British Thoracic Society (BTS) Winter Meeting
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FeNO and Blood Eosinophils as Biomarkers in Predicting Asthma Exacerbations

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Abstract

Introduction: With advances in new therapies that target airway inflammation, there is an urgent need for accurate and easy-to-use biomarkers to predict asthma exacerbations and likely patient responses to treatment.[1] Blood and sputum eosinophilia are used to predict the response of patients with asthma to steroid therapy.[1] Similarly, fractional exhaled nitric oxide (FeNO) concentrations has been shown to predict response to antiinflammatory therapy.[2] Efforts have been made to correlate FeNO and blood eosinophil counts as composite biomarkers but so far results have been inconsistent.[1,3]

Aims: We aimed to determine if raised blood eosinophil counts combined with raised FeNO concentrations are associated with increased frequency of severe asthma exacerbations.

Methods: We used a large, national database to select patients with active asthma for a cross-sectional study. Patients were matched according to blood eosinophil counts (high vs. nonhigh) and FeNO concentrations (high vs. nonhigh); these markers were correlated with the frequency of asthma exacerbations.

Results: Patients in the cohort with high blood eosinophils and nonhigh FeNO had a greater exacerbation rate as did patients in the high FeNO and nonhigh blood eosinophils cohort (unadjusted rate ratio: 1.41 [95% CI 0.91, 2.19] and 1.35 [95% CI 0.99, 1.84], respectively). Patients in the cohort with both biomarkers raised had a significantly greater exacerbation rate (1.72 [95% CI 1.00, 2.93]).

Conclusions: Using the combination of two biomarkers, FeNO and blood eosinophilia, provides a simple measurement that is associated with a greater asthma exacerbation rate.

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Introduction

- Blood eosinophil counts and fractional exhaled nitric oxide (FeNO) concentrations are established biomarkers in asthma[1,3]
- Although patients with raised blood eosinophils are at an increased risk of asthma exacerbations, it is unclear whether raised FeNO concentrations are associated with further increased risk[3]

Aim

We sought to determine whether raised blood eosinophil counts combined with raised FeNO concentrations are associated with increased frequency of severe asthma exacerbations.

Methods

Definitions

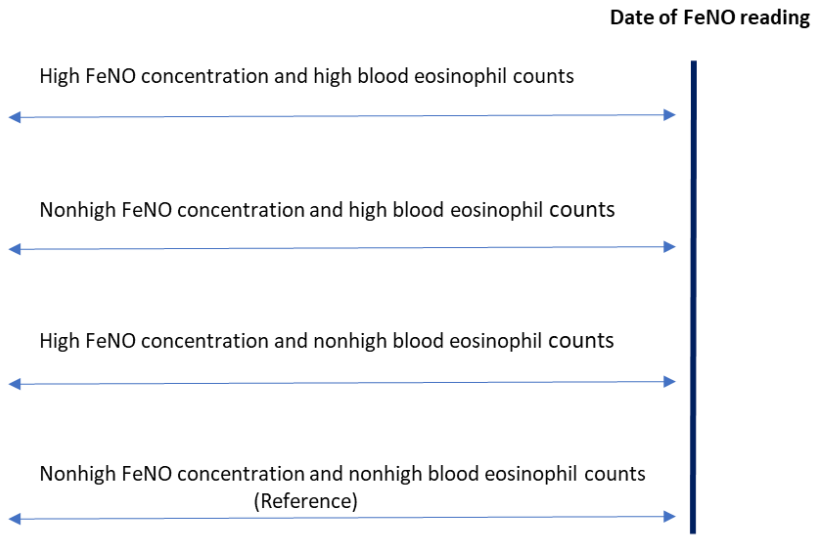
- Active asthma: asthma with a quality and outcomes framework (QOF) diagnostic code or ≥1 prescription for asthma medication in the year before the index date with no chronic obstructive pulmonary disease (COPD) diagnosis and no recorded forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC)<0.7 or COPD Read code and long-acting muscarinic antagonist (LAMA) prescription
- Exacerbation: the occurrence of (1) respiratory-related hospitalization (inpatient admission) AND/OR (2) emergency department attendance AND/OR (3) an acute course of oral corticosteroids
- High blood eosinophil count: $\geq 0.25 \times 10^9$ cells/L, based on previous work[4]
- High FeNO concentration: ≥35 parts per billion (ppb), based on previous work[2]
- Index date: the date of the most recent FeNO reading

