Does treatment guided by exhaled nitric oxide fraction improve outcomes in subgroups of children with asthma?

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Some children with asthma may have better outcomes than others if their treatment is guided by exhaled nitric oxide <http://bit.ly/2VahxJV>

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ABSTRACT

Introduction: Exhaled nitric oxide fraction (F_{ENO}), a biomarker of eosinophilic airway inflammation, may be useful to guide asthma treatment. F_{ENO} -guided treatment may be more effective in certain subgroups for improving asthma outcomes compared to standard treatment.

Methods: An individual patient data analysis was performed using data from seven randomised clinical trials (RCTs) which used F_{ENO} to guide asthma treatment. The incidence of an asthma exacerbation and loss of control, and the time to first exacerbation and loss of control were described between five subgroups of RCT participants.

Results: Data were available in 1112 RCT participants. Among those not treated with leukotriene receptor antagonists (LTRA), but not among those who were treated with LTRA, F_{ENO} -guided treatment was associated with reduced exacerbation risk (OR 0.68, 95% CI 0.49–0.94), longer time to first exacerbation (hazard ratio (HR) 0.76, 95% CI 0.57–0.99) and borderline reduced risk for loss of control (OR 0.70, 95% CI 0.49–1.00). Nonobese children, compared to obese children, were less likely to lose asthma control when treatment was guided by F_{ENO} (OR 0.69, 95% CI 0.48–0.99) and time to loss of control was longer (HR 0.77, 95% CI 0.61–0.99).

Conclusions: Asthma treatment guided by F_{ENO} may be more effective in achieving better asthma outcomes for patients who are not treated with LTRA and who are not obese, compared to standard practice.

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Introduction

Asthma is a common chronic condition which affects 1 million children in the UK [1], 6 million children in the US [2] and 235 million children and adults around the world [3]. There is effective treatment to control asthma symptoms and guidelines recommend that treatment should be titrated to asthma symptoms [4–6]. There remains a widely accepted recognition that an objective measurement to guide asthma treatment is required [7].

Exhaled nitric oxide (F_{ENO}) has many of the characteristics required of an objective tool to measure asthma symptoms. For example, F_{ENO} rises before symptoms occur [8, 9], falls when asthma treatment is administered [10, 11], can be measured with minimal discomfort to the patient and results are available within a few minutes using commercially available apparatus [12]. A meta-analysis including eight clinical trials in children and young adults found that addition of F_{ENO} measurements to symptom-guided treatment did not reduce asthma symptoms [13], but that F_{ENO} guided treatment reduced asthma exacerbations [13].

Asthma is a heterogeneous condition and what we do not know is whether there are patient subgroups in whom using F_{ENO} to guide asthma treatment may be beneficial [7]. In one randomised controlled trial (RCT), the intervention was more effective in participants who had more positive skin tests and who were obese, but age, sex, asthma severity and initial F_{ENO} concentration were not associated with a different outcome from the intervention [14]. In a second RCT there was no evidence of improved outcomes between individuals who were concordant or discordant for F_{ENO} and symptoms [15].

Our group has pooled the data collected from seven of the eight published RCTs where the efficacy of F_{ENO} used to guide asthma treatment was examined, compared to standard management [16]. Here we use data from 1112 participants to test the hypothesis that there are particular subgroups of patients where F_{ENO} -guided treatment is more effective in improving asthma outcomes compared to standard treatment.

Methods

Study design

Authors of all published RCTs where measurements of F_{ENO} were used to guide asthma treatment in children [17] were contacted and asked to provide data, as described previously [16]. The children who took part in the studies were recruited from hospital clinics and were followed-up for between 6 and 12 months. The primary outcome was the presence of any asthma exacerbation during follow-up [13]. Secondary outcomes were loss of control among those who were initially controlled and time to first exacerbation and time to first loss of control. Institutional ethical approval was provided for each trial which contributed data.

Details of each population

FRITSCH *et al.* [18] undertook a study of 47 children with asthma attending a hospital asthma clinic in Vienna (Austria) and collected data (including F_{ENO} , asthma symptom score and history of recent exacerbations) at 6-week intervals over 6 months. PEIRSMAN *et al.* [19] recruited 99 participants with persistent asthma attending hospital asthma clinics across Belgium and collected data at 3-month intervals over 12 months. PETSKEY *et al.* [20] recruited 63 children from hospital clinics in Australia and Hong Kong, and data were collected on eight occasions over 12 months (at 1, 2, 3, 4, 6, 8, 10 and 12 months). PIJNENBURG *et al.* [21] included 86 participants attending a single hospital clinic in the Netherlands and data were collected at baseline, 3, 6, 9 and 12 months. PIKE *et al.* [22] recruited 90 participants in clinics in four UK hospitals and collected data at 2-month intervals over a year. SZEFLER *et al.* [14] recruited 546 participants from the community in the USA and collected post-randomisation information over 46 weeks including at 3 months, 6 months, 8 months and 10 months. VOOREND-VAN BERGEN *et al.* [23] undertook a study of 181 participants attending hospital clinics in the Netherlands and collected data at 4-month intervals over a year. The treatment algorithms in F_{ENO} -guided and standard-practice arms in each RCT were different to other RCTs (table 1).

