 (97.8)	137.7 (196.0)		
	Median (IQR)	84.0 (84.0)	84.0 (126.0)		
Total costs not inc ICS	N (% non-missing)	52 (98.1)	53 (100.0)	0.8500	19.3
	Mean (SD)	142.6 (122.6)	176.3 (213.3)		
	Median (IQR)	95.0 (124.0)	97.0 (145.0)		
Total costs inc ICS	N (% non-missing)	52 (98.1)	53 (100.0)	0.7006	14.4
	Mean (SD)	351.1 (256.9)	393.4 (325.4)		
	Median (IQR)	307.5 (289.0)	262.0 (256.0)		

Table 180: Healthcare costs.

*P-value computed from Mann Whitney test. Where data is missing, percentages are given as a percentage of the non-missing variables

15.11 Matched comparison of high BEC vs low BEC and low FeNO (categorisation 2)

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
Gender	N (% non-missing)	186 (100.0)	186 (100.0)	1.0000	0.0
	Male	77 (41.4)	77 (41.4)		
Age	N (% non-missing)	186 (100.0)	186 (100.0)	0.9834	0.7
	Mean (SD)	51.9 (13.1)	51.8 (13.7)		
	Median (IQR)	55.0 (20.0)	53.5 (20.0)		
Age group	N (% non-missing)	186 (100.0)	186 (100.0)	0.1919	10.2
	Under 35	22 (11.8)	24 (12.9)		
	35-65	141 (75.8)	127 (68.3)		
	44-80	23 (12.4)	35 (18.8)		

Smoking status	N (% non-missing)	186 (100.0)	186 (100.0)	1.0000	0.0
	Non-smoker	67 (36.0)	67 (36.0)		
	Ex-smoker	22 (11.8)	22 (11.8)		
	Current smoker	67 (36.0)	67 (36.0)		
Height	N (% non-missing)	178 (95.7)	181 (97.3)	0.2969	0.7
	Mean (SD)	166.58 (9.63)	166.50 (15.09)		
	Median (IQR)	165.00 (14.00)	167.00 (12.00)		
Weight	N (% non-missing)	176 (94.6)	181 (97.3)	0.5636	3.7
	Mean (SD)	82.9 (18.9)	82.2 (21.4)		
	Median (IQR)	80.0 (25.8)	79.4 (27.8)		

Table 181: Demographic summary

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
BMI	N (% non-missing)	184 (98.4)	184 (98.4)	0.0492	17.1
	Mean (SD)	30.1 (6.3)	29.0 (6.7)		
	Median (IQR)	29.5 (9.0)	27.8 (7.8)		
BMI	N (% non-missing)	184 (98.4)	184 (98.4)	0.4626	16.5
	Underweight	1 (0.5)	3 (1.6)		
	Normal	41 (22.0)	51 (27.4)		
	Overweight	60 (32.3)	61 (32.8)		
	Obese	82 (44.1)	68 (36.6)		
COPD diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.4104	8.5
	Yes	2 (1.1)	4 (2.2)		
FeNO reading	N (% non-missing)	186 (100.0)	186 (100.0)	<0.0001	70.2
	Mean (SD)	16.5 (7.8)	28.9 (23.8)		
	Median (IQR)	16.0 (12.0)	23.0 (22.0)		

Blood reading	eosinophil	N (% non-missing)	186 (100.0)	184 (98.9)	<0.0001	212.9
		Mean (SD)	0.2 (0.1)	0.4 (0.2)		
		Median (IQR)	0.2 (0.1)	0.4 (0.2)		

Table 182: Clinical measurements

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD	
Acute corticosteroid prescriptions	oral	N (% non-missing)	186 (100.0)	186 (100.0)	0.6395	12.9
		0	134 (72.0)	128 (68.8)		
		1	33 (17.7)	29 (15.6)		
		2	14 (7.5)	21 (11.3)		
		3	4 (2.2)	6 (3.2)		
		4+	1 (0.5)	2 (1.1)		
Acute corticosteroid prescriptions days apart	oral >14	N (% non-missing)	186 (100.0)	186 (100.0)	0.3135	15.8
		0	134 (72.0)	128 (68.8)		
		1	36 (19.4)	32 (17.2)		
		2	15 (8.1)	20 (10.8)		
		3	1 (0.5)	5 (2.7)		
		4+	0 (0.0)	1 (0.5)		
Acute corticosteroid (yes/no)	oral use	N (% non-missing)	186 (100.0)	186 (100.0)	0.4954	7.1
		Yes	52 (28.0)	58 (31.2)		
Antibiotics		N (% non-missing)	186 (100.0)	186 (100.0)	0.5985	10.1
		Mean (SD)	0.2 (0.5)	0.3 (0.6)		
		Median (IQR)	0.0 (0.0)	0.0 (0.0)		
Antibiotic courses		N (% non-missing)	186 (100.0)	186 (100.0)	0.5320	10.1
		0	151 (81.2)	148 (79.6)		
		1	28 (15.1)	25 (13.4)		
		2	6 (3.2)	10 (5.4)		
		3	1 (0.5)	3 (1.6)		

	4+	0 (0)	0 (0)		
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Table 183: Acute asthma treatment

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
Active eczema diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.1876	13.7
	Yes	5 (2.7)	10 (5.4)		
Active rhinitis diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.0720	18.7
	Yes	49 (26.3)	65 (34.9)		
Eczema diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.2273	12.5
	Yes	57 (30.6)	68 (36.6)		
Rhinitis diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.0272	23.0
	Yes	67 (36.0)	88 (47.3)		
Cardiovascular diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.2563	11.8
	Yes	25 (13.4)	18 (9.7)		
IHD diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.4564	7.7
	Yes	7 (3.8)	10 (5.4)		
Heart failure diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.3167	10.4
	Yes	0 (0.0)	1 (0.5)		
Hypertension diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.3212	10.3
	Yes	46 (24.7)	38 (20.4)		

Table 184: Comorbidities 1

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
Diabetes diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.5736	5.8
	Yes	14 (7.5)	17 (9.1)		
Osteoporosis diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.3114	10.5
	Yes	3 (1.6)	6 (3.2)		
GERD diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	1.0000	0.0
	Yes	29 (15.6)	29 (15.6)		
GERD active diagnosis	N (% non-missing)	186 (100.0)	186 (100.0)	0.4352	8.1
	Yes	26 (14.0)	21 (11.3)		
Anxiety or depression	N (% non-missing)	186 (100.0)	186 (100.0)	0.5170	6.7
	Yes	70 (37.6)	64 (34.4)		
Chronic Kidney Disease	N (% non-missing)	186 (100.0)	186 (100.0)	0.1471	15.0
	Yes	33 (17.7)	23 (12.4)		
Cerebrovascular disease	N (% non-missing)	186 (100.0)	186 (100.0)	0.1259	15.9
	Yes	8 (4.3)	3 (1.6)		
Myocardial infarct	N (% non-missing)	186 (100.0)	186 (100.0)	0.3147	10.4
	Yes	3 (1.6)	1 (0.5)		

Table 185: Comorbidities 2

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
Current peak flow	N (% non-missing)	100 (53.8)	101 (54.3)	0.7875	5.4
	Mean (SD)	426.1 (111.6)	432.7 (129.4)		
	Median (IQR)	405.0 (150.0)	430.0 (160.0)		
Predicted Peak Flow	N (% non-missing)	98 (52.7)	101 (54.3)	0.8525	7.1

	Mean (SD)	515.7 (75.3)	517.3 (76.2)		
	Median (IQR)	485.0 (141.8)	485.6 (137.3)		
Percentage predicted peak flow	N (% non-missing)	98 (52.7)	101 (54.3)	0.8826	0.0
	Mean (SD)	83.0 (16.8)	83.0 (19.3)		
	Median (IQR)	84.8 (21.1)	82.3 (21.2)		
% predicted peak flow groups	N (% non-missing)	98 (52.7)	101 (54.3)	0.9058	6.2
	<=50%, n (%)	4 (4.1)	5 (5.0)		
	>50% to <80%, n (%)	35 (35.7)	38 (37.6)		
	>=80%, n (%)	59 (60.2)	58 (57.4)		