- Reference population: patients with nonhigh blood eosinophil counts and nonhigh FeNO concentrations

Study design

- This was a cross-sectional study in which anonymized longitudinal patient data were assessed for 1 year preceding the index date (baseline year; **Figure 1**)
- Study data were extracted from enhanced medical records in the Optimum Patient Care Research Database (OPCRD). The OPCRD contained data from 3.4 million patients of >600 UK primary care practices at the time of the study[5]
- Ethical approvals were obtained from the Anonymised Data Ethics & Protocol Transparency (ADEPT) committee

Figure 1. Study design



FeNO, fractional exhaled nitric oxide.

Patient selection

- Patients aged 18–80 years (inclusive) with active asthma (QOF or ≥1 prescription for asthma medication), ≥1 blood eosinophil count recorded without recent exacerbation (within 2 weeks) at most ≤5 years before FeNO reading, and 1 consecutive year of data before the index date were included
- Patients were excluded from the study for any COPD Read code, any LAMA prescription, FEV_1/FVC <0.7, and other chronic respiratory conditions

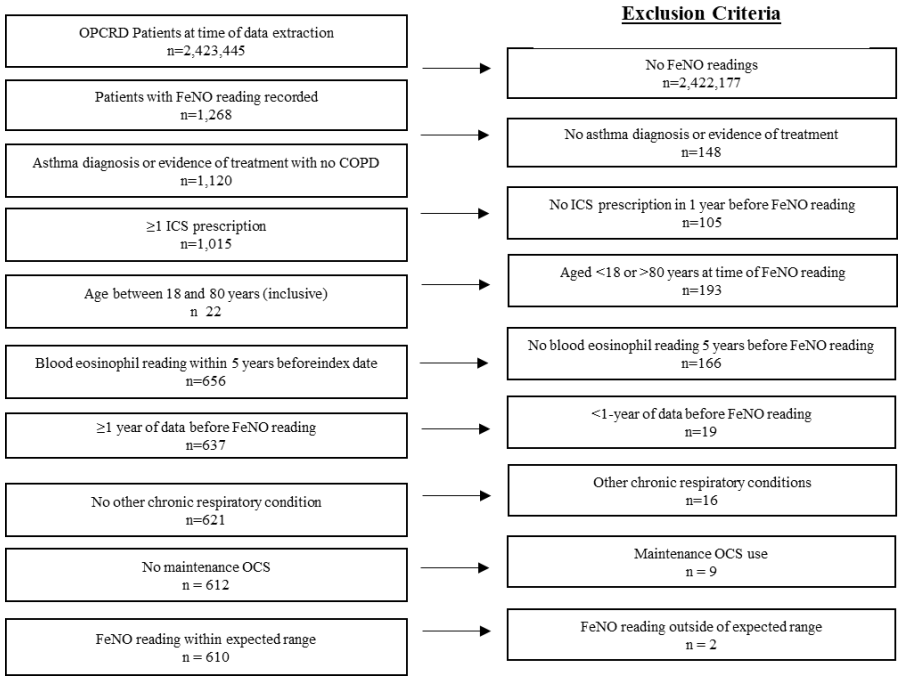
Data analysis

- Conditional Poisson regression was used to estimate exacerbation rate ratios (RRs) with 95% confidence intervals (CIs) during the outcome year for groups categorized by:
    - Blood eosinophil count: $\geq 0.25 \times 10^9$ cells/L vs. $< 0.25 \times 10^9$ cells/L
    - FeNO concentrations: ≥35 ppb and <35 ppb[2]
    - Matched for sex, age (within 10 years), and smoking status

Results

- The unmatched study population consisted of 610 patients (mean age 52 years, 38% male, 46% nonsmokers; **Figure 2**)

Figure 2. Patient Selection from OPCRD



COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; OCS, oral corticosteroid; OPCRD, Optimum Patient Care Research Database.

