Using fractional exhaled nitric oxide to guide step-down treatment decisions in patients with asthma: a systematic review and individual patient data meta-analysis

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In nonsmoking patients with mild-to-moderate well-controlled asthma, stepping down treatment when F_{ENO} is <50 ppb reduces prescribing of inhaled corticosteroids without increasing exacerbations
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ABSTRACT

Background: High exhaled nitric oxide fraction (F_{ENO}) levels are associated with greater risk of asthma exacerbation. However, it is not clear how F_{ENO} can be used to guide safe reductions in inhaled corticosteroid (ICS) doses in asthma patients. This study assesses the ability of F_{ENO} to guide ICS reductions.

Methods: Systematic searching of electronic databases identified prospective observational studies and randomised controlled trials which recruited participants with mild-to-moderate asthma aged ⩾12 years and measured F_{ENO} before reducing ICS. We performed multilevel mixed-effects logistic regression in relation to acute exacerbations and estimated each participant's exacerbation risk using our logistic regression model.

Results: We included data from seven out of eight eligible studies, representing 384 participants. ICS doses were halved in four studies and withdrawn in three studies. A baseline F_{ENO} measurement of ⩾50 ppb was associated with increased risk of exacerbations (crude OR 3.14, 95% CI 1.41–7.00, p=0.005; adjusted OR 3.08, 95% CI 1.36–6.98, p=0.007) and corresponded to an estimated exacerbation risk cut-off of 15%. Reducing ICS when estimated exacerbation risk was <15% *versus* <10% would result in fewer patients remaining on the same ICS dose (40 (10.4%) out of 384 *versus* 141 (36.7%) out of 384), but similar proportions of patients avoiding exacerbations (222 (91.4%) out of 243, 95% CI 87.1–94.6% *versus* 311 (90.4%) out of 344, 95% CI 86.8–93.3%).

Conclusion: In patients with mild-to-moderate asthma, gradual ICS reduction when F_{ENO} is <50 ppb may help decrease ICS use without increasing exacerbations. Future research should aim to validate these findings in larger populations.

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Introduction

Asthma is a complex condition characterised by marked variation in underlying pathophysiology and response to treatment. Inhaled corticosteroids (ICS) are considered to be the mainstay of treatment to prevent acute asthma exacerbations. However, only asthma driven by the type 2 pathway of airway inflammation is likely to respond to ICS [1].

Approximately 80% of UK asthma patients receive ICS [2]. However, despite an increase of almost one-third in ICS prescribing costs between 2008 and 2018 [3], asthma-related hospitalisation and exacerbation rates have not improved [2, 4]. Unnecessary ICS treatment can increase risk of local and systemic side-effects [5, 6]; therefore, clinical guidelines recommend that clinicians should consider gradually reducing treatment when patients have been stable for ⩾3 months [7].

Systematic reviews of randomised controlled trials (RCTs) comparing ICS dose maintenance with ICS reduction or withdrawal have reported inconsistent findings. One review found that stopping ICS in stable asthma patients was associated with significantly increased risk of exacerbations [8]. However, another concluded that reducing ICS by ⩾50% did not significantly increase exacerbation risk [9]. A Cochrane review [10] did not find differences in exacerbations between adults whose ICS dose was maintained *versus* reduced by 50–60%, but found that data were limited and of low quality.

The type 2 pathway of airway inflammation is driven by a range of cytokines, including interleukin (IL)-4, IL-13 and IL-5. IL-13 in particular has been described as having key roles in many aspects of asthma pathogenesis including mucus hypersecretion, goblet cell hyperplasia, subepithelial fibrosis and airway hyperresponsiveness [11, 12]. In addition, IL-13 activates inducible nitric oxide synthase, leading to increased production of nitric oxide in the airway [13]. Therefore, exhaled nitric oxide fraction (F_{ENO}) is an indicator of IL-13-driven corticosteroid-responsive airway inflammation. However, a systematic review and qualitative synthesis found insufficient evidence to determine the ability of F_{ENO} to guide ICS reductions [14].

A meta-analysis of data from RCTs which compared F_{ENO}-guided monitoring with guideline- or symptom-based monitoring found a significant reduction in exacerbations, but no difference in final daily ICS dose [15]. However, the clinical implications of this remain uncertain due to differences between studies in F_{ENO} cut-offs for adjusting treatment, characteristics of F_{ENO}-guided management algorithms and definition of exacerbations. An individual patient data meta-analysis can address these issues by using a consistent definition of exacerbations across all studies and analysing data from participants in whom treatment changes were not guided by prespecified cut-offs. Our study examines the ability of F_{ENO} to guide safe ICS reductions in asthma patients.

Methods

Our study protocol is registered on the PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO/; identifier number CRD42017071826).

Data sources and study selection

We performed systematic electronic database searches of MEDLINE and MEDLINE In-Process (OvidSP) [1946–], Embase (OvidSP) [1974–], Cochrane Central Register of Controlled Trials (Cochrane Library, John Wiley & Sons) and Web of Science Core Databases (Web of Science, Thomson Reuters) until September 13, 2019 with no language restrictions. Appendix 1 summarises our MEDLINE search strategy.

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In addition, we searched clinicaltrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/Default.aspx) to identify trial protocols. To avoid omission of relevant studies, we screened the reference lists of included studies and relevant systematic and narrative reviews and consulted experts in the field.