Table 186: Peak flow

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
FEV ₁	N (% non-missing)	30 (16.1)	36 (19.4)	0.8368	7.4
	Mean (SD)	2.5 (0.9)	2.5 (1.0)		
	Median (IQR)	2.4 (0.9)	2.5 (1.3)		
FVC	N (% non-missing)	56 (30.1)	52 (28.0)	0.9955	1.0
	Mean (SD)	3.4 (1.0)	3.4 (1.1)		
	Median (IQR)	3.3 (1.3)	3.3 (1.3)		
FEV ₁ /FVC_ratio	N (% non-missing)	27 (14.5)	27 (14.5)	0.1504	37.8
	Mean (SD)	0.8 (0.1)	0.7 (0.1)		
	Median (IQR)	0.8 (0.1)	0.7 (0.2)		
FEV ₁ Percent Predicted	N (% non-missing)	30 (16.1)	24 (12.9)	0.7146	11.3
	Mean (SD)	89.1 (22.5)	91.4 (17.4)		
	Median (IQR)	88.5 (27.0)	94.0 (26.0)		
FEV1 % predicted groups	N (% non-missing)	30 (16.1)	24 (12.9)	0.8163	9.8
	50% or less	1 (3.3)	0 (0.0)		
	>50% to <80%	8 (26.7)	7 (29.2)		
	80% to <100%	11 (36.7)	8 (33.3)		

	100%+	10 (33.3)	9 (37.5)		
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Table 187: Lung function

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
Asthma consultations	N (% non-missing)	186 (100.0)	186 (100.0)	0.9655	5.6
	Mean (SD)	1.8 (1.4)	1.9 (1.6)		
	Median (IQR)	2.0 (1.0)	2.0 (1.0)		
Asthma consultations	N (% non-missing)	186 (100.0)	186 (100.0)	0.7419	2.2
	0, n (%)	27 (14.5)	25 (13.4)		
	1, n (%)	59 (31.7)	66 (35.5)		
	2+, n (%)	100 (53.8)	95 (51.1)		
Asthma related accident and emergency	N (% non-missing)	186 (100.0)	186 (100.0)	0.3167	10.4
	1	0 (0.0)	1 (0.5)		
Asthma related unplanned inpatient admission	N (% non-missing)	186 (100.0)	186 (100.0)	0.1562	14.7
	1	0 (0.0)	2 (1.1)		

Table 188: Healthcare Resource Utilisation

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
LAMA prescriptions per patient	N (% non-missing)	186 (100.0)	186 (100.0)	0.1528	15.2
	Mean (SD)	0.0 (0.4)	0.2 (1.3)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		

ICS/LABA prescriptions per patient	N (% non-missing)	186 (100.0)	186 (100.0)	0.0404	16.7
	Mean (SD)	3.8 (3.9)	4.4 (3.8)		
	Median (IQR)	3.0 (6.0)	4.0 (5.0)		
Mono prescriptions per patient	N (% non-missing)	186 (100.0)	186 (100.0)	0.0362	34.4
	Mean (SD)	1.3 (2.5)	0.7 (1.6)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
LTRA prescriptions per patient	N (% non-missing)	186 (100.0)	186 (100.0)	0.9754	0.9
	Mean (SD)	0.7 (2.1)	0.7 (2.4)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
THEO prescriptions per patient	N (% non-missing)	186 (100.0)	186 (100.0)	0.7431	5.8
	Mean (SD)	0.1 (0.8)	0.1 (1.1)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
SAMA prescriptions per patient	N (% non-missing)	186 (100.0)	186 (100.0)	0.0076	20.0
	Mean (SD)	0.1 (0.6)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		

Table 189: Asthma prescriptions per patient

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
LABA prescription (yes/no)	N (% non-missing)	186 (100.0)	186 (100.0)	0.6525	4.7
	Yes	2 (1.1)	3 (1.6)		
LAMA prescription (yes/no)	N (% non-missing)	186 (100.0)	186 (100.0)	0.1528	14.8
	Yes	2 (1.1)	6 (3.2)		
SAMA prescription (yes/no)	N (% non-missing)	186 (100.0)	186 (100.0)	0.0076	27.9
	Yes	7 (3.8)	0 (0.0)		
LTRA prescription (yes/no)	N (% non-missing)	186 (100.0)	186 (100.0)	1.0000	0.0
	Yes	26 (14.0)	26 (14.0)		
Theophylline prescription (yes/no)	N (% non-missing)	186 (100.0)	186 (100.0)	0.7358	3.5
	Yes	5 (2.7)	4 (2.2)		

Table 190: Asthma prescriptions yes/no

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
SABA prescriptions	N (% non-missing)	186 (100.0)	186 (100.0)	0.3947	2.5
	Mean (SD)	3.3 (3.5)	3.2 (3.9)		
	Median (IQR)	2.0 (4.0)	2.0 (3.0)		
SABA inhalers	N (% non-missing)	186 (100.0)	186 (100.0)	0.3701	4.6
	Mean (SD)	3.9 (4.5)	3.7 (4.7)		
	Median (IQR)	2.0 (4.0)	2.0 (4.0)		
Daily SABA dosage	N (% non-missing)	186 (100.0)	186 (100.0)	0.3971	4.1
	Mean (SD)	209.3 (243.4)	199.1 (254.9)		
	Median (IQR)	109.6 (219.2)	109.6 (219.2)		

Table 191: SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
Number of SABA prescriptions	N (% non-missing)	186 (100.0)	186 (100.0)	0.6334	5.7
	0	34 (18.3)	43 (23.1)		
	1-3	92 (49.5)	86 (46.2)		
	4-6	35 (18.8)	30 (16.1)		
	>=7	25 (13.4)	27 (14.5)		
Number of SABA inhalers	N (% non-missing)	186 (100.0)	186 (100.0)	0.6492	7.0
	0	34 (18.3)	43 (23.1)		
	1-3	84 (45.2)	76 (40.9)		
	4-6	33 (17.7)	35 (18.8)		

	>=7	35 (18.8)	32 (17.2)		
Mean daily SABA dosage (mcg)	N (% non-missing)	186 (100.0)	186 (100.0)	0.2585	8.1
	<100	63 (33.9)	71 (38.2)		
	100-200	57 (30.6)	48 (25.8)		
	201-400	35 (18.8)	45 (24.2)		
	>400	31 (16.7)	22 (11.8)		

Table 192: Categorized SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
ICS daily dose	N (% non-missing)	186 (100.0)	186 (100.0)	0.8042	6.3
	Mean (SD)	603.9 (491.1)	574.1 (456.2)		
	Median (IQR)	421.9 (684.9)	463.0 (558.9)		
ICS/LABA or mono ICS inhalers	N (% non-missing)	186 (100.0)	186 (100.0)	0.6632	0.6
	Mean (SD)	6.7 (5.0)	6.7 (4.7)		
	Median (IQR)	5.0 (7.0)	6.0 (7.0)		
ICS/LABA or mono ICS prescriptions	N (% non-missing)	186 (100.0)	186 (100.0)	0.7889	0.6
	Mean (SD)	5.2 (3.6)	5.2 (3.4)		
	Median (IQR)	4.0 (5.0)	4.0 (5.0)		
ICS adherence	N (% non-missing)	186 (100.0)	186 (100.0)	0.8806	5.6
	Mean (SD)	69.2 (55.2)	66.2 (53.3)		
	Median (IQR)	54.8 (71.2)	56.1 (57.5)		

Table 193: ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
Number of ICS/LABA or mono ICS prescriptions	N (% non-missing)	186 (100.0)	186 (100.0)	1.0000	0.0
	1-3	72 (38.7)	72 (38.7)		
	4-6	64 (34.4)	64 (34.4)		
	>=7	50 (26.9)	50 (26.9)		
Number of ICS/LABA or mono ICS inhalers	N (% non-missing)	186 (100.0)	186 (100.0)	0.7473	7.7
	1-3, n (%)	58 (31.2)	53 (28.5)		
	4-6, n (%)	55 (29.6)	53 (28.5)		
	>=7, n (%)	73 (39.2)	80 (43.0)		
Mean daily ICS dosage (mcg)	N (% non-missing)	186 (100.0)	186 (100.0)	0.5008	1.3
	<250	56 (30.1)	50 (26.9)		
	250-<500	48 (25.8)	58 (31.2)		
	>=500	82 (44.1)	78 (41.9)		
ICS adherence(%)	N (% non-missing)	186 (100.0)	186 (100.0)	0.4072	8.6
	<40, n (%)	59 (31.7)	58 (31.2)		
	40-79, n (%)	58 (31.2)	66 (35.5)		
	80-120, n (%)	42 (22.6)	45 (24.2)		
	>120, n (%)	27 (14.5)	17 (9.1)		