- Patients were matched 1:1 with the reference population (nonhigh blood eosinophil count and nonhigh FeNO concentration)
    - 186 patients were matched in the high blood eosinophil and nonhigh FeNO cohort (**Table 1**)
    - 98 were matched in the high FeNO and nonhigh blood eosinophil cohort (**Table 2**)
    - 53 were matched in the high blood eosinophil and high FeNO cohort (**Table 3**)

- With 1:1 matching, both the (1) high blood eosinophils and nonhigh FeNO cohort (n=186) and the (2) high FeNO and nonhigh blood eosinophils cohort (n=98) demonstrated a trend toward greater exacerbation rates (unadjusted RR: 1.41 [95% CI 0.91, 2.19] and 1.35 [95% CI 0.99, 1.84], respectively) in comparison with the reference group (**Table 4**)
- When both biomarkers were raised (n=53), a significantly greater exacerbation rate was observed (1.72 [95% CI 1.00, 2.93]) (**Table 4**)

Table 1. Characteristics of Cohorts with Nonhigh Eosinophil Counts and Nonhigh FeNO Concentrations vs. High Blood Eosinophil Counts[a]

		Nonhigh blood eosinophil counts and nonhigh FeNO concentrations (n=186)	High eosinophil counts (n=186)	SMD[c]
Sex	N (% nonmissing)	186 (100.0)	186 (100.0)	0.0
	Male	77 (41.4)	77 (41.4)	
Age	N (% nonmissing)	186 (100.0)	186 (100.0)	10.2
	<35 years	22 (11.8)	24 (12.9)	
	35–65 years	141 (75.8)	127 (68.3)	
	66–80 years	23 (12.4)	35 (18.8)	
Smoking status	N (% nonmissing)	186 (100.0)	186 (100.0)	0.0
	Nonsmoker	67 (36.0)	67 (36.0)	
	Ex-smoker	22 (11.8)	22 (11.8)	
	Current smoker	67 (36.0)	67 (36.0)	
BMI	N (% nonmissing)	184 (98.4)	184 (98.4)	16.5

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	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)	
Active[b] eczema diagnosis	N (% nonmissing)	186 (100.0)	186 (100.0)	13.7
	Yes	5 (2.7)	10 (5.4)	
Active[b] rhinitis diagnosis	N (% nonmissing)	186 (100.0)	186 (100.0)	18.7
	Yes	49 (26.3)	65 (34.9)	
IHD diagnosis	N (% nonmissing)	186 (100.0)	186 (100.0)	7.7
	Yes	7 (3.8)	10 (5.4)	
Heart failure diagnosis	N (% nonmissing)	186 (100.0)	186 (100.0)	10.4
	Yes	0 (0.0)	1 (0.5)	
Hypertension diagnosis	N (% nonmissing)	186 (100.0)	186 (100.0)	10.3
	Yes	46 (24.7)	38 (20.4)	
Diabetes diagnosis	N (% nonmissing)	186 (100.0)	186 (100.0)	5.8
	Yes	14 (7.5)	17 (9.1)	

GERD active[b] diagnosis	N (% nonmissing)	186 (100.0)	186 (100.0)	8.1
	Yes	26 (14.0)	21 (11.3)	
Predicted peak flow	N (% nonmissing)	98 (52.7)	101 (54.3)	6.2
	≤50%	4 (4.1)	5 (5.0)	
	>50% to <80%	35 (35.7)	38 (37.6)	
	≥80%	59 (60.2)	58 (57.4)	
ICS/LABA prescriptions per patient	N (% nonmissing)	186 (100.0)	186 (100.0)	16.7
	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 (% nonmissing)	186 (100.0)	186 (100.0)	34.4
	Mean (SD)	1.3 (2.5)	0.7 (1.6)	
	Median (IQR)	0.0 (1.0)	0.0 (1.0)	
Mean daily SABA dosage	N (% nonmissing)	186 (100.0)	186 (100.0)	8.1
	<100 µg	63 (33.9)	71 (38.2)	
	100–200 µg	57 (30.6)	48 (25.8)	
	201–400 µg	35 (18.8)	45 (24.2)	

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>400 µg	31 (16.7)	22 (11.8)

BMI, body mass index; FeNO, fractional exhaled nitric oxide; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; IHD, ischemic heart disease; IQR, interquartile range; LABA, long-acting β_2-agonist; SABA, short-acting β_2 agonist; SD, standard deviation; SMD, standardized mean difference.

[a]All values in table are n (%).

[b]Active means diagnosed in year before FeNO reading or treated in year before FeNO reading.

[c]SMD ≥10 indicates relative imbalance.