One reviewer (KW) screened article titles to exclude studies that were obviously irrelevant. Two reviewers (KW, JV) independently assessed abstracts and full-text articles for eligibility and resolved any disagreements by discussion.

We included prospective observational studies or RCTs conducted in community healthcare settings which recruited participants aged ⩾12 years with clinician-diagnosed asthma treated with low- or moderate-dose ICS (*i.e.* <1000 µg fluticasone propionate equivalents per day [7]), and measured F_{ENO} before reducing ICS. We excluded studies that recruited highly selected populations (*e.g.* occupational asthma), stepped down ICS only in individuals whose F_{ENO} measurements were below predefined decision thresholds, introduced alternative treatments after stepping down ICS, or did not collect data on acute exacerbations.

We defined acute exacerbations as acute asthma-related episodes requiring systemic corticosteroids or antibiotics, hospital admission or unscheduled healthcare visits due to asthma during the 12-week period after stepping down ICS. Study authors were asked to provide data on these outcomes as separate variables where possible. However, composite outcome data on acute exacerbations were accepted if definitions of these were consistent with our study definition.

Data extraction and quality assessment

Authors whose studies met eligibility criteria were approached for provision of individual patient data including baseline characteristics (age, sex, smoking status, body mass index, atopy), baseline ICS dose, F_{ENO} before ICS dose was stepped down, and acute exacerbations. Original individual patient data were kept on a secure server and prepared in a consistent format for all studies.

Study quality was independently assessed by two reviewers (JB and AF-N) using a modified version of the Quality in Prognosis Studies tool [16] (appendix 2). Discrepancies were resolved by discussion involving a third reviewer (KW). Study-level data were summarised and compared with published findings. Study authors were contacted for assistance with clarifying any discrepancies identified.

Data analysis

We conducted a one-stage individual patient data meta-analysis using mixed effects multilevel logistic regression using the melogit command in STATA (version 14; StataCorp, College Station, TX, USA). Our primary outcome was presence of one or more acute exacerbations during the 12-week period after stepping down ICS. Our secondary outcome was acute exacerbations requiring systemic corticosteroids. Our regression models accounted for within-study clustering and included age, sex and F_{ENO} as baseline covariates.

F_{ENO} was classified as low (⩽20 ppb), intermediate (>20–<50 ppb) or high (⩾50 ppb), thus incorporating cut-offs recommended for children and adults by the American Thoracic Society guidelines [17]. We assessed model performance by calculating C-statistics with 95% confidence intervals and used our regression equation to estimate acute exacerbation risk for each participant. We set hypothetical decision thresholds based on the distribution of estimated exacerbation risks and summarised percentages of clinical decisions which were appropriate according to each threshold with 95% confidence intervals.

We conducted prespecified subgroup analyses according to age (12–59 years inclusive *versus* ⩾60 years), smoking status and baseline ICS dose before stepping down treatment. Baseline ICS dose was classified as below, within or above the range associated with greatest therapeutic benefit (100–250 µg fluticasone propionate equivalents per day) [18].

Results

Study selection

Figure 1 summarises the results of our electronic database search, which retrieved 13 757 articles excluding duplicates and animal studies. We assessed 29 full-text articles, of which eight were suitable for inclusion [19–26]. The authors of four studies provided individual patient data for all participants who met our eligibility criteria [20, 23, 24, 26]. The authors of one study [25] were unable to provide individual patient data from participants recruited at three recruitment centres due to internal reasons, but provided individual patient data for all other participants. Data from two studies [21, 22] were obtained from the National Heart, Lung, and Blood Institute Biologic Specimen and Data Repository Information Coordinating Center repository. The authors of one study [19] declined to provide individual patient data.

