Additional file 1: Table S1. Statistically significant differences between unmatched patient groups (categorisation 1)

Characteristics		Non-high blood eosinophil and low FeNO	Non-high blood eosinophil and medium FeNO	Non-high blood eosinophil and high FeNO	High blood eosinophil and low FeNO	High blood eosinophil and medium FeNO	High blood eosinophil and 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)	
Sex	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)	
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)	
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)	
FEV_1 % 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)	
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)	
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)	
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)	
ICS	n (% non-	296 (100.0)	72 (100.0)	26 (100.0)	122 (100.0)	67 (100.0)	27 (100.0)	0.0043

prescriptions	missing)							
	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)	
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 (µg)	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 to <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)	

All values in the table are n (%) unless otherwise specified. High FeNO defined as ≥50 ppb; medium FeNO, 25 to <50 ppb; low FeNO <25 ppb; high blood eosinophil count defined as ≥0.300×10^9 cells/L; non-high blood eosinophil count <0.300×10^9 cells/L.

BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV, forced expiratory volume; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; ppb, parts per billion; SABA, short-acting β2-agonist; SD, standard deviation

Additional file 1: Table S2. Statistically significant difference between unmatched patient groups (categorisation 2)

Characteristics		Non-high eosinophil and non-high FeNO	Non-high eosinophil and high FeNO	High eosinophil and non-high FeNO	High eosinophil and high FeNO	p-value
Sex	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)	
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)	
	Obese	147 (42.4)	16 (34.0)	69 (42.9)	12 (21.8)	
Mean daily ICS dosage (μg)	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 to <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	n (% non-	340 (98.0)	45 (95.7)	158 (98.1)	55 (100.0)	0.0062

cost	missing)					
	Mean (SD)	268.5 (228.1)	189.6 (222.1)	285.6 (238.2)	251.6 (231.6)	
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)	
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)	
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)	
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)	
Asthma related	n (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0177

accident and emergency attendance	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)	
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)	
Percentage predicted	n (% non-missing)	347 (100.0)	47 (100.0)	161 (100.0)	55 (100.0)	0.0418

peak flow	Mean (SD)	-66.7 (2103.7)	84.5 (17.5)	91.6 (16.0)	86.8 (17.9)	
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)	

All values in the table are n (%) unless otherwise specified. High FeNO defined as $\geq$35 ppb; non-high FeNO <35 ppb; high blood eosinophil count defined as $\geq 0.300 \times 10^9$ cells/L; non-high blood eosinophil count $<0.300 \times 10^9$ cells/L.

BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV, forced expiratory volume; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; IHD, ischaemic heart disease; IQR, interquartile range; LABA, long-acting β_2-agonist; OCS, oral corticosteroids; ppb, parts per billion; SABA, short-acting β_2-agonist; SD, standard deviation.

Additional file S1: Table 3. Frequency of exacerbations between matched biomarker groups

Categorisation 1

Asthma exacerbations	Non-high FeNO and non-high blood eosinophils (n=27)	High FeNO and high blood eosinophils (n=27)	p-value
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)	
Mean # exacerbations (SD)	0.2 (0.4)	0.8 (1.0)	0.0109
	Non-high FeNO and non-high blood eosinophils (n=200)	High FeNO OR high blood eosinophils (n=200)	
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)	
Mean # exacerbations (SD)	0.4 (0.6)	0.5 (0.8)	0.3423
Categorisation 2			
	Non-high FeNO and non-high blood eosinophils (n=186)	Non-high FeNO and high blood eosinophil (n=186)	

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 # exacerbations (SD)	0.4 (0.7)	0.5 (0.9)	0.3134
	Non-high FeNO and non-high blood eosinophils (n=98)	**High FeNO and non-high blood eosinophils (n=98)**	
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 # exacerbations (SD)	0.3 (0.6)	0.5 (0.7)	0.1332
	Non-high FeNO and non-high blood eosinophils (n=53)	**High FeNO and high blood eosinophils (n=53)**	
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 # exacerbations	0.4 (0.7)	0.7 (0.9)	0.1166

(SD)			

FeNO, fractional exhaled nitric oxide; SD, standard deviation.