Table 2. Characteristics of Cohorts with Nonhigh Eosinophil Counts and Nonhigh FeNO Concentrations vs. High FeNO Concentrations[a]

		Nonhigh blood eosinophil counts and nonhigh FeNO concentrations (n=98)	High FeNO concentrations (n=98)	SMD[c]
Gender	N (% nonmissing)	98 (100.0)	98 (100.0)	0.0
	Male	41 (41.8)	41 (41.8)	
Age	N (% nonmissing)	98 (100.0)	98 (100.0)	10.1
	<35 years	23 (23.5)	24 (24.5)	
	35–65 years	65 (66.3)	57 (58.2)	
	66–80 years	10 (10.2)	17 (17.3)	
Smoking status	N (% nonmissing)	98 (100.0)	98 (100.0)	0.0
	No-smoker	53 (54.1)	53 (54.1)	
	Ex-smoker	8 (8.2)	8 (8.2)	
	Current smoker	23 (23.5)	23 (23.5)	
BMI	N (% nonmissing)	98 (100.0)	98 (100.0)	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)	
Active[b] eczema diagnosis	N (% nonmissing)	98 (100.0)	98 (100.0)	4.5
	Yes	26 (26.5)	28 (28.6)	
Active[b] rhinitis diagnosis	N (% nonmissing)	98 (100.0)	98 (100.0)	4.5
	Yes	26 (26.5)	28 (28.6)	
IHD diagnosis	N (% nonmissing)	98 (100.0)	98 (100.0)	5.5
	Yes	4 (4.1)	3 (3.1)	
Heart failure diagnosis	N (% nonmissing)	98 (100.0)	98 (100.0)	0.0
	Yes	0 (0.0)	0 (0.0)	
Hypertension diagnosis	N (% nonmissing)	98 (100.0)	98 (100.0)	23.8
	Yes	29 (29.6)	19 (19.4)	
Diabetes diagnosis	N (% nonmissing)	98 (100.0)	98 (100.0)	8.5
	Yes	7 (7.1)	5 (5.1)	

GERD active[b] diagnosis	N (% nonmissing)	98 (100.0)	98 (100.0)	7.4
	Yes	9 (9.2)	7 (7.1)	
Predicted peak flow	N (% nonmissing)	55 (56.1)	71 (72.4)	13.7
	≤50%	32 (58.2)	35 (49.3)	
	>50% to <80%	0 (0.0)	3 (4.2)	
	≥80%	23 (41.8)	33 (46.5)	
ICS/LABA prescriptions per patient	N (% nonmissing)	98 (100.0)	98 (100.0)	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 (% nonmissing)	98 (100.0)	98 (100.0)	28.5
	Mean (SD)	1.6 (2.8)	0.9 (1.9)	
	Median (IQR)	0.0 (2.0)	0.0 (1.0)	
Mean daily SABA dosage	N (% nonmissing)	98 (100.0)	98 (100.0)	8.5
	<100 µg	31 (31.6)	40 (40.8)	
	100–200 µg	32 (32.7)	22 (22.4)	
	201–400 µg	20 (20.4)	22 (22.4)	

>400 µg	15 (15.3)	14 (14.3)

BMI, body mass index; FeNO, fractional exhaled nitric oxide; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; IHD, ischemic heart disease; IQR, interquartile range; LABA, long-acting β2-agonist; SABA, short-acting β_2 agonist; SD, standard deviation; SMD, standardized mean difference.

[a]All values in table are n (%).

[b]Active denotes diagnosed in year before FeNO reading or treated in year before FeNO reading.

[c]SMD ≥10 indicates relative imbalance.

Table 3. Characteristics of Cohorts with Nonhigh Eosinophil Counts and Nonhigh FeNO Concentrations vs. High Blood Eosinophil Counts and High FeNO Concentrations[a]

		Nonhigh blood eosinophil counts and nonhigh FeNO concentrations (n=53)	High blood eosinophil counts and high FeNO concentrations (n=53)	SMD[c]
Gender	N (% nonmissing)	53 (100.0)	53 (100.0)	0.0
	Male	48.4 (16.7)	48.2 (16.9)	
Age	N (% nonmissing)	53 (100.0)	53 (100.0)	5.7
	<35 years	14 (26.4)	14 (26.4)	
	35–65 years	31 (58.5)	29 (54.7)	
	66–80 years	8 (15.1)	10 (18.9)	
Smoking status	N (% nonmissing)	46 (86.8)	46 (86.8)	0.0
	Nonsmoker	31 (58.5)	31 (58.5)	
	Ex-smoker	4 (7.5)	4 (7.5)	
	Current smoker	11 (20.8)	11 (20.8)	
BMI	N (% nonmissing)	53 (100.0)	53 (100.0)	25.1

Commented [MJ6]: Authors please confirm data for males. Should it be 48 (90.6) each for nonhigh and high counts?