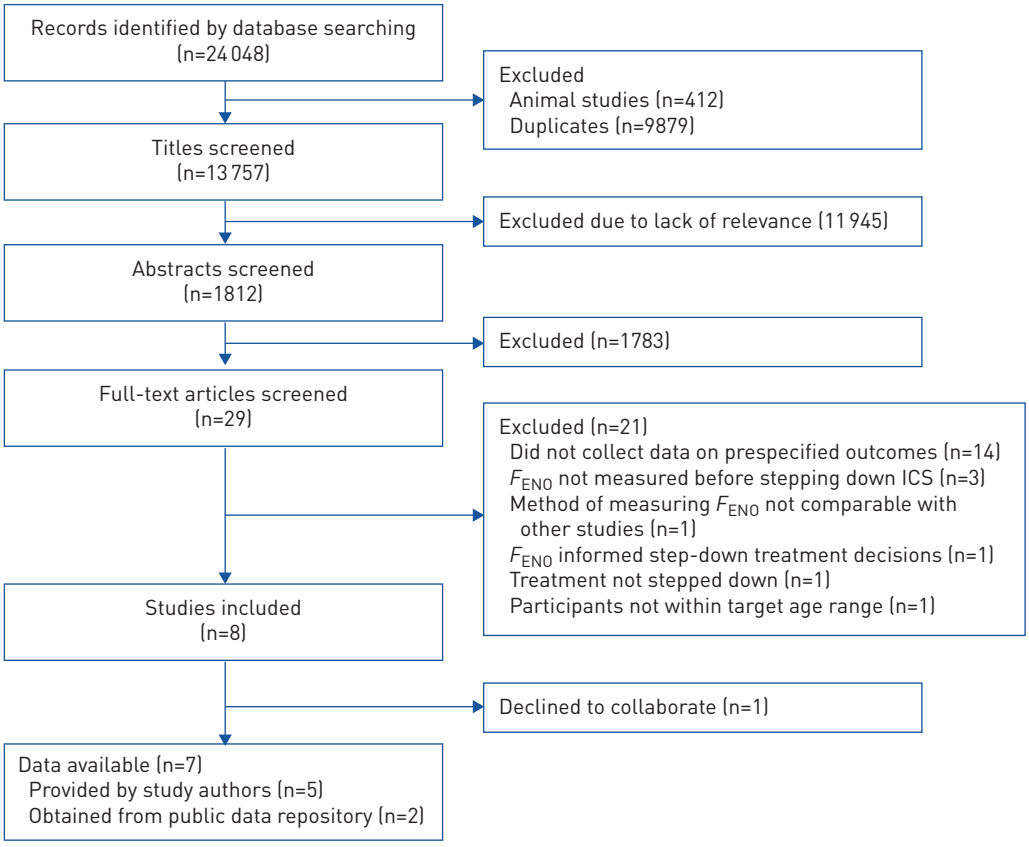

FIGURE 1 Study selection. F_{ENO}: exhaled nitric oxide fraction; ICS: inhaled corticosteroids.

Another study [27], which involved ICS reductions at 8-week intervals was considered, but not included, because its method of measuring F_{ENO} resulted in values which were not comparable to those obtained by other included studies, and we were unable to identify a method for converting these values to measurements which would have been comparable.

Overview of studies that provided individual patient data

Studies whose authors agreed to provide individual patient data were published between 2001 and 2016. Table 1 summarises the characteristics of our included studies.

Three studies were conducted in outpatient clinics [20, 24, 25] and one in primary care [26]. The other three studies were conducted in academic centres and the surrounding community [21–23]. Four studies included patients with asthma diagnosed according to Global Initiative for Asthma (GINA) [20, 24, 25] or American Thoracic Society [21] guidelines. One study included primary care patients with a recorded diagnosis of asthma [26]. Other studies diagnosed asthma based on symptoms [23] or spirometry and airway hyperresponsiveness [22].

We included data from two prospective observational studies which halved ICS doses in all participants [25, 26] and two open-label RCTs [20, 24] which included groups in which ICS dose was halved. In two studies, ICS and long-acting β_2-agonist (LABA) doses were halved [24, 25]. Additionally, we included data from the placebo groups of three RCTs which involved an initial ICS treatment period followed by use of placebo inhalers [21–23]. Furthermore, we included data from the "rescue beclometasone" group of one RCT [23], whereby ICS dose was reduced from regular use to rescue use only.

Four studies included participants whose asthma had been well controlled for $\geqslant$3 months [20, 24–26]. Three RCTs included participants whose asthma had been well controlled for 6 weeks [21, 22] or 4 weeks [23] and included some participants who had not previously used controller treatment. Two studies defined well-controlled asthma based on GINA criteria [24, 25], one based on US National Asthma Education and Prevention Program asthma care guidelines [23], and three according to clinical criteria [20, 21, 26]. One study did not define well-controlled asthma [22], but withdrew participants who experienced a significant exacerbation during the initial ICS treatment phase.

TABLE 1 Characteristics of included studies

First author, year [ref.]	Design	Setting	Method of F_{ENO} measurement	Participant eligibility criteria	Method of stepping down ICS	Definition of acute exacerbations of asthma
Harada, 2016 [20]#	Open-label RCT	Hospital outpatient clinic, Japan	NOA 280i (Sievers, Boulder, CO, USA); flow rate 50 mL·s^{-1}	Patients with mild persistent asthma aged ⩾20 years, well controlled for ⩾3 months. No COPD or other respiratory disorder, history of near-fatal asthma, treatment with oral corticosteroids, hospitalisation due to asthma in previous 6 months, treatment with other asthma medications during previous 3 months	ICS dose halved	Requirement for treatment with systemic steroid. Hospitalisation or visit to emergency department reported as separate outcome
Lazarus, 2001 [21]¶	Blinded placebo-controlled RCT	University-based ambulatory care centres, USA	NOA 280 (Sievers)	Aged 12–65 years, persistent asthma, nonsmokers, no serious medical illness other than asthma, no respiratory tract infection or asthma exacerbation within 6 weeks of ICS run-in period	ICS withdrawn	Requirement for prednisone, emergency department or urgent care visit or hospitalisation
Martin, 2007 [22]+	Blinded placebo-controlled RCT	Communities surrounding testing and referral centres (ACRN, USA)	NIOX analyser (Aerocrine, Solna, Sweden); flow rate 50 mL·s^{-1}##	Patients with asthma aged 18–55 years, nonsmokers, no ICS or systemic corticosteroids ⩾4 weeks before study enrolment, no respiratory infection within 6 weeks before study screening period, no other respiratory disease or significant medical illness	ICS withdrawn	Requirement for systemic corticosteroids
Martinez, 2011 [23]§	Blinded placebo-controlled RCT	Clinical centres, USA	NIOX analyser (Aerocrine); flow rate 50 mL·s^{-1}¶¶	Aged 6–18 years, mild persistent asthma during previous 2 years, symptomatically well controlled. Exclusions: FEV_1 <60% predicted, hospitalised for asthma in previous year, asthma exacerbation in previous 3 months or ⩾2 exacerbations in previous year, history of life-threatening asthma exacerbations	ICS withdrawn (placebo group) or used as rescue treatment only (rescue beclometasone group)	Requirement for 12 puffs of albuterol in 24 h (excluding preventive use before exercise), a peak expiratory flow of <70% of reference value before each albuterol use, symptoms that led to inability to sleep or do daily activities for ⩾2 consecutive days, a peak expiratory flow of <50% of reference value despite reliever treatment, or worsening asthma symptoms requiring an emergency room visit or treatment with prednisone
Mori, 2016 [24]#	Open-label RCT	Hospital outpatient clinic, Japan	NIOX MINO (Aerocrine); measurements performed according to ATS/ERS recommendations	Aged >18 years with asthma treated with budesonide/formoterol 320/9 µg twice a day for ⩾3 months; well controlled based on GINA criteria for ⩾3 months, agreed to receive step-down treatment. Exclusions: changed asthma treatment <3 months before beginning of study, current smokers or had a smoking history of >10 pack-years, other chronic pulmonary disease	ICS dose halved	Requirement for unexpected or emergency visit to hospital, hospitalisation, or systemic corticosteroid treatment for >3 days