Data collected

Covariates collected at baseline in all trials included age, sex, height, weight, treatment arm, dose of inhaled corticosteroid (ICS, as daily budesonide equivalent dose), prescribed long-acting β -agonist (LABA) or not, prescribed leukotriene receptor agonist (LTRA) or not, and an asthma control score. Ethnicity was available in four cohorts [14, 21–23]. Body mass index (BMI) was derived and International Obesity Task Force weight categories created [28]; obesity is defined as equivalent to adult BMI $\geq 30 \text{ kg}\cdot\text{m}^{-2}$. Forced expiratory volume in 1 s (FEV_1) (% predicted) was calculated according to the Global Lung Initiative standard [29], apart from in two trials [21, 22] in which only percentage FEV_1 standardised to other references was available. F_{ENO} was measured in all studies in accordance with the 2005 guideline [30]. At

TABLE 1 A summary of characteristics of the randomised controlled trials whose data were used for the present analysis

First author, year [ref.] country	Age years	Inclusion criteria (in addition to child diagnosed with asthma)	Definition of asthma control	Treatment strategy		Treatment options (same for both groups in all studies)	What did the trial find? (F_{ENO} treatment compared to standard care)
				Intervention group	Control group		
FRITSCH, 2006 [18] Austria	11.5±3.1	Age 6–18 years Sensitised to inhaled allergens No systemic corticosteroids 1 month before recruitment	FEV ₁ >80% pred, <6 doses of SABA over 14 days and no or mild symptoms	Step up if control lost regardless of F_{ENO} Step down if controlled and $F_{ENO} \leq 20$ ppb If $F_{ENO} > 20$ ppb and controlled, step up, unless already on ICS (in which case no change)	Step up if either FEV ₁ <80% pred or symptoms severe or ≥ 6 doses of SABA over previous 14 days Step down if controlled	Four treatment steps	Higher mid-expiratory flow, higher dose of ICS
PEIRSMAN, 2014 [19] Belgium	10.7±2.1	Sensitised to inhaled allergens No exacerbation or systemic corticosteroids 3 months before recruitment	A score of ≤ 3 from the first four (of seven) questions on ACT, FEV ₁ >80% and ≤ 2 doses of SABA over a week	Step up if $F_{ENO} > 20$ ppb regardless of control Consider stepping up if $F_{ENO} \leq 20$ ppb and partly/fully uncontrolled Step down if controlled and $F_{ENO} \leq 20$ ppb	Step up if uncontrolled, consider stepping up if partly controlled Step down if controlled	Step up and down options if on the following preventers: ICS alone; LTRA alone; ICS + LABA; ICS + LTRA	Reduced exacerbations, increased LTRA and ICS dose No difference in primary outcome
PETSKY, 2015 [20] Australia	10.0±3.2	Age >4 years Prescribed asthma preventer Adherent to treatment	Symptom score [#] no more than 15% higher than previous assessment (only used for the control group)	Step up or down based only on $F_{ENO} > 10$ or ≤ 10 ppb if nonatopic, >12 or ≤ 12 ppb with 1 positive skin test, >20 or ≤ 20 for >1 positive skin test	Step up if symptoms score >15% higher than previously Step down if symptoms score <10	Seven steps (none including LTRA)	Reduced exacerbation, increased ICS dose
PIJNENBURG, 2005 [21] The Netherlands	12.3±2.8	Age 6–18 years Sensitised to inhaled allergens ICS dose unchanged for ≥ 3 months at recruitment	Score of >14 on validated symptom diary [†]	Step up if $F_{ENO} > 30$ ppb regardless of control Treatment stepped down if symptoms controlled and $F_{ENO} \leq 30$ ppb No change if symptoms not controlled but $F_{ENO} \leq 30$ ppb	Step up if symptoms uncontrolled Step down if controlled for second assessment No change if controlled on first assessment	Nine steps (none including LABA or LTRA)	Reduced F_{ENO} and bronchial hyperresponsiveness No increase in ICS dose
PIKE, 2013 [22] UK	11.9±2.6	Age 6–17 years Prescribed ≥ 400 µg ICS daily (budesonide equivalent) Adherent to treatment No history of life-threatening asthma or requiring maintenance oral corticosteroids	Modified validated symptom diary ⁺ , FEV ₁ $\geq 80\%$ and <1 SABA dose per week	Step up ICS if $F_{ENO} \geq 25$ ppb (or more than twice baseline value) regardless of control or FEV ₁ Step up with LABA if poorly controlled and $F_{ENO} < 25$ ppb Step down if $F_{ENO} \leq 15$ ppb and controlled on two consecutive assessments	Step up if uncontrolled Step down if controlled on two consecutive assessments	Eight treatment steps	No differences in outcomes