	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)	
Active[b] eczema	N (% nonmissing)	53 (100.0)	53 (100.0)	0.0
diagnosis	Yes	2 (3.8)	2 (3.8)	
Active[b] rhinitis	N (% nonmissing)	53 (100.0)	53 (100.0)	16.1
diagnosis	Yes	15 (28.3)	19 (35.8)	
IHD diagnosis	N (% nonmissing)	53 (100.0)	53 (100.0)	11.3
	Yes	1 (1.9)	2 (3.8)	
Heart failure	N (% nonmissing)	53 (100.0)	53 (100.0)	0.0
diagnosis	Yes	0 (0.0)	0 (0.0)	
Hypertension	N (% nonmissing)	53 (100.0)	53 (100.0)	32.2
diagnosis	Yes	15 (28.3)	8 (15.1)	
Diabetes diagnosis	N (% nonmissing)	53 (100.0)	53 (100.0)	0.0
	Yes	3 (5.7)	3 (5.7)	

GERD active[b] diagnosis	N (% nonmissing)	53 (100.0)	53 (100.0)	12.8
	Yes	6 (11.3)	4 (7.5)	
Predicted peak flow	N (% nonmissing)	35 (66.0)	39 (73.6)	14.8
	≤50%	24 (68.6)	23 (59.0)	
	>50% to <80%	0 (0.0)	2 (5.1)	
	≥80%	11 (31.4)	14 (35.9)	
ICS/LABA prescriptions per patient	N (% nonmissing)	53 (100.0)	53 (100.0)	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 (% nonmissing)	53 (100.0)	53 (100.0)	23.3
	Mean (SD)	1.3 (2.3)	0.8 (1.7)	
	Median (IQR)	0.0 (1.0)	0.0 (1.0)	
Mean daily SABA dosage	N (% nonmissing)	53 (100.0)	53 (100.0)	5.3
	<100 µg	15 (28.3)	16 (30.2)	
	100–200 µg	19 (35.8)	14 (26.4)	
	201–400 µg	10 (18.9)	14 (26.4)	

>400 µg	9 (17.0)	9 (17.0)

BMI, body mass index; FeNO, fractional exhaled nitric oxide; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; IHD, ischemic heart disease; IQR, interquartile range; LABA, long-acting β_2-agonist; SABA, short-acting β_2 agonist; SD, standard deviation; SMD, standardized mean difference.

[a]All values in table are n (%).

[b]Active denotes diagnosed in year before FeNO reading or treated in year before FeNO reading.

[c]SMD ≥10 indicates relative imbalance.

Table 4. Rate Ratios of Comparison with Reference Population for Number of Severe Asthma Exacerbations in year Before FeNO Reading

	Rate ratio of exacerbations compared with nonhigh blood eosinophil count/nonhigh FeNO concentration	***P* value**	**Smaller 95% CI**	**Greater 95% CI**
High blood eosinophil count (n=186)	1.41	0.124	0.91	2.19
High FeNO concentration (n=98)	1.35	0.054	0.99	1.84
High blood eosinophil count and high FeNO concentration (n=53)	1.72	0.050	1.00	2.93

CI, confidence interval; FeNO, fractional exhaled nitric oxide.

Conclusions

- The combination of raised FeNO concentrations and raised blood eosinophil counts was associated with a greater exacerbation rate compared with neither biomarker raised
- FeNO concentrations and blood eosinophil counts are simple primary care measurements that, together, could reliably predict the exacerbation risk for patients with asthma
- Results of this study need to be confirmed with a prospective study within a larger population

References

1. Fowler SJ, et al. J Allergy Clin Immunol. 2015;135(3):822□24.
2. Dweik RA, et al. Am J Respir Crit Care Med. 2010;181(10):1033□41.
3. Dweik RA, et al. Am J Respir Crit Care Med. 2011;184(5):602□15.
4. Tran TN, et al. Ann Allergy Asthma Immunol. 2014;113(1):19□24.
5. Care OP. The Optimum Patient Care Research Database (OPCRD) 2017; http://optimumpatientcare.org/database-overview/. Accessed October 31, 2017.

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