Continued

TABLE 1 Continued

First author, year [ref.]	Design	Setting	Method of F_{ENO} measurement	Participant eligibility criteria	Method of stepping down ICS	Definition of acute exacerbations of asthma
Shirai, 2014 [25]#	Prospective observational study	Hospital outpatient clinic, Japan	NIOX MINO (Aerocrine); measurements performed according to ATS/ERS recommendations	Age >18 years, asthma for ⩾6 months, symptomatically well controlled on formoterol/budesonide 4.5/160 μg twice daily for ⩾3 months. Exclusions: current smokers or smoking history of >10 pack-years, other chronic respiratory condition, previous exacerbation requiring hospitalisation within the past year or emergency department visit or systemic corticosteroid within the past 3 months	ICS dose halved	Requirement for hospitalisation, emergency department visit, systemic corticosteroid treatment or >12 puffs of short-acting β_2-agonist for 3 days due to asthma symptoms
Wilson, 2014 [26]f	Prospective observational study	Primary care, UK	Flex Flow (Aerocrine); flow rate 50 mL·s^{-1}	Aged 18–75 years with recorded asthma diagnosis and received at least one ICS prescription in the past year, nonsmokers (<10 pack-years). Exclusions: poorly compliant participants, previous exacerbation requiring oral steroids in past 12 weeks, ACQ-5 score >1.5 (poor control)	ICS dose halved	Requirement for course of antibiotics or oral steroids

F_{ENO}: exhaled nitric oxide fraction; ICS: inhaled corticosteroids; RCT: randomised controlled trial; ACRN: Asthma Clinical Research Network; FEV_1: forced expiratory volume in 1 s; ATS: American Thoracic Society; ERS: European Respiratory Society; GINA: Global Initiative for Asthma; ACQ-5: five-item Asthma Control Questionnaire. #: asthma diagnosed according to GINA guidelines; ¶: asthma diagnosed according to ATS guidelines; +: asthma diagnosed in individuals with evidence of obstructive lung disease on spirometry testing and airway hyperresponsiveness on methacholine challenge; §: asthma diagnosed based on symptomatic criteria (>2 days per week with symptoms (*e.g.* wheezing), >2 days a week on which they had to use albuterol to control symptoms, or more than two awakenings at night per month when not using controller medication, or if they had to use daily controller treatment to keep their disorder well controlled); f: asthma patients identified based on diagnosis of asthma being recorded in primary care records; ##: method of F_{ENO} measurement not described in published paper, but detailed in ACRN General Manual of Operations Appendix VII September 9th, 2008 (Juno Pak, National Jewish Health, Denver, CO, USA; personal communication); ¶¶: method of F_{ENO} measurement not described in published paper but detailed in Childhood Asthma Research and Education Network Exhaled Nitric Oxide Manual version 2.6 May 1, 2008 (Dave Mauger, Penn State University, Hershey, PA, USA; personal communication).

TABLE 2 Risk of bias

First author, year [ref.]	Study participation	Study attrition	Measurement of F_{ENO}	Measurement of acute exacerbations	Confounding	Statistical analysis and reporting
Harada, 2016 [20]	Low	Low	Low	Low	Low	Low
Lazarus, 2001 [21]	High	Low	Low	Low	Low	Low
Martin, 2007 [22]	Low	Unclear	Unclear#	Low	Low	Low
Martinez, 2011 [23]	Low	Low	Unclear#	Low	Low	Low
Mori, 2016 [24]	Low	Low	Low	Low	Low	Low
Shirai, 2014 [25]	Low	Low	Low	Low	High	Moderate
Wilson, 2014 [26]	Low	Low	Low	Low	Unclear	Unclear

F_{ENO}: exhaled nitric oxide fraction. #: these studies did not describe the devices or methods used to measure F_{ENO} in their published papers, but did provide these details in their manuals of operations (Juno Pak (National Jewish Health, Denver, CO, USA) and Dave Mauger (Penn State University, Hershey, PA, USA); personal communications regarding [22] and [23], respectively).