Continued

TABLE 1 Continued

First author, year [ref.] country	Age years	Inclusion criteria (in addition to child diagnosed with asthma)	Definition of asthma control	Treatment strategy		Treatment options (same for both groups in all studies)	What did the trial find? (F_{ENO} treatment compared to standard care)
				Intervention group	Control group		
SZEFLER, 2008 [14] USA	14.4±2.1	Age 12–20 years Living in community where ≥20% households were below poverty threshold Persistent or uncontrolled asthma if on long-term preventer Nonsmoker	Four levels of control depending on a symptom score (ACT) and a series of FEV ₁ , cut offs (FEV ₁ ≥80% pred, 70–79% pred or >70% pred)	Step up by one, two or three treatment levels depending on symptoms score, FEV ₁ and F_{ENO} 0–20, 20.1–30, 30.1–40 or >40 ppb Step down if controlled on two consecutive assessments and F_{ENO} ≤20 ppb	Step up by one, two or three treatment levels depending on symptoms score and FEV ₁ Step down if controlled on two consecutive assessments	Seven treatment steps (including low-dose theophylline)	Reduced exacerbations, increased ICS dose No difference in primary outcome
VOOREND-VAN BERGEN, 2010 [23] The Netherlands	10.2±3.0	Age 4–18 years Sensitised to inhaled allergens >9% bronchodilator response Prescribed ICS for ≥3 months Nonsmoker No history of multiple ICU admissions for asthma	ACT score ≥20	Step up if controlled and F_{ENO} ≥50 ppb or uncontrolled and F_{ENO} ≥25 ppb Step down if controlled and F_{ENO} <25 ppb Otherwise no change	Step up if uncontrolled Step down/no change if controlled	Seven treatment steps	Increased asthma control No difference in outcomes

F_{ENO} : exhaled nitric oxide fraction; FEV₁: forced expiratory volume in 1 s; % pred: % predicted; SABA: short-acting β-agonist; ICS: inhaled corticosteroids; ACT: Asthma Control Test [24]; LTRA: leukotriene receptor antagonist; LABA: long-acting β-agonist; ICU: intensive care unit. #: [25]; †: [26]; *: [27].

each follow-up visit an assessment of asthma control was made (table 1) and history of any asthma attack since the previous assessment was recorded (defined as receipt of oral corticosteroids for an asthma exacerbation [16]). The trials used different symptom score methodology and loss of control was defined as per trial protocol by reaching a pre-agreed symptom score.

Analysis

Asthma outcomes were compared between participants in the F_{ENO} -guided and standard treatment arms of RCTs for the following five subgroups defined at baseline and previously associated with differences in F_{ENO} . The five subgroups were stratified by dose of ICS (≤ 400 μ g budesonide equivalent or >400 μ g) [10], use of LTRA [31], obesity [14], ethnicity (white *versus* other) [32] and atopic (*i.e.* positive skin-prick test or positive type-specific IgE) [14]. Any exacerbation during follow-up and time to first exacerbation and any loss of control and time to loss of control were calculated (the latter restricted to those who were controlled at baseline). Time to first exacerbation or to loss of control was determined using data collected at the scheduled study assessments, and supplementary table S1 describes the time in weeks between baseline and each follow-up assessment in each RCT. For example, if a participant experienced an exacerbation after their 3-month assessment but before the 6-month assessment, time was censored at 6 months. Logistic regression was used to relate any exacerbation or any loss of control to an interaction term between each baseline characteristic and treatment arm; a significant interaction term ($p < 0.05$) would indicate that outcomes were different between F_{ENO} -guided and standard treatment for a subgroup. Cox proportional hazards models were used to investigate time to first exacerbation or time to first loss of control. Each subgroup was considered separately and all models included adjustment for covariates associated with the outcome, including age, a variable for each RCT and ICS dose at baseline (this was not included in the ICS-dose subgroup model). Standard statistical software was used (Stata version 14; StataCorp, College Station, TX, USA) and significance was assumed at 5%. All analyses were exploratory, so no adjustment was made for multiple comparisons.

