

Appendix 4 Characteristics of studies

First author, Publication year, Follow-up time	Study design	Characteristics of patients: analyzed/recruited (n), (women %), mean age (years)	Atopy or allergy ^{1,2,3)}	Asthma severity	Baseline FEV1, % pred (deviation)	Exhalation flow rate in FeNO measurement (ml/s)	Baseline FeNO ppb mean (deviation)	Was inflammatory phenotype assessed?	Was predictive ability of FeNO assessed in relation to inflammatory phenotype?	Funding and support
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Study question 1: Does increased FeNO predict a favourable response to ICS in steroid-naïve asthmatics?

Cowan 2010 Follow-up: at minimum 28 days	Prospective cohort related to FeNO (steroid response was compared in eosinophilic asthma (EA) vs. non-eosinophilic asthma (NEA))	n=88/94 (EA: 69 %; NEA: 31 %), women 64 %. Age: 43 (SD 13)	EA: 77 %; NEA: 86 %	not detailed	88 (SD 16)	50	EA: geometric mean 29.6 (95 % CI 24.7 to 35.6); NEA: 24.1 (95 % CI 18.9 to 30.7)	Yes. 65 (69 %) of the subjects had sputum eosinophils \geq 2 % (eosinophilic asthma) and 29 (31 %) had sputum eosinophils < 2 % (noneosinophilic asthma).	Yes	Lottery Health New Zealand
Szeffler 2002 Follow-up: 24 weeks	Prospective cohort related to FeNO (randomized to two ICS intervention groups which were combined in the analysis of this review)	n=21/30 (women 23 %). Age: 30 (SD 7.5)	no information provided	not detailed	74.2 (SD 11.1)	no information provided	19.3 (SD 11)	Group median values for sputum eosinophils and neutrophils are given, but individuals were not categorised into different inflammatory phenotypes.	No	National and academic organisations
Szeffler 2005 Follow-up: 8 week	Prospective cohort related to FeNO (randomized crossover trial related to medication (ICS vs. LTRA); in this review considered only ICS -data)	n=111/144 (girls 41%). Age: 11 (SD 3.4)	2.8 ¹⁾	mild-to-moderate	95 (\pm 12.9)	50	39.5 (95 % CI 34.2 to 44.7)	Group median values for blood eosinophil count and serum ECP level are given, but individuals were not categorised into different inflammatory phenotypes.	No	National and academic organisations. Equipment support by Aerocrine, Inc. Chicago, 111

Study question 2: Does increased FeNO predict risk of exacerbation in asthmatic patients on regular stable ICS treatment?

Gelb 2006 Follow-up: 1.5 years	Prospective cohort related to FeNO	n= 44/44 (women 55 %). Age: 48.5	no information provided	mild-to-severe	69 (\pm 14)*; 72(\pm 25)**	100	9 \pm 5*; 35 \pm 14**	No	No	No information provided. Authors were from independent organisations
Kupczyk 2014 Follow-up: 1 year	Prospective cohort related to FeNO	In total 169 patients: 93 with severe and 76 with mild-to-moderate asthma (women 59%). Age: 46.5 (range 18-72)	45%	Subgroups: mild-to-moderate, and severe	severe asthma 70.4 \pm 2.1; mild-to-moderate asthma 88.7 \pm 2.1	50	severe asthma 46.3 \pm 6.2; mild-to-moderate 40.1 \pm 4.1	Group means for sputum eosinophils and neutrophils are given and in the subgroup of frequent exacerbators it is stated that 83.3 % of subjects had high levels of sputum eosinophils.	No	the European Union and several national funding bodies. Unconditional support from Aerocrine AB
Ozier 2011	Prospective cohort of adults. Baseline characteristics not reported for those 55 patients with controlled asthma (the subgroup considered in this review).					50		No	No	Phadia provided the MINO analyser, but did not participate in the collection, analysis and interpretation of the data or in the writing of the manuscript

Study question 3: Does increased FeNO in asthmatic patients on regular stable ICS treatment predict further benefit from augmenting the glucocorticoid treatment?

Kupczyk 2013 Follow-up: likely 2 weeks but remains unclear	Prospective cohort related to FeNO (placebo-controlled trial related to medication; half of the patients in blinded design, half in open design)	In total 146 patients: 84 with severe and 62 with mild-to-moderate asthma (women 57.5%). Age: 47.5 (range 18-72)	40.4%	Subgroups: mild-to-moderate, and severe	severe asthma 73.2 \pm 2.3 ; mild or moderate asthma 89.9 \pm 2.5	50	severe asthma 46.9 \pm 6.6 ; mild-to-moderate asthma 39.3 \pm 4.4	Group mean values for sputum eosinophils and neutrophils and blood eosinophil count are given, but individuals were not categorised into different inflammatory phenotypes.	No	the European Union and several national funding bodies. Unconditional support from Aerocrine AB
Little 2000 Follow-up: 2 weeks	Prospective cohort related to FeNO	n=37/37(women 51 %). Age: 48.6 (SD 12.2)	no information provided	not detailed	76.3 (SD 21.9)	no information provided	Baseline FeNO > 10 ppb in 32% of patients (cut-off value for increased FeNO 10 ppb)	11 out of 30 subjects had sputum eosinophilia \geq 4 % and 19 subjects had sputum eosinophils < 4 %.	No	National Asthma Campaign

Michils 2008 Follow-up: not reported	Prospective cohort related to FeNO	In this review, considered only those 82 patients whose ICS dose was over 500 µg/day equ BDP. Age: no information provided but adults however.	88 % ²⁾	uncontrolled asthma	84.1 ± 19.0 (patients with over 500 µg/day equ BDP).	50	Geometric mean 20.5 (geometrical interval 9.0 - 46.7) (patients with ICS dose over 500 µg/day equ BDP).	No	No	No information provided. Authors were from university hospital
Perez-de-Llano 2010 Follow-up: 1 and 2 months	Prospective cohort related to FeNO	n=102/102 (women 72 %). Age: 56 ± 15	46.5 % ²⁾	uncontrolled asthma	72 ± 24	50	43.1 ± 45.6 (range 4-222)	No	No	No information provided. Authors were from hospitals

Study questions 4: If an asthmatic patient on low dose ICS has good asthma control for at least 3 months, does low baseline FeNO predict successful withdrawal of ICS without asthma relapse?
Study questions 5: If an asthmatic patient on low dose ICS has good asthma control for at least 3 months and the ICS is withdrawn, does increased FeNO level during the follow-up predict asthma relapse?

Pijnenburg 2005 Follow-up: 2, 4, 12 and 24 weeks	Prospective cohort related to FeNO	n=37/40 (girls 43 %). Age: 12 (range 7–17)	78%	not detailed	99.5 (range 73–134)	50	Children with asthma relapse: geometric mean 14.8 (95% CI 8.5 to 25.8); children without asthma relapse: 10.5 (95% CI 7.3)	No	No	Funding provided by independent foundation organisation
Ferrer 2011 Follow-up: 6 months	Prospective cohort related to FeNO	n=28/28 (girls 25 %). Age: 11 (range 6–14)	93 % ³⁾	not detailed	> 80	50	median 48 (range 12–144)	No	No	No information provided.

¹⁾ number of positive skin tests out of 8 allergens tested

²⁾ positive skin test, (%)

³⁾ subjects of allergen immunotherapy, (%)

*FeNO ≤ 22

**FeNO > 22

SD = standard deviation

CI = confidence interval