Two studies provided individual patient data on exacerbations as a single variable [24, 25]. Other included studies provided exacerbation data as separate variables for exacerbations requiring systemic corticosteroids [20–23, 26], hospital admissions [20, 21], unscheduled healthcare visits [21] or antibiotics [26].

Risk of bias

Risk of bias was generally low for study participation, study attrition and measurement of acute exacerbations (table 2). Risk of bias for study participation was only considered high in one study [21], which only collected baseline F_{ENO} measurements in 26 (46%) out of 56 participants in the placebo group.

The findings of one study [25] were felt to be at high risk of confounding, as the analysis did not stratify or adjust for differences in baseline characteristics between participants with high (⩾37 ppb) or low (<37 ppb) F_{ENO}. Another study stated that differences in F_{ENO} and clinical measurements between participants who remained stable *versus* those who had exacerbations after reducing ICS were not statistically significant, but did not present findings to substantiate this [26]. Therefore, risk of bias was considered to be unclear in relation to confounding, statistical analysis and reporting. No important issues were identified in checking individual patient data.

Characteristics of included participants

Individual patient data were provided for 417 participants, out of which 33 (7.9%) were excluded from our dataset due to missing data on baseline F_{ENO} measurements before ICS treatment was stepped down (n=30 [21], n=2 [26], n=1 [24]). Among the 384 participants included in our dataset, 43 (11.2%) had an acute exacerbation within 12 weeks of stepping down their ICS dose (n=0 [20], n=3 [21], n=2 [22], n=6 [23], n=7 [24], n=1 [25], n=24 [26]).

Table 3 summarises baseline participant characteristics. Approximately three-quarters of participants had never smoked and nearly two-thirds had a history of atopy. F_{ENO} was ⩽20 ppb in approximately half of participants.

Multilevel logistic regression analysis

Risk of exacerbation after stepping down ICS was significantly greater in participants with high *versus* low F_{ENO} after adjustment for within-study clustering (crude OR 2.70, 95% CI 1.16–6.26; p=0.021). This finding was still statistically significant after further adjustment for age and sex (adjusted OR 2.56, 95% CI 1.08–6.09; p=0.033).

No significant differences in exacerbation risk were demonstrated between participants with intermediate *versus* low F_{ENO} (crude OR 0.67, 95% CI 0.31–1.43, p=0.299; adjusted OR 0.64, 95% CI 0.29–1.37, p=0.248). However, risk of exacerbation was significantly greater in participants with high *versus* intermediate F_{ENO} (crude OR 4.03, 95% CI 1.57–10.4, p=0.004; adjusted OR 4.03, 95% CI 1.55–10.5, p=0.004) and in participants with high *versus* low or intermediate F_{ENO} (crude OR 3.14, 95% CI 1.41–7.00, p=0.005; adjusted OR 3.08, 95% CI 1.36–6.98, p=0.007).

Our crude model (adjusted for within-study clustering and F_{ENO}) performed modestly in relation to predicting acute exacerbations (C-statistic 0.61, 95% CI 0.53–0.70). Additional adjustment for age and sex as baseline covariates did not significantly improve model performance (C-statistic 0.65, 95% CI 0.56–0.74).

TABLE 3 Participant characteristics

	All	First author, year [ref.]						
		Harada, 2016 [20]	**Lazarus, 2001** [21]	**Martin, 2007** [22]	**Martinez, 2011** [23]	**Mori, 2016** [24]	**Shirai, 2014** [25]	**Wilson, 2014** [26]
Subjects	384	20	26	35	47	42	25	189
Age years	46.2±18.9	56.5±15.6	31.3±9.7	33.2±9.5	13.9±1.5	54.5±15.2	56.3±14.3	54.5±13.0
Male	171 (44.5)	9 (45.0)	8 (30.8)	18 (51.4)	26 (55.3)	17 (40.5)	11 (44.0)	82 (43.4)
Smoking status								
Never-smokers	285 (74.2)	15 (75.0)	16 (61.5)	27 (77.1)	47 (100.0)[¶]	34 (81.0)	20 (80.0)	126 (66.7)
Ex-smokers	99 (25.8)	5 (25.0)	10 (38.5)	8 (22.9)	0 (0.0)	8 (19.1)	5 (20.0)	63 (33.3)
History of atopy	246 (64.1)	16 (80.0)[+]	22 (84.6)[§]	33 (94.3)[§]	44 (93.6)[§]	31 (73.8)[f]	18 (72.0)[##]	82 (43.4)[f]
BMI kg·m^{-2}	26.3±5.9[¶¶]	21.2±3.4	NC	NC	23.0±5.2	25.1±5.9	24.1±6.7	28.3±5.4
ICS dose[#]								
Low (⩽200 µg fluticasone propionate equivalents per day)	227 (59.1)	20 (100.0)	26 (100.0)	0 (0.0)	47 (100.0)	0 (0.0)	25 (100.0)	109 (57.7)
Moderate (>200 to <1000 µg fluticasone propionate equivalents per day)	157 (40.9)	0 (0.0)	0 (0.0)	35 (100.0)	0 (0.0)	42 (100.0)	0 (0.0)	80 (42.3)
F_{ENO} ppb	19.8 (3.1–129)	42.4 (14.8–129)	14.3 (7.5–41)	13.6 (3.5–44.5)	18.8 (4.9–68.7)	24.5 (8–117)	24.0 (9–109)	19.3 (3.1–121.8)
F_{ENO} categories								
Low (⩽20 ppb)	200 (52.1)	1 (5.0)	16 (61.5)	28 (80.0)	26 (55.3)	17 (40.5)	11 (44.0)	101 (53.4)
Intermediate (>20 ppb to <50 ppb)	144 (37.5)	13 (65.0)	10 (38.5)	7 (20.0)	18 (38.3)	18 (42.9)	12 (48.0)	66 (34.9)
High (⩾50 ppb)	40 (10.4)	6 (30.0)	0 (0.0)	0 (0.0)	3 (6.4)	7 (16.7)	2 (8.0)	22 (11.6)