Table 194: Categorized ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
Asthma exacerbations	N (% non-missing)	186 (100.0)	186 (100.0)	0.2149	17.0
	0, n (%)	134 (72.0)	128 (68.8)		
	1, n (%)	36 (19.4)	31 (16.7)		
	2, n (%)	15 (8.1)	20 (10.8)		
	3, n (%)	1 (0.5)	6 (3.2)		
	N (% non-missing)	0 (0.0)	1 (0.5)	0.3134	17.0

Asthma exacerbations	ATS	Mean (SD)	0.4 (0.7)	0.5 (0.9)		
		Median (IQR)	0.0 (1.0)	0.0 (1.0)		
Acute event	respiratory	N (% non-missing)	186 (100.0)	186 (100.0)	0.2981	18.3
		0, n (%)	123 (66.1)	113 (60.8)		
		1, n (%)	39 (21.0)	39 (21.0)		
		2, n (%)	21 (11.3)	24 (12.9)		
		3, n (%)	3 (1.6)	8 (4.3)		
		4+, n (%)	0 (0.0)	2 (1.1)		
Acute event	respiratory	N (% non-missing)	186 (100.0)	186 (100.0)	0.1778	18.6
		Mean (SD)	0.5 (0.8)	0.6 (1.0)		
		Median (IQR)	0.0 (1.0)	0.0 (1.0)		

Table 195: Exacerbations

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=186)	High eosinophil (n=186)	P value*	SDD
Medication costs not inc ICS	N (% non-missing)	184 (98.9)	183 (98.4)	0.4758	0.8
	Mean (SD)	36.9 (71.1)	37.5 (93.0)		
	Median (IQR)	11.0 (23.0)	10.0 (21.0)		
Medication costs inc ICS	N (% non-missing)	184 (98.9)	183 (98.4)	0.8140	0.9
	Mean (SD)	271.9 (228.7)	273.9 (232.3)		
	Median (IQR)	201.0 (292.0)	212.0 (283.0)		
Physician costs	N (% non-missing)	186 (100.0)	186 (100.0)	0.6143	6.4
	Mean (SD)	89.6 (82.6)	96.4 (124.5)		
	Median (IQR)	84.0 (84.0)	84.0 (84.0)		
Total costs not inc ICS	N (% non-missing)	184 (98.9)	183 (98.4)	0.6901	5.2
	Mean (SD)	126.6 (122.5)	133.9 (155.3)		
	Median (IQR)	89.0 (102.5)	88.0 (122.0)		
Total costs inc ICS	N (% non-missing)	184 (98.9)	183 (98.4)	0.8213	3.4
	Mean (SD)	361.5 (256.1)	370.3 (265.7)		
	Median (IQR)	296.0 (302.0)	312.0 (325.0)		

Table 196: Healthcare costs.

*P-value computed from Mann Whitney test. Where data is missing, percentages are given as a percentage of the non-missing variables

15.12 Matched characterisation of high FeNO vs low BEC and low FeNO (categorisation 2)

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
Gender	N (% non-missing)	98 (100.0)	98 (100.0)	1.0000	0.0
	Male	41 (41.8)	41 (41.8)		
Age	N (% non-missing)	98 (100.0)	98 (100.0)	1.0000	1.3
	Mean (SD)	48.8 (15.3)	48.6 (15.6)		
	Median (IQR)	53.0 (27.0)	53.0 (27.0)		
Age group	N (% non-missing)	98 (100.0)	98 (100.0)	0.3072	10.1
	Under 35	23 (23.5)	24 (24.5)		
	35-65	65 (66.3)	57 (58.2)		
	66-80	10 (10.2)	17 (17.3)		
Smoking status	N (% non-missing)	98 (100.0)	98 (100.0)	1.0000	0.0
	Non-smoker	53 (54.1)	53 (54.1)		
	Ex-smoker	8 (8.2)	8 (8.2)		
	Current smoker	23 (23.5)	23 (23.5)		
Height	N (% non-missing)	95 (96.9)	94 (95.9)	0.4027	2.5
	Mean (SD)	167.55 (9.48)	167.17 (19.54)		
	Median (IQR)	168.00 (14.00)	167.50 (12.00)		
Weight	N (% non-missing)	95 (96.9)	94 (95.9)	0.0783	20.1
	Mean (SD)	82.5 (19.1)	78.4 (21.8)		
	Median (IQR)	80.0 (29.7)	75.0 (23.0)		

Table 197: Demographic summary

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
BMI	N (% non-missing)	96 (98.0)	94 (95.9)	0.0063	40.2
	Mean (SD)	29.3 (6.2)	26.9 (5.8)		
	Median (IQR)	27.9 (8.6)	25.7 (7.6)		
BMI	N (% non-missing)	98 (100.0)	98 (100.0)	0.2016	24.6
	Underweight	1 (1.0)	2 (2.0)		
	Normal	25 (25.5)	38 (38.8)		
	Overweight	32 (32.7)	27 (27.6)		
	Obese	38 (38.8)	27 (27.6)		
COPD diagnosis	N (% non-missing)	98 (100.0)	98 (100.0)	0.3123	14.4
	Yes	1 (1.0)	3 (3.1)		
FeNO reading	N (% non-missing)	98 (100.0)	98 (100.0)	<0.0001	182.6
	Mean (SD)	17.7 (7.9)	60.0 (31.8)		
	Median (IQR)	17.0 (10.0)	50.0 (25.0)		
Blood eosinophil reading	N (% non-missing)	98 (100.0)	97 (99.0)	<0.0001	100.6
	Mean (SD)	0.2 (0.1)	0.3 (0.3)		
	Median (IQR)	0.2 (0.1)	0.3 (0.3)		

Table 198: Clinical measurements

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
Acute oral corticosteroid prescriptions	N (% non-missing)	98 (100.0)	98 (100.0)	0.7168	16.5
	0	72 (73.5)	63 (64.3)		
	1	16 (16.3)	22 (22.4)		

	2	8 (8.2)	10 (10.2)		
	3	1 (1.0)	2 (2.0)		
	4+	1 (1.0)	1 (1.0)		
Acute oral corticosteroid prescriptions >14 days apart	N (% non-missing)	98 (100.0)	98 (100.0)	0.4309	22.0
	0	72 (73.5)	63 (64.3)		
	1	20 (20.4)	25 (25.5)		
	2	6 (6.1)	9 (9.2)		
	3	0 (0.0)	1 (1.0)		
	4+	0 (0.0)	0 (0.0)		
Acute oral corticosteroid use (yes/no)	N (% non-missing)	98 (100.0)	98 (100.0)	0.1650	19.8
	Yes	26 (26.5)	35 (35.7)		
Antibiotics	N (% non-missing)	98 (100.0)	98 (100.0)	0.3399	13.6
	Mean (SD)	0.2 (0.5)	0.3 (0.6)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
Antibiotic courses	N (% non-missing)	98 (100.0)	98 (100.0)	0.2668	13.6
	0	81 (82.7)	76 (77.6)		
	1	15 (15.3)	17 (17.3)		
	2	1 (1.0)	5 (5.1)		
	3	1 (1.0)	0 (0.0)		
	4+	0 (0)	0 (0)		

Table 199: Acute asthma treatment

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
Active eczema diagnosis	N (% non-missing)	98 (100.0)	98 (100.0)	1.0000	0.0
	Yes	4 (4.1)	4 (4.1)		
	N (% non-missing)	98 (100.0)	98 (100.0)	0.7492	4.5