Results

Study subjects

Data from seven RCTs were analysed [14, 18–23], totalling 1112 participants. Characteristics of participants at baseline have been described previously [16] and are presented in table 2. The majority of participants (58%) were male and the mean $\pm$ SD age was 12.6 ± 3.1 years. Characteristics of participants in the five subgroups are presented in supplementary table S2, *i.e.* LTRA treatment (yes/no), ICS dose ≤ 400 μ g/ >400 μ g, obese (yes/no), atopic (yes/no) and white *versus* other ethnic group.

F_{ENO} intervention and asthma exacerbation outcomes

Any exacerbation

Of the 1047 participants for whom exacerbation data were available, 296 (28%) had at least one exacerbation, with the first occurring after a median (interquartile range (IQR)) 22 (14–38) weeks. Table 3 shows the effect of treatment group was different for the two LTRA subgroups (interaction p -value 0.039). Those not treated with LTRA had lower odds for one or more exacerbations in the F_{ENO} -guided group compared to standard care (OR 0.68, 95% CI 0.49–0.94), but there was no difference observed between F_{ENO} -guided and control groups for those on LTRA (table 3). The number needed to treat with F_{ENO} -guided management to prevent one exacerbation among those not treated with LTRA was 15. Interactions between treatment arm and other baseline characteristics (ICS dose, obesity, atopy and white ethnicity) were not significant when predicting exacerbation (table 3).

Time to first exacerbation

Overall, the median (IQR) time to first exacerbation was 22 (14–38) weeks in the standard arm and 22 (13–34) weeks in the F_{ENO} -guided arm. The interaction term between treatment arm and LTRA was of borderline significance for time to first exacerbation ($p = 0.049$), and among those not treated with LTRA at baseline, the time to first asthma exacerbation was slightly longer for participants receiving F_{ENO} -guided treatment compared to standard care (hazard ratio (HR) 0.76, 95% CI 0.57–0.99; $p = 0.048$) (table 4 and figure 1). Time to first exacerbation was no different between treatment groups for those treated with LTRA. The interaction terms with treatment arm were not significant for ICS dose, atopy, obesity or ethnicity (table 4).

F_{ENO} intervention and asthma control outcomes

Any loss of asthma control

There were 787 participants who were controlled at baseline; 336 (43%) remained controlled until completion of the trial, 344 (44%) lost control and 107 (14%) were lost to follow-up for this outcome. The median (IQR) time to loss of control in these 344 patients was 22 (13–30) weeks. There was no difference

TABLE 2 Characteristics of study participants at the baseline visit in each study

	FRICTSCH [18]	PEIRSMAN [19]	PETSKY [20]	PIJNENBURG [21]	PIKE [22]	SZEFLER [14]	VOOREND-VAN BERGEN [23]	All populations combined
Participants n	47	99	63	86	90	546	181	1112
Male % (n)	60 [28]	67 [66]	49 [31]	65 [56]	57 [51]	53 [288]	68 [123]	58 [643]
Age years	11.5±3.1	10.7±2.1	10.0±3.2	12.3±2.8	10.9±2.6	14.4±2.1	10.2±3.0	12.6±3.1
F_{ENO} ppb	34 [18.6–58.6] n=46	31 [14–69] n=49	26 [12.2–47.5] n=61	32 [16.6–52.5] n=86	26 [10–48] n=90	20 [11.2–40.6] n=546	18 [10.2–30.4] n=179	22 [11.6–43.0] n=1057
FEV₁ % pred	93.5±15.7 n=47	91.4±15.7 n=98	90.7±15.6 n=54	97.5±17.5 n=86	89.2±14.3 n=90	90.9±16.6 n=546	93.8±13.0 n=157	93.5±18.1 n=1078
Atopic	100	100	38 [24/63]	100	76 [68/90]	88 [467/531]	100	89 [972/1097]
Obese	8 [4/47]	1 [1/99]	2 [1/58]	4 [4/85]	8 [7/89]	31 [165/526]	3 [5/181]	17 [187/1085]
LTRA	28 [13/47]	60 [59/99]	10 [6/58]	0 [0/86]	51 [46/90]	15 [80/546]	13 [23/181]	21 [227/1107]
LABA	38 [18/47]	32 [32/99]	67 [39/58]	38 [33/86]	76 [68/90]	66 [360/546]	46 [84/181]	57 [634/1107]
ICS dose µg	400 [0–800]	320 [200–400]	400 [250–500]	800 [400–1000]	800 [400–1000]	1000 [400–2000]	400 [400–800]	400 [400–1000]
>400 µg BUD	30 [14/47]	15 [15/99]	49 [31/63]	66 [57/86]	59 [53/90]	53 [287/546]	33 [59/181]	46 [516/1112]
White ethnic group	Not stated	82 [69/84]	Not stated	Not stated	92 [83/90]	0 [0/526]	89 [160/179]	35 [312/901]
Control status								
Controlled	49 [23/47]	75 [49/65]	72 [41/57]	57 [44/77]	97 [87/90]	80 [421/528]	67 [122/181]	75 [787/1045]
Not controlled	51 [24/47]	25 [16/65]	28 [16/57]	43 [33/77]	3 [3/90]	20 [107/528]	33 [59/181]	24 [258/1045]