Data are presented as n, mean±SD n (%) or median (range). BMI: body mass index; ICS: inhaled corticosteroids; F_{ENO}: exhaled nitric oxide fraction; NC: not collected. [#]: categorisation of ICS doses based on British Thoracic Society/Scottish Intercollegiate Guidelines Network guidelines [7]; [¶]: smoking status data not formally collected, but participants assumed to be never-smokers given that study was conducted in children; [+]: no details provided on how atopy was defined; [§]: atopy defined based on allergy skin test results [21–23] or history of eczema [23]; [f]: atopy defined based on history of atopic disorders (atopic asthma [24], allergic rhinitis [24, 26], eczema [26]); [##]: atopy defined based on positive specific IgE antibodies to at least one common inhalant antigen; [¶¶]: based on available data from 323 participants.

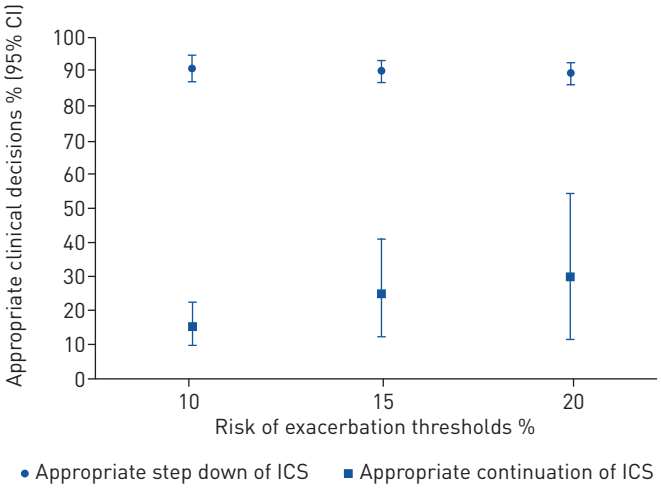

FIGURE 2 Appropriateness of clinical decisions guided by different risk of exacerbation thresholds. Appropriate step down of inhaled corticosteroids (ICS) was defined as reductions in ICS dose in patients whose estimated risk of exacerbation was below a given threshold and in whom no acute exacerbation was observed during the following 12-week period. Appropriate continuation of ICS was defined as maintaining the same ICS dose in a patient whose estimated risk of exacerbation was at or above a given threshold, thereby potentially preventing an acute exacerbation during the following 12-week period.

The distribution of estimated exacerbation risks calculated for each participant using our regression model (linear predictor = −2.417 + (0.0008 × age (years) + (0.623 if male) + (−0.453 if F_{ENO} >20 ppb and <50 ppb) + (0.941 if F_{ENO} ⩾50 ppb)) was positively skewed (median 8.7%, range 5.4–31.1%). Based on this distribution, we set hypothetical decision thresholds of 10%, 15% and 20% in relation to estimated risk of exacerbations and summarised the numbers and percentages of clinical decisions which were appropriate at each of these thresholds with 95% confidence intervals. Based on our model, similar percentages of participants would not have an exacerbation after stepping down ICS, or potentially avoid an exacerbation as a result of their ICS dose being maintained, irrespective of which risk of exacerbation threshold was used to guide these decisions (figure 2, appendix 3). However, the same ICS dose would be continued in fewer participants if ICS was stepped down in patients whose estimated risk was <15% (40 (10.4%) out of 384, 95% CI 7.5–13.9%) *versus* <10% (141 (36.7%) out of 384, 95% CI 31.9–41.8%). A F_{ENO} cut-off of 50 ppb corresponded to an estimated exacerbation risk cut-off of 15% (table 4).

We were unable to perform our planned secondary outcome analysis because we were only able to identify 14 acute exacerbations requiring systemic corticosteroids (n=0 [20], n=3 [21], n=2 [22], n=6 [23], n=3 [26]).