Active rhinitis diagnosis	Yes	26 (26.5)	28 (28.6)		
Eczema diagnosis	N (% non-missing)	98 (100.0)	98 (100.0)	0.8763	2.2
	Yes	29 (29.6)	30 (30.6)		
Rhinitis diagnosis	N (% non-missing)	98 (100.0)	98 (100.0)	0.4546	10.6
	Yes	32 (32.7)	37 (37.8)		
Cardiovascular diagnosis	N (% non-missing)	98 (100.0)	98 (100.0)	0.2274	17.2
	Yes	12 (12.2)	7 (7.1)		
IHD diagnosis	N (% non-missing)	98 (100.0)	98 (100.0)	0.7003	5.5
	Yes	4 (4.1)	3 (3.1)		
Heart failure diagnosis	N (% non-missing)	98 (100.0)	98 (100.0)		0.0
	Yes	0 (0.0)	0 (0.0)		
Hypertension diagnosis	N (% non-missing)	98 (100.0)	98 (100.0)	0.0967	23.8
	Yes	29 (29.6)	19 (19.4)		

Table 200: Comorbidities 1

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
Diabetes diagnosis	N (% non-missing)	98 (100.0)	98 (100.0)	0.5513	8.5
	Yes	7 (7.1)	5 (5.1)		
Osteoporosis diagnosis	N (% non-missing)	98 (100.0)	98 (100.0)	0.5607	8.3
	Yes	1 (1.0)	2 (2.0)		
GERD diagnosis	N (% non-missing)	98 (100.0)	98 (100.0)	0.3452	13.4
	Yes	12 (12.2)	8 (8.2)		
GERD active diagnosis	N (% non-missing)	98 (100.0)	98 (100.0)	0.6018	7.4
	Yes	9 (9.2)	7 (7.1)		
Anxiety or depression	N (% non-missing)	98 (100.0)	98 (100.0)	0.8803	2.1
	Yes	34 (34.7)	33 (33.7)		
	N (% non-missing)	98 (100.0)	98 (100.0)	0.8486	2.7

Chronic Kidney Disease	Yes	16 (16.3)	17 (17.3)		
Cerebrovascular disease	N (% non-missing)	98 (100.0)	98 (100.0)	0.3123	14.4
	Yes	3 (3.1)	1 (1.0)		
Myocardial infarct	N (% non-missing)	98 (100.0)	98 (100.0)	1.0000	0.0
	Yes	1 (1.0)	1 (1.0)		

Table 201: Comorbidities 2

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
Current peak flow	N (% non-missing)	55 (56.1)	71 (72.4)	0.2219	22.8
	Mean (SD)	442.7 (105.7)	416.7 (121.6)		
	Median (IQR)	400.0 (170.0)	400.0 (120.0)		
Predicted Peak Flow	N (% non-missing)	55 (56.1)	71 (72.4)	0.6615	7.1
	Mean (SD)	520.7 (67.4)	515.9 (68.6)		
	Median (IQR)	490.8 (137.4)	493.7 (125.0)		
Percentage predicted peak flow	N (% non-missing)	55 (56.1)	71 (72.4)	0.1447	27.5
	Mean (SD)	84.6 (13.8)	80.2 (18.1)		
	Median (IQR)	84.1 (21.8)	78.9 (20.9)		
% predicted peak flow groups	N (% non-missing)	55 (56.1)	71 (72.4)	0.2304	13.7
	<=50%, n (%)	32 (58.2)	35 (49.3)		
	>50% to <80%, n (%)	0 (0.0)	3 (4.2)		
	>=80%, n (%)	23 (41.8)	33 (46.5)		

Table 202: Peak flow

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
	N (% non-missing)	13 (13.3)	18 (18.4)	0.7186	12.1

FeV ₁	Mean (SD)	2.7 (0.9)	2.8 (1.0)		
	Median (IQR)	2.3 (0.4)	2.8 (1.4)		
FVC	N (% non-missing)	22 (22.4)	22 (22.4)	0.2312	28.6
	Mean (SD)	3.4 (1.0)	3.7 (1.0)		
	Median (IQR)	3.2 (0.7)	3.8 (1.2)		
FEV ₁ /FVC_ratio	N (% non-missing)	12 (12.2)	17 (17.3)	0.3870	28.5
	Mean (SD)	0.8 (0.1)	0.7 (0.1)		
	Median (IQR)	0.8 (0.1)	0.8 (0.1)		
FEV ₁ Percent Predicted	N (% non-missing)	12 (12.2)	11 (11.2)	0.3721	45.3
	Mean (SD)	89.2 (21.2)	80.4 (17.4)		
	Median (IQR)	86.5 (34.0)	81.0 (27.0)		
FEV1 % predicted groups	N (% non-missing)	12 (12.2)	11 (11.2)	0.2378	24.2
	50% or less	0 (0.0)	0 (0.0)		
	>50% to <80%	5 (41.7)	4 (36.4)		
	80% to <100%	3 (25.0)	6 (54.5)		
	100%+	4 (33.3)	1 (9.1)		

Table 203:Lung function

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
Asthma consultations	N (% non-missing)	98 (100.0)	98 (100.0)	0.1343	33.3
	Mean (SD)	1.8 (1.4)	2.4 (2.2)		
	Median (IQR)	1.5 (1.0)	2.0 (2.0)		
Asthma consultations	N (% non-missing)	98 (100.0)	98 (100.0)	0.6625	11.7
	0	14 (14.3)	10 (10.2)		
	1	35 (35.7)	35 (35.7)		
	2+	49 (50.0)	53 (54.1)		
Asthma related accident and emergency	N (% non-missing)	98 (100.0)	98 (100.0)	0.3161	14.3
	1	0 (0.0)	1 (1.0)		

Asthma related unplanned inpatient admission	N (% non-missing)	98 (100.0)	98 (100.0)	0.1552	20.3
	1	0 (0.0)	2 (2.0)		

Table 204: Healthcare Resource Utilisation

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
LAMA prescriptions per patient	N (% non-missing)	98 (100.0)	98 (100.0)	0.1562	19.9
	Mean (SD)	0.0 (0.0)	0.1 (0.7)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
ICS/LABA prescriptions per patient	N (% non-missing)	98 (100.0)	98 (100.0)	0.1318	23.7
	Mean (SD)	2.6 (3.1)	3.4 (3.7)		
	Median (IQR)	1.0 (4.0)	2.0 (5.0)		
Mono ICS prescriptions per patient	N (% non-missing)	98 (100.0)	98 (100.0)	0.0295	28.5
	Mean (SD)	1.6 (2.8)	0.9 (1.9)		
	Median (IQR)	0.0 (2.0)	0.0 (1.0)		
LTRA prescriptions per patient	N (% non-missing)	98 (100.0)	98 (100.0)	0.4758	12.4
	Mean (SD)	0.4 (1.5)	0.6 (2.1)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
THEO prescriptions per patient	N (% non-missing)	98 (100.0)	98 (100.0)	0.1562	17.7
	Mean (SD)	0.1 (0.7)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		
SAMA prescriptions per patient	N (% non-missing)	98 (100.0)	98 (100.0)	0.1562	16.8
	Mean (SD)	0.1 (0.5)	0.0 (0.0)		
	Median (IQR)	0.0 (0.0)	0.0 (0.0)		

Table 205: Asthma prescriptions per patient

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
LABA prescription (yes/no)	N (% non-missing)	98 (100.0)	98 (100.0)	0.3123	14.4
	Yes	3 (3.1)	1 (1.0)		
LAMA prescription (yes/no)	N (% non-missing)	98 (100.0)	98 (100.0)	0.1552	20.3
	Yes	0 (0.0)	2 (2.0)		
SAMA prescription (yes/no)	N (% non-missing)	98 (100.0)	98 (100.0)	0.1552	20.3
	Yes	2 (2.0)	0 (0.0)		
LTRA prescription (yes/no)	N (% non-missing)	98 (100.0)	98 (100.0)	0.4884	9.9
	Yes	9 (9.2)	12 (12.2)		
Theophylline prescription (yes/no)	N (% non-missing)	98 (100.0)	98 (100.0)	0.1552	20.3
	Yes	2 (2.0)	0 (0.0)		

Table 206: Asthma prescriptions yes/no

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
SABA prescriptions	N (% non-missing)	98 (100.0)	98 (100.0)	0.7606	5.6
	Mean (SD)	3.1 (3.4)	3.3 (3.9)		
	Median (IQR)	2.0 (3.0)	2.0 (3.0)		
SABA inhalers	N (% non-missing)	98 (100.0)	98 (100.0)	0.7160	7.2
	Mean (SD)	3.8 (4.7)	4.2 (5.5)		
	Median (IQR)	2.0 (3.0)	2.0 (5.0)		
Daily SABA dosage	N (% non-missing)	98 (100.0)	98 (100.0)	0.6399	6.3
	Mean (SD)	209.2 (256.3)	226.8 (304.0)		
	Median (IQR)	109.6 (164.4)	109.6 (219.2)		

Table 207: SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations.