Subgroup analyses

Table 5 summarises the results of our prespecified subgroup analyses. Due to limited numbers of participants with exacerbations in each subgroup, only crude odds ratios with 95% confidence intervals were calculated. Exacerbation risk was significantly higher in individuals with high *versus* intermediate F_{ENO} in participants who had never smoked (crude OR 3.71, 95% CI 1.15–11.9; p=0.028) and participants aged ⩾60 years (crude OR 10.2, 95% CI 1.76–59.2; p=0.010). In addition, exacerbation risk was

TABLE 4 Distribution of exhaled nitric oxide fraction (F_{ENO}) measurements according to estimated risk of exacerbation

	F_{ENO} ppb	
	Below decision threshold	**Greater than or equal to decision threshold**
Risk of exacerbation decision threshold %		
10	20.2 (3.1–49.6)	18.4 (3.5–129)
15	18.2 (3.1–49.6)	69.6 (50.4–129)
20	18.9 (31–129)	71.6 (50.4–117.6)

Data are presented as median (range).

TABLE 5 Prespecified subgroup analyses for exhaled nitric oxide fraction (F_{ENO}) in relation to acute exacerbations of asthma after stepping down inhaled corticosteroids

	Subjects	Low F_{ENO}	Intermediate F_{ENO}	High F_{ENO}	Intermediate *versus* low F_{ENO}	p-value	High *versus* low F_{ENO}	p-value	High *versus* intermediate F_{ENO}	p-value
Age 12–59 years inclusive	263	13/147 (8.8)	9/93 (9.7)	5/23 (21.7)	1.10 (0.45–2.70)	0.827	2.86 (0.91–8.98)	0.071	2.59 (0.78–8.66)	0.122
Age ⩾60 years	121	9/53 (17.0)	2/51 (3.9)	5/17 (29.4)	0.20 (0.04–0.97)	0.046	2.04 (0.57–7.22)	0.271	10.2 (1.76–59.2)	0.010
Never-smokers	285	18/158 (11.4)	8/102 (7.8)	6/25 (24.0)	0.67 (0.28–1.58)	0.354	2.46 (0.87–6.95)	0.091	3.71 (1.15–11.9)	0.028
Ex-smokers	99	4/42 (9.5)	3/42 (7.1)	4/15 (26.7)	0.73 (0.15–3.49)	0.694	3.45 (0.74–16.1)	0.115	4.73 (0.92–24.4)	0.063
ICS below optimal therapeutic range	57	2/32 (6.3)	2/22 (9.1)	2/3 (66.7)						
ICS within optimal therapeutic range	200	11/100 (11.0)	5/79 (6.3)	2/21 (9.5)	0.55 (0.18–1.64)	0.282	0.85 (0.17–4.16)	0.843	1.56 (0.28–8.66)	0.613
ICS above optimal therapeutic range	127	9/68 (13.2)	4/43 (9.3)	6/16 (37.5)	0.67 (0.19–2.34)	0.532	3.93 (1.15–13.5)	0.029	5.85 (1.38–24.8)	0.016

Data are presented as n, n/N[#](%) or crude OR (95% CI), unless otherwise stated. Definition of F_{ENO} categories: high (⩾50 ppb), intermediate (>20 to <50 ppb), low (⩽20 ppb). Optimal therapeutic range for inhaled corticosteroids (ICS) defined as 100–250 μg fluticasone propionate equivalents per day [18]. Crude OR adjusted for within-study clustering only. [#]: number of participants with ⩾1 exacerbation/total number of participants.

significantly higher in individuals with high *versus* low F_{ENO} (crude OR 3.93, 95% CI 1.15–13.5; p=0.029) and high *versus* intermediate F_{ENO} (crude OR 5.85, 95% CI 1.38–24.8; p=0.016) in the subgroup whose ICS dose was above the optimal therapeutic range.

Post hoc *analyses*

Appendix 4 summarises the results of two *post hoc* analyses. Our first *post hoc* analysis excluded data from participants in the study by Wilson *et al.* [26], which contributed 189 (49.2%) out of 384 participants in our dataset including 24 (55.8%) out of 43 participants who had an acute exacerbation. After excluding these data, exacerbation risk was still significantly higher in individuals with high *versus* intermediate F_{ENO} (crude OR 3.75, 95% CI 1.06–13.2; p=0.040). However, the same comparison was no longer statistically significant when only data from participants from Wilson *et al.* [26] were included (crude OR 4.19, 95% CI 0.99–17.8; p=0.051). Our second *post hoc* analysis was stratified according to whether ICS treatment was halved *versus* withdrawn or reduced to as-needed use. In the withdrawn subgroup, exacerbation risk was significantly higher in individuals with high *versus* low or intermediate F_{ENO}, but crude OR estimates were associated with very wide 95% confidence intervals since exacerbations were observed in only 11 out of 108 participants.

We examined LABA use as an effect modifier by performing an additional *post hoc* sensitivity analysis excluding data from studies whose participants were on ICS/LABA preparations [24, 25]. The findings of this analysis were consistent with those of our main analysis. Risk of exacerbation after stepping down ICS was significantly greater in participants with high *versus* low F_{ENO} (adjusted OR 2.94, 95% CI 1.10–7.82; p=0.031), intermediate F_{ENO} (adjusted OR 4.00, 95% CI 1.37–11.7; p=0.011) and intermediate or low F_{ENO} (adjusted OR 3.32, 95% CI 1.31–8.39; p=0.011). However, no statistically significant difference in risk was observed between participants with intermediate *versus* low F_{ENO} (adjusted OR 0.73, 95% CI 0.32–1.71; p=0.474).