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
Number of SABA prescriptions	N (% non-missing)	98 (100.0)	98 (100.0)	0.8378	1.1
	0	17 (17.3)	21 (21.4)		
	1-3	52 (53.1)	47 (48.0)		
	4-6	16 (16.3)	15 (15.3)		
	>=7	13 (13.3)	15 (15.3)		
Number of SABA inhalers	N (% non-missing)	98 (100.0)	98 (100.0)	0.8948	4.1
	0	17 (17.3)	21 (21.4)		
	1-3	45 (45.9)	41 (41.8)		
	4-6	18 (18.4)	18 (18.4)		
	>=7	18 (18.4)	18 (18.4)		
Mean daily SABA dosage (mcg)	N (% non-missing)	98 (100.0)	98 (100.0)	0.3731	8.5
	<100	31 (31.6)	40 (40.8)		
	100-200	32 (32.7)	22 (22.4)		
	201-400	20 (20.4)	22 (22.4)		
	>400	15 (15.3)	14 (14.3)		

Table 208: Categorized SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
ICS daily dose	N (% non-missing)	98 (100.0)	98 (100.0)	0.9821	0.8
	Mean (SD)	487.2 (403.1)	490.7 (455.9)		
	Median (IQR)	328.8 (580.8)	328.8 (372.6)		
ICS/LABA or mono ICS inhalers	N (% non-missing)	98 (100.0)	98 (100.0)	0.8225	6.5
	Mean (SD)	5.5 (4.2)	5.8 (4.8)		

	Median (IQR)	4.0 (6.0)	4.0 (6.0)		
ICS/LABA or mono ICS prescriptions	N (% non-missing)	98 (100.0)	98 (100.0)	0.8637	6.0
	Mean (SD)	4.3 (3.2)	4.5 (3.5)		
	Median (IQR)	3.0 (4.0)	3.0 (4.0)		
ICS adherence	N (% non-missing)	98 (100.0)	98 (100.0)	0.4778	13.4
	Mean (SD)	58.1 (43.5)	65.7 (67.6)		
	Median (IQR)	49.3 (57.5)	49.3 (54.8)		

Table 209: ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
Asthma ATS exacerbations	N (% non-missing)	98 (100.0)	98 (100.0)	0.3126	24.2
	0, n (%)	72 (73.5)	63 (64.3)		
	1, n (%)	20 (20.4)	24 (24.5)		
	2, n (%)	6 (6.1)	9 (9.2)		
	3, n (%)	0 (0.0)	2 (2.0)		
	4, n (%)	0 (0.0)	0 (0.0)		
Asthma ATS exacerbations	N (% non-missing)	98 (100.0)	98 (100.0)	0.1332	24.2
	Mean (SD)	0.3 (0.6)	0.5 (0.7)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		
Acute respiratory event	N (% non-missing)	98 (100.0)	98 (100.0)	0.1971	27.7
	0, n (%)	67 (68.4)	54 (55.1)		
	1, n (%)	21 (21.4)	29 (29.6)		
	2, n (%)	9 (9.2)	11 (11.2)		
	3, n (%)	1 (1.0)	4 (4.1)		
	4+, n (%)	0 (0.0)	0 (0.0)		
Acute respiratory event	N (% non-missing)	98 (100.0)	98 (100.0)	0.0537	27.7
	Mean (SD)	0.4 (0.7)	0.6 (0.8)		
	Median (IQR)	0.0 (1.0)	0.0 (1.0)		

Table 210: Exacerbations

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil/low FeNO (n=98)	High FeNO (n=98)	P value*	SDD
Medication costs not inc ICS	N (% non-missing)	95 (96.9)	96 (98.0)	0.4699	18.8
	Mean (SD)	24.6 (51.9)	37.9 (85.9)		
	Median (IQR)	8.0 (18.0)	10.5 (18.5)		
Medication costs inc ICS	N (% non-missing)	95 (96.9)	96 (98.0)	0.9124	10.3
	Mean (SD)	206.0 (177.3)	227.3 (232.2)		
	Median (IQR)	150.0 (248.0)	146.0 (255.0)		
Physician costs	N (% non-missing)	98 (100.0)	98 (100.0)	0.2274	27.2
	Mean (SD)	94.0 (94.3)	132.3 (175.7)		
	Median (IQR)	84.0 (84.0)	84.0 (126.0)		
Total costs not inc ICS	N (% non-missing)	95 (96.9)	96 (98.0)	0.1380	30.4
	Mean (SD)	119.0 (129.7)	170.0 (199.0)		
	Median (IQR)	84.0 (89.0)	91.5 (156.5)		
Total costs inc ICS	N (% non-missing)	95 (96.9)	96 (98.0)	0.5825	21.5
	Mean (SD)	300.4 (226.9)	359.3 (314.3)		
	Median (IQR)	267.0 (233.0)	232.5 (275.5)		

Table 211: Healthcare Resource Utilisation costs:

*P-value computed from Mann Whitney test. Where data is missing, percentages are given as a percentage of the non-missing variables

15.13 Unmatched characterisation of currently smoking patients (categorisation 1)

Characterisation was not carried out using categorisation 2 due to low numbers.

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Gender	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.3207
	Male	37 (37.0)	8 (42.1)	3 (75.0)	16 (38.1)	13 (59.1)	2 (33.3)	
Age	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.8038
	Mean (SD)	56.4 (11.5)	53.2 (13.0)	56.0 (11.2)	55.6 (10.8)	57.2 (11.6)	47.2 (18.8)	
	Median (IQR)	58.0 (15.5)	56.0 (22.0)	55.0 (19.0)	55.5 (16.0)	58.5 (15.0)	49.5 (34.0)	
Age group	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.1330
	Under 35	4 (4.0)	2 (10.5)	0 (0.0)	1 (2.4)	1 (4.5)	2 (33.3)	
	35-65	79 (79.0)	14 (73.7)	3 (75.0)	31 (73.8)	14 (63.6)	3 (50.0)	
	44-80	17 (17.0)	3 (15.8)	1 (25.0)	10 (23.8)	7 (31.8)	1 (16.7)	
Smoking status	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	NA
	Non-smoker	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Ex-smoker	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Current smoker	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	
Height	N (% non-missing)	98 (98.0)	19 (100.0)	4 (100.0)	42 (100.0)	20 (90.9)	6 (100.0)	0.2476
	Mean (SD)	1.66 (0.09)	1.65 (0.10)	1.72 (0.10)	1.65 (0.09)	1.70 (0.07)	1.66 (0.09)	
	Median (IQR)	1.64 (0.14)	1.65 (0.16)	1.70 (0.14)	1.64 (0.12)	1.70 (0.09)	1.65 (0.13)	
Weight	N (% non-missing)	95 (95.0)	19 (100.0)	4 (100.0)	41 (97.6)	21 (95.5)	5 (83.3)	0.0419
	Mean (SD)	84.5 (19.7)	82.6 (17.4)	61.8 (9.8)	82.5 (20.0)	84.2 (27.7)	65.3 (10.9)	
	Median (IQR)	83.0 (25.0)	78.9 (20.0)	62.5 (16.5)	79.0 (27.3)	81.0 (19.7)	64.0 (10.3)	

Table 212: Demographic summary

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
BMI	N (% non-missing)	95 (95.0)	19 (100.0)	4 (100.0)	41 (97.6)	20 (90.9)	5 (83.3)	0.0023

	Mean (SD)	30.7 (6.7)	30.1 (5.1)	20.7 (1.8)	30.2 (7.0)	29.2 (9.3)	24.0 (2.0)	
	Median (IQR)	30.0 (8.6)	30.4 (7.1)	20.2 (2.4)	28.1 (7.1)	29.1 (8.7)	25.0 (2.9)	
BMI	N (% non-missing)	95 (95.0)	19 (100.0)	4 (100.0)	41 (97.6)	20 (90.9)	5 (83.3)	0.0053
	Underweight	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	
	Normal	18 (18.9)	4 (21.1)	4 (100.0)	9 (22.0)	5 (25.0)	3 (60.0)	
	Overweight	29 (30.5)	3 (15.8)	0 (0.0)	16 (39.0)	7 (35.0)	2 (40.0)	
	Obese	48 (50.5)	12 (63.2)	0 (0.0)	16 (39.0)	7 (35.0)	0 (0.0)	
FENO value	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	<0.0001
	Mean (SD)	13.9 (5.7)	33.0 (5.8)	91.5 (40.9)	15.0 (5.5)	31.5 (5.6)	81.5 (34.6)	
	Median (IQR)	13.5 (9.0)	31.0 (10.0)	80.5 (63.0)	14.0 (9.0)	30.0 (8.0)	72.0 (43.0)	
Eosinophil count	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	<0.0001
	Mean (SD)	0.2 (0.1)	0.2 (0.1)	0.1 (0.1)	0.4 (0.2)	0.5 (0.2)	0.5 (0.2)	
	Median (IQR)	0.2 (0.1)	0.2 (0.1)	0.2 (0.2)	0.4 (0.1)	0.4 (0.2)	0.5 (0.3)	
COPD diagnosis	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.4324
	Yes	3 (3.0)	1 (5.3)	0 (0.0)	1 (2.4)	0 (0.0)	1 (16.7)	

Table 213: Clinical measurements

* P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Acute oral corticosteroid prescriptions	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.0322
	0	68 (68.0)	14 (73.7)	3 (75.0)	33 (78.6)	20 (90.9)	3 (50.0)	
	1	25 (25.0)	4 (21.1)	1 (25.0)	4 (9.5)	2 (9.1)	1 (16.7)	
	2	7 (7.0)	1 (5.3)	0 (0.0)	4 (9.5)	0 (0.0)	1 (16.7)	
	3	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (16.7)	
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Acute oral corticosteroid	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.0005
	0	68 (68.0)	14 (73.7)	3 (75.0)	33 (78.6)	20 (90.9)	3 (50.0)	
	1	24 (24.0)	4 (21.1)	1 (25.0)	4 (9.5)	2 (9.1)	1 (16.7)	

prescriptions >14 days apart	2	8 (8.0)	0 (0.0)	0 (0.0)	4 (9.5)	0 (0.0)	1 (16.7)	0.2103	
	3	0 (0.0)	1 (5.3)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)		
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)		
Acute oral corticosteroid use (yes/no)	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)		
	Yes	32 (32.0)	5 (26.3)	1 (25.0)	9 (21.4)	2 (9.1)	3 (50.0)		
Antibiotics	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)		0.5683
	Mean (SD)	1.2 (1.5)	1.0 (1.4)	0.3 (0.5)	1.2 (1.9)	0.8 (1.2)	1.5 (2.3)		
	Median (IQR)	1.0 (2.0)	0.0 (2.0)	0.0 (0.5)	0.0 (2.0)	0.0 (2.0)	1.0 (1.0)		
Antibiotic courses	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.8179	
	0	43 (43.0)	10 (52.6)	3 (75.0)	22 (52.4)	14 (63.6)	2 (33.3)		
	1	25 (25.0)	4 (21.1)	1 (25.0)	7 (16.7)	1 (4.5)	3 (50.0)		
	2	15 (15.0)	2 (10.5)	0 (0.0)	6 (14.3)	5 (22.7)	0 (0.0)		
	3	5 (5.0)	1 (5.3)	0 (0.0)	3 (7.1)	1 (4.5)	0 (0.0)		
	4+	12 (12.0)	2 (10.5)	0 (0.0)	4 (9.5)	1 (4.5)	1 (16.7)		

Table 214: Acute asthma treatment

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Active eczema diagnosis	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.4599
	Yes	6 (6.0)	1 (5.3)	1 (25.0)	3 (7.1)	0 (0.0)	0 (0.0)	
Active rhinitis diagnosis	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.9160
	Yes	39 (39.0)	6 (31.6)	1 (25.0)	16 (38.1)	10 (45.5)	3 (50.0)	
Eczema diagnosis	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.1476
	Yes	29 (29.0)	10 (52.6)	1 (25.0)	18 (42.9)	4 (18.2)	2 (33.3)	
Rhinitis diagnosis	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.6113
	Yes	49 (49.0)	7 (36.8)	1 (25.0)	23 (54.8)	12 (54.5)	4 (66.7)	
	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.5468

Cardiovascular diagnosis	Yes	24 (24.0)	4 (21.1)	0 (0.0)	7 (16.7)	2 (9.1)	1 (16.7)	
IHD diagnosis	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.9031
	Yes	9 (9.0)	2 (10.5)	0 (0.0)	3 (7.1)	1 (4.5)	1 (16.7)	
Heart failure diagnosis	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.9374
	Yes	1 (1.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	
Hypertension diagnosis	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.6965
	Yes	38 (38.0)	6 (31.6)	2 (50.0)	12 (28.6)	6 (27.3)	1 (16.7)	

Table 215: Comorbidities 1

* P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Diabetes diagnosis	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.2787
	Yes	12 (12.0)	1 (5.3)	1 (25.0)	6 (14.3)	6 (27.3)	0 (0.0)	
Osteoporosis diagnosis	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.0737
	Yes	1 (1.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (16.7)	
GERD diagnosis	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.5283
	Yes	26 (26.0)	3 (15.8)	0 (0.0)	9 (21.4)	5 (22.7)	0 (0.0)	
GERD active diagnosis	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.7164
	Yes	20 (20.0)	3 (15.8)	0 (0.0)	7 (16.7)	5 (22.7)	0 (0.0)	
Anxiety or depression	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.3175
	Yes	45 (45.0)	11 (57.9)	3 (75.0)	18 (42.9)	6 (27.3)	2 (33.3)	
Chronic Kidney Disease	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.5440
	Yes	17 (17.0)	2 (10.5)	0 (0.0)	4 (9.5)	1 (4.5)	1 (16.7)	
Cerebrovascular disease	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.9300
	Yes	7 (7.0)	2 (10.5)	0 (0.0)	3 (7.1)	1 (4.5)	0 (0.0)	
Myocardial infarct	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.9174
	Yes	3 (3.0)	1 (5.3)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	

Table 216: Comorbidities 2

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Current peak flow	N (% non-missing)	49 (49.0)	13 (68.4)	2 (50.0)	22 (52.4)	10 (45.5)	5 (83.3)	0.1240
	Mean (SD)	427.8 (118.8)	388.1 (122.2)	445.0 (7.1)	401.1 (166.5)	503.7 (120.5)	304.0 (131.6)	
	Median (IQR)	410.0 (133.0)	360.0 (145.0)	445.0 (10.0)	350.0 (260.0)	535.0 (190.0)	400.0 (230.0)	
Predicted peak flow	N (% non-missing)	49 (49.0)	13 (68.4)	2 (50.0)	22 (52.4)	10 (45.5)	5 (83.3)	0.5761
	Mean (SD)	503.1 (75.6)	500.7 (81.3)	593.5 (32.1)	508.9 (81.0)	533.6 (61.3)	506.0 (94.1)	
	Median (IQR)	479.5 (137.9)	475.8 (121.7)	593.5 (45.4)	470.5 (124.0)	544.1 (96.1)	463.2 (146.6)	
Percentage predicted peak flow	N (% non-missing)	49 (49.0)	13 (68.4)	2 (50.0)	22 (52.4)	10 (45.5)	5 (83.3)	0.0434
	Mean (SD)	84.6 (17.8)	76.6 (17.3)	75.1 (5.3)	77.1 (24.0)	93.7 (17.0)	59.1 (22.7)	
	Median (IQR)	85.1 (21.6)	74.7 (17.7)	75.1 (7.4)	75.7 (46.4)	91.7 (26.1)	64.4 (31.0)	
% predicted PF groups	N (% non-missing)	49 (49.0)	13 (68.4)	2 (50.0)	22 (52.4)	10 (45.5)	5 (83.3)	0.0260
	>33% to <50%	1 (2.0)	1 (7.7)	0 (0.0)	2 (9.1)	0 (0.0)	2 (40.0)	
	>=50%	48 (98.0)	12 (92.3)	2 (100.0)	19 (86.4)	10 (100.0)	3 (60.0)	