Discussion

Summary of main findings

In nonsmoking patients with mild-to-moderate well-controlled asthma, stepping down ICS when F_{ENO} is <50 ppb on existing treatment is associated with reduced ICS prescribing without increasing exacerbations in the following 12 weeks. A F_{ENO} cut-off of 50 ppb corresponds to an estimated exacerbation risk of 15%.

Comparison with existing literature

Previous study findings suggest lower F_{ENO} cut-offs to guide ICS dose reductions. In children with stable asthma, a F_{ENO} of ⩾22 ppb is a significant predictor of future exacerbations [28]. Additionally, a study in adults with well-controlled moderate asthma concluded that halving ICS/LABA doses was safe in patients with F_{ENO} of ⩽28 ppb since no significant differences in numbers of exacerbations were observed before and after reducing treatment [29].

Conversely, a longitudinal analysis found that a higher baseline F_{ENO} was associated with lower risk of severe exacerbations in adults with mild-to-moderate asthma [30]. However, it was not possible to determine whether exacerbations were due to ICS dose reductions or other causes because the follow-up period was long (⩾12 months) and only approximately three-quarters of participants were using ICS at baseline.

Strengths and limitations

We managed to obtain individual patient data from seven out of eight relevant studies. Our findings are unlikely to have been unduly influenced by omission of the study whose authors declined to provide individual patient data [19], which only included 32 children aged 7–14 years.

Data on baseline F_{ENO} measurements were missing from <8% of participants, justifying a complete case analysis, and our regression models accounted for potential within-study clustering of exacerbation outcomes, which may have occurred due to differences between study populations in baseline F_{ENO} measurements and other potential prognostic factors. We acknowledge that we were only able to include data from a relatively small number of patients. However, the generalisability of our findings to patients with clinician-diagnosed asthma is strengthened by our inclusion of studies which used pragmatic approaches to diagnosing asthma, thereby reflecting current clinical practice for establishing asthma diagnoses in community and outpatient healthcare settings.

For pragmatic reasons, we examined the predictive value of clinic F_{ENO} measurements but were unable to account for factors which may have affected these, including eosinophilic chronic rhinosinusitis [31], ICS adherence [32] and recent allergen exposure [33]. In addition, did not have sufficient data to examine F_{ENO} measurement process or device as a potential confounder, as only two studies used Sievers rather

than Aerocrine analysers [20, 21] and only three participants across these two studies had one or more exacerbations. All except one study [24] excluded patients with recent exacerbations. Data on other risk factors, such as seasonal exacerbation patterns [34, 35], raised blood eosinophil counts [36] and duration of symptom stability before reducing medication [37] were not available.

We chose a 12-week follow-up period based on guidelines for identifying patients in whom ICS reductions should be considered [7]. While extending this period may have provided a more complete reflection of asthma stability, this may also have resulted in inclusion of later exacerbations due to reasons unrelated to reducing ICS, for example acute respiratory tract infections [38] or poor medication adherence [39]. Additionally, most exacerbations in asthma symptoms occur within 28 days of reducing ICS [40, 41]. We did not examine the value of F_{ENO} in predicting single *versus* multiple exacerbations, as UK primary care data suggest that only 3–5% of asthma patients experience multiple exacerbations over a 1-year period [36, 42].

The findings of our subgroup and *post hoc* analyses should be interpreted with caution. Due to low numbers of acute exacerbations observed in the groups analysed, only crude odds ratios could be calculated; the 95% confidence intervals associated with these were too wide to be able to draw robust conclusions about their clinical importance. Furthermore, we were unable to estimate pooled sensitivities and specificities in relation to specific F_{ENO} thresholds because one study had no exacerbation events [20].

Implications of findings for clinical practice and future research

Our findings provide evidence to support safe gradual ICS reductions in nonsmoking patients with well-controlled mild-to-moderate asthma if F_{ENO} is <50 ppb. However, successful maintenance of these reductions should also address broader patient-level factors, including chronic upper airway complications and medication adherence [43], and involve ongoing monitoring of F_{ENO} levels before further reductions are considered.

Future research should aim to validate our findings using longer follow-up periods and larger populations, which will allow more robust evaluation of the predictive value of F_{ENO} in relevant subgroups. In particular, RCT evidence is needed to compare the safety and effectiveness of different F_{ENO} decision thresholds and ICS dose reduction strategies. More research is also needed to determine the value of F_{ENO} in predicting single *versus* multiple exacerbations, as well as the predictive value of follow-up F_{ENO} measurements. Variability in F_{ENO} is reported around the time of exacerbations [44]. F_{ENO} at 4 weeks after withdrawing ICS is also reported to be a strong predictor of deterioration in exacerbation frequency [45].

The predictive value of F_{ENO} alongside other biomarkers of airway inflammation should also be investigated. Concurrently raised F_{ENO} and blood eosinophil counts are associated with increased exacerbation risk in adults with asthma [46]. Conversely, low peak expiratory flow rate variability, high serum IL-10 and low serum IL-33 are reported as significant predictors of good symptomatic control in adults with asthma following a 50% reduction in ICS [47].

Conclusions

Clinicians may consider gradual reduction of ICS in nonsmoking, well-controlled, mild-to-moderate asthma patients whose F_{ENO} is <50 ppb on existing treatment. Future research should aim to prospectively validate these findings in larger study populations and explore ways of enhancing the value of F_{ENO} in predicting future exacerbations.

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