Table 217: Peak flow

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
FeV ₁	N (% non-missing)	27 (27.0)	2 (10.5)	2 (50.0)	14 (33.3)	3 (13.6)	1 (16.7)	0.6540
	Mean (SD)	16.2 (29.8)	2.4 (0.3)	2.9 (0.1)	9.2 (26.2)	2.8 (0.9)	2.4 (.)	
	Median (IQR)	2.7 (2.0)	2.4 (0.4)	2.9 (0.1)	2.1 (1.0)	3.2 (1.7)	2.4 (0.0)	
FVC	N (% non-missing)	43 (43.0)	3 (15.8)	2 (50.0)	18 (42.9)	6 (27.3)	2 (33.3)	0.4033

	Mean (SD)	3.3 (0.8)	4.3 (1.1)	3.9 (0.1)	3.3 (0.6)	3.7 (1.3)	2.5 (1.4)	
	Median (IQR)	3.2 (1.2)	3.9 (2.1)	3.9 (0.2)	3.3 (0.9)	3.6 (2.1)	2.5 (2.0)	
FEV ₁ /FVC_ratio	N (% non-missing)	20 (20.0)	1 (5.3)	2 (50.0)	10 (23.8)	3 (13.6)	2 (33.3)	0.5590
	Mean (SD)	0.7 (0.1)	0.7 (.)	0.8 (0.0)	0.7 (0.1)	0.6 (0.0)	0.8 (0.2)	
	Median (IQR)	0.8 (0.2)	0.7 (0.0)	0.8 (0.0)	0.7 (0.2)	0.6 (0.1)	0.8 (0.2)	
FEV ₁ Percent Predicted	N (% non-missing)	27 (27.0)	2 (10.5)	2 (50.0)	15 (35.7)	3 (13.6)	2 (33.3)	0.5452
	Mean (SD)	73.5 (37.4)	78.0 (15.6)	40.0 (56.6)	57.1 (44.1)	30.3 (52.5)	40.5 (57.3)	
	Median (IQR)	83.0 (35.6)	78.0 (22.0)	40.0 (80.0)	67.0 (100.0)	0.0 (91.0)	40.5 (81.0)	
FEV1 % predicted groups	N (% non-missing)	27 (27.0)	2 (10.5)	2 (50.0)	15 (35.7)	3 (13.6)	2 (33.3)	0.6316
	50% or less	5 (18.5)	0 (0.0)	1 (50.0)	5 (33.3)	2 (66.7)	1 (50.0)	
	>50% to <80%	8 (29.6)	1 (50.0)	0 (0.0)	5 (33.3)	0 (0.0)	0 (0.0)	
	80% to <100%	7 (25.9)	1 (50.0)	1 (50.0)	1 (6.7)	1 (33.3)	1 (50.0)	
	100%+	7 (25.9)	0 (0.0)	0 (0.0)	4 (26.7)	0 (0.0)	0 (0.0)	

Table 218: Lung function

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Asthma consultations	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.6241
	Mean (SD)	1.9 (1.7)	1.9 (1.6)	3.8 (5.5)	2.0 (1.5)	1.4 (0.9)	1.2 (0.8)	
	Median (IQR)	2.0 (1.0)	2.0 (2.0)	1.0 (5.5)	2.0 (1.0)	1.0 (1.0)	1.0 (1.0)	
Asthma consultations	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.7862
	0	9 (9.0)	3 (15.8)	0 (0.0)	3 (7.1)	3 (13.6)	1 (16.7)	
	1	38 (38.0)	5 (26.3)	3 (75.0)	16 (38.1)	10 (45.5)	3 (50.0)	
	2+	53 (53.0)	11 (57.9)	1 (25.0)	23 (54.8)	9 (40.9)	2 (33.3)	
Asthma related accident and emergency attendance	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	NA
	Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	
	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	NA

Asthma related accident and emergency attendance	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Asthma related unplanned inpatient attendance	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	NA
	Mean	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Asthma related unplanned inpatient attendance	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	NA
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Table 219: Healthcare Resource Utilisation

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
LAMA prescriptions per patient	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.2680
	Mean (SD)	0.0 (0.2)	0.2 (0.7)	0.0 (0.0)	0.6 (2.5)	0.0 (0.0)	0.7 (1.6)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	
ICS/LABA prescriptions per patient	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.1270
	Mean (SD)	5.1 (4.0)	2.9 (2.6)	2.0 (1.8)	4.4 (3.5)	3.8 (3.9)	3.2 (2.8)	
	Median (IQR)	4.0 (6.0)	3.0 (5.0)	2.0 (3.0)	4.0 (6.0)	3.0 (3.0)	3.0 (5.0)	
Mono ICS prescriptions per patient	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.3169
	Mean (SD)	1.0 (2.2)	1.6 (2.8)	1.5 (3.0)	0.9 (2.0)	0.6 (2.0)	2.0 (2.9)	
	Median (IQR)	0.0 (0.5)	0.0 (2.0)	0.0 (3.0)	0.0 (1.0)	0.0 (0.0)	0.5 (4.0)	
LTRA prescriptions per patient	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.2242
	Mean (SD)	0.6 (2.0)	0.5 (1.4)	0.0 (0.0)	1.7 (4.0)	0.1 (0.6)	1.2 (2.9)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	
THEO prescriptions per patient	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.8036
	Mean (SD)	0.1 (0.7)	0.1 (0.5)	0.0 (0.0)	0.4 (2.0)	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	

Table 220: Asthma prescriptions per patient

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
LABA prescription (yes/no)	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.8656
	Yes	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
LAMA prescription (yes/no)	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.2794
	Yes	2 (2.0)	1 (5.3)	0 (0.0)	3 (7.1)	0 (0.0)	1 (16.7)	
SAMA prescription (yes/no)	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.5787
	Yes	4 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
LTRA prescription (yes/no)	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.2487
	Yes	11 (11.0)	3 (15.8)	0 (0.0)	10 (23.8)	1 (4.5)	1 (16.7)	
Theophylline prescription (yes/no)	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.8046
	Yes	2 (2.0)	1 (5.3)	0 (0.0)	2 (4.8)	0 (0.0)	0 (0.0)	

Table 221: Asthma prescriptions yes/no

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
SABA prescriptions	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.0564
	Mean (SD)	3.3 (3.3)	4.3 (4.4)	2.0 (2.7)	2.8 (3.4)	1.5 (1.4)	6.5 (6.0)	
	Median (IQR)	2.0 (4.0)	3.0 (4.0)	1.0 (3.0)	1.5 (4.0)	1.0 (3.0)	5.5 (8.0)	
SABA inhalers	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.0173
	Mean (SD)	3.9 (4.2)	6.1 (6.5)	2.0 (2.7)	2.9 (3.4)	1.7 (1.7)	7.7 (6.7)	
	Median (IQR)	2.0 (4.5)	3.0 (8.0)	1.0 (3.0)	2.0 (4.0)	1.0 (3.0)	5.5 (13.0)	
SABA daily dose	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.0202
	Mean (SD)	1.1 (1.2)	1.7 (1.8)	0.5 (0.7)	0.8 (0.9)	0.5 (0.5)	2.1 (1.8)	

	Median (IQR)	0.6 (1.1)	0.8 (2.2)	0.3 (0.8)	0.6 (1.1)	0.3 (0.8)	1.5 (3.6)	
SABA dosage	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.0202
	Mean (SD)	212.5 (241.7)	333.4 (356.5)	109.6 (148.4)	156.6 (184.6)	92.2 (93.2)	420.1 (369.5)	
	Median (IQR)	109.6 (219.2)	164.4 (438.4)	54.8 (164.4)	109.6 (219.2)	54.8 (164.4)	301.4 (712.3)	

Table 222: SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Number of SABA prescriptions	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.2680
	0	22 (22.0)	2 (10.5)	1 (25.0)	13 (31.0)	7 (31.8)	0 (0.0)	
	1-3	41 (41.0)	9 (47.4)	2 (50.0)	17 (40.5)	14 (63.6)	2 (33.3)	
	4-6	22 (22.0)	4 (21.1)	1 (25.0)	5 (11.9)	1 (4.5)	2 (33.3)	
	>=7	15 (15.0)	4 (21.1)	0 (0.0)	7 (16.7)	0 (0.0)	2 (33.3)	
Number of SABA inhalers	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.1292
	0	22 (22.0)	2 (10.5)	1 (25.0)	13 (31.0)	7 (31.8)	0 (0.0)	
	1-3	37 (37.0)	9 (47.4)	2 (50.0)	16 (38.1)	13 (59.1)	2 (33.3)	
	4-6	22 (22.0)	1 (5.3)	1 (25.0)	6 (14.3)	2 (9.1)	2 (33.3)	
	>=7	19 (19.0)	7 (36.8)	0 (0.0)	7 (16.7)	0 (0.0)	2 (33.3)	
Mean daily SABA dosage (mcg)	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.0383
	<100	33 (33.0)	4 (21.1)	3 (75.0)	20 (47.6)	12 (54.5)	1 (16.7)	
	100-200	26 (26.0)	7 (36.8)	0 (0.0)	9 (21.4)	8 (36.4)	1 (16.7)	
	201-400	29 (29.0)	2 (10.5)	1 (25.0)	8 (19.0)	2 (9.1)	2 (33.3)	
	>400	12 (12.0)	6 (31.6)	0 (0.0)	5 (11.9)	0 (0.0)	2 (33.3)	

Table 223: Categorised SABA usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
ICS daily dose	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.2306
	Mean (SD)	646.7 (481.2)	590.1 (421.6)	449.3 (669.3)	599.9 (422.7)	418.2 (340.7)	593.6 (279.8)	
	Median (IQR)	526.0 (715.1)	493.1 (526.0)	158.9 (767.1)	493.1 (613.7)	367.1 (328.8)	493.1 (191.8)	
ICS/LABA or mono ICS inhalers	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.5596
	Mean (SD)	7.4 (4.6)	6.5 (3.5)	5.5 (7.0)	7.0 (5.1)	5.9 (4.2)	7.0 (3.2)	
	Median (IQR)	7.0 (7.0)	6.0 (5.0)	2.5 (8.0)	6.5 (6.0)	5.0 (7.0)	6.0 (3.0)	
ICS/LABA or mono ICS prescriptions	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.0969
	Mean (SD)	6.2 (3.6)	4.7 (2.3)	4.0 (4.8)	5.3 (3.4)	4.5 (3.8)	5.5 (2.0)	
	Median (IQR)	6.0 (6.0)	5.0 (3.0)	2.0 (6.0)	4.0 (4.0)	3.0 (3.0)	6.0 (1.0)	
ICS adherence	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.4419
	Mean (SD)	70.5 (43.6)	76.2 (45.1)	56.2 (72.6)	66.2 (50.8)	57.2 (40.3)	81.3 (45.6)	
	Median (IQR)	65.8 (65.7)	74.0 (63.0)	26.1 (79.4)	56.1 (57.5)	41.1 (82.2)	73.9 (54.8)	

Table 224: ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
ICS/LABA or mono ICS inhalers	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.0736
	1-3	26 (26.0)	4 (21.1)	3 (75.0)	11 (26.2)	9 (40.9)	0 (0.0)	
	4-6	22 (22.0)	8 (42.1)	0 (0.0)	10 (23.8)	6 (27.3)	4 (66.7)	
	>=7	52 (52.0)	7 (36.8)	1 (25.0)	21 (50.0)	7 (31.8)	2 (33.3)	
Mean daily ICS dosage (mcg)	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.0873
	<250	23 (23.0)	4 (21.1)	3 (75.0)	9 (21.4)	7 (31.8)	0 (0.0)	
	250-<500	26 (26.0)	6 (31.6)	0 (0.0)	13 (31.0)	10 (45.5)	4 (66.7)	
	>=500	51 (51.0)	9 (47.4)	1 (25.0)	20 (47.6)	5 (22.7)	2 (33.3)	
ICS adherence(%)	N (% non-missing)	99 (99.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.4887
	<40	27 (27.3)	3 (15.8)	3 (75.0)	14 (33.3)	9 (40.9)	1 (16.7)	

	40-79	31 (31.3)	9 (47.4)	0 (0.0)	16 (38.1)	4 (18.2)	2 (33.3)
	80-120	30 (30.3)	4 (21.1)	0 (0.0)	8 (19.0)	7 (31.8)	2 (33.3)
	>120	11 (11.1)	3 (15.8)	1 (25.0)	4 (9.5)	2 (9.1)	1 (16.7)

Table 225: Categorised ICS usage

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

		Low eosinophil, low FeNO	Low eosinophil, med FeNO	Low eosinophil, high FeNO	High eosinophil, low FeNO	High eosinophil, med FeNO	High eosinophil, high FeNO	P value*
Asthma ATS exacerbations	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.0322
	0	68 (68.0)	14 (73.7)	3 (75.0)	33 (78.6)	20 (90.9)	3 (50.0)	
	1	25 (25.0)	4 (21.1)	1 (25.0)	4 (9.5)	2 (9.1)	1 (16.7)	
	2	7 (7.0)	1 (5.3)	0 (0.0)	4 (9.5)	0 (0.0)	1 (16.7)	
	3	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (16.7)	
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Asthma ATS exacerbations	N (% non-missing)	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.181
	Mean (SD)	0.4 (0.6)	0.3 (0.6)	0.3 (0.5)	0.4 (0.8)	0.1 (0.3)	1 (1.3)	
Acute respiratory event	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.7479
	0	38 (38.0)	9 (47.4)	2 (50.0)	20 (47.6)	13 (59.1)	2 (33.3)	
	1	26 (26.0)	4 (21.1)	2 (50.0)	7 (16.7)	5 (22.7)	0 (0.0)	
	2	19 (19.0)	3 (15.8)	0 (0.0)	8 (19.0)	3 (13.6)	2 (33.3)	
	3	6 (6.0)	0 (0.0)	0 (0.0)	4 (9.5)	1 (4.5)	1 (16.7)	
Acute respiratory event	N (% non-missing)	100 (100.0)	19 (100.0)	4 (100.0)	42 (100.0)	22 (100.0)	6 (100.0)	0.2829
	Mean (SD)	1.3 (1.4)	1.2 (1.5)	0.5 (0.6)	1.2 (1.6)	0.6 (0.9)	2.0 (1.9)	

Table 226: Exacerbations

*P-value computed from chi-squared test for categorical variables, or Mann-Whitney test, for continuous variables. Where variables are presented as both continuous and categorical, the P-value is from the Mann-Whitney test. Summary statistics presented as counts and percentages unless stated otherwise. Where data is missing, percentages for categorical variables are given as a percentage of the non-missing observations

Anonymous practice id	Asthma Patients	Patients with FENO reading
id1	1510	175
id2	1765	126
id3	5607	109
id4	4921	86
id5	1148	62
id6	893	49
id7	964	44
id8	613	44
id9	2382	33
id10	3271	33
id11	4128	27
id12	1543	25
id13	1214	24
id14	1829	18
id15	1488	17
id16	2180	16
id17	2972	15
id18	809	15
id19	3285	15
id20	543	13
id21	1406	13
id22	5340	12
id23	3817	12
id24	4978	10
id25	1921	9
id26	1540	9

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id27	3870	9
id28	489	9
id29	2480	9
id30	2648	8
id31	2388	8
id32	2677	8
id33	3836	8
id34	911	8
id35	822	7
id36	3013	7
id37	3954	7
id38	5242	7
id39	1678	7
id40	444	7
id41	2161	5
id42	2218	5
id43	719	5
id44	1000	5
id45	1659	4
id46	580	4
id47	508	4
id48	1872	3
id49	3043	3
id50	2228	3
id51	2866	3
id52	1199	3
id53	2037	3

id54	1862	3
id55	1944	3
id56	538	2
id57	1343	2
id58	3693	2
id59	1419	1
id60	2052	1
id61	1770	1
id62	181	1
id63	7522	1
id64	1460	1
id65	652	1
id66	3539	1
id67	2498	1
id68	1136	1
id69	301	1
Total	150519	1193

Table 227: FeNO readings and patients with asthma diagnosis by practice