Data are presented as mean±SD, median (interquartile range) or % (n/N), unless otherwise stated. F_{ENO}: exhaled nitric oxide fraction; FEV₁: forced expiratory volume in 1 s; % pred: % predicted; LTRA: leukotriene receptor antagonist; LABA: long-acting β-agonist; ICS: inhaled corticosteroid; BUD: budesonide-equivalent ICS.

TABLE 3 Proportion of individuals with any asthma exacerbation in exhaled nitric oxide fraction (F_{ENO})-guided and standard management arms of clinical trials with stratification for baseline patient characteristics

	≥ 1 exacerbation in each treatment arm		F_{ENO} versus standard	p-value for interaction [#]
	F_{ENO} -guided management	Standard management		
LTRA treatment				
Yes	49/109 [45]	40/104 [38]	1.46 [0.76–2.79]	0.039
No	88/410 [21]	119/419 [28]	0.68 [0.49–0.94]	
ICS dose				
≤ 400 μg BUD	48/289 [17]	58/279 [21]	0.72 [0.46–1.11]	0.493
> 400 μg BUD	89/232 [38]	101/247 [41]	0.88 [0.60–1.28]	
Obese[¶]				
Yes	30/88 [34]	36/81 [44]	0.63 [0.33–1.21]	0.342
No	107/425 [25]	119/433 [27]	0.90 [0.65–1.24]	
Atopic				
Yes	113/458 [25]	138/481 [29]	0.83 [0.61–1.13]	0.391
No	14/47 [30]	13/31 [42]	0.53 [0.20–1.41]	
Ethnic group				
White	34/148 [23]	31/164 [17]	1.28 [0.70–2.33]	0.177
Non-white	86/270 [32]	97/254 [38]	0.78 [0.54–1.14]	

Data are presented as n/N [%] or OR [95% CI], unless otherwise stated. LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; BUD: budesonide equivalent. [#]: adjusted for randomised controlled trial population, age and (except the analysis for higher versus lower ICS dose) dose of ICS (budesonide equivalent); [¶]: defined by International Obesity Task Force criteria.

in mean $\pm$ SD age between those who did and did not lose control (12.8 $\pm$ 3.0 and 12.6 $\pm$ 2.9 years, respectively) and no difference in baseline ICS dose (median (IQR) 400 (400–1000) μg for both those who did and did not lose control). The interaction terms between treatment arm and the five baseline participant characteristics for loss of asthma control were nonsignificant (supplementary table S3).

TABLE 4 Results from Cox regression models[#] analysing time to first exacerbation for subgroups of participants

	Time to first exacerbation for participants where treatment was guided by F_{ENO} compared to standard care		Interaction p-value
	HR (95% CI)	p-value	
LTRA treatment			
Yes	0.76 [0.57–0.99]	0.048	0.049
No	1.26 [0.82–1.90]	0.292	
ICS dose			
≤ 400 μg BUD	0.76 [0.52–1.12]	0.166	0.393
> 400 μg BUD	0.94 [0.71–1.25]	0.667	
Obese			
Yes	0.96 [0.74–1.25]	0.787	0.456
No	0.78 [0.48–1.27]	0.321	
Atopic			
Yes	0.61 [0.29–1.31]	0.207	0.347
No	0.90 [0.70–1.16]	0.412	
Ethnic group			
White	1.24 [0.76–2.02]	0.391	0.268
Non-white	0.90 [0.67–1.20]	0.469	

F_{ENO} : exhaled nitric oxide fraction; HR: hazard ratio; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; BUD: budesonide equivalent. [#]: these models are fitted as time = subgroup + treatment group + subgroup * treatment + age + study ID + baseline ICS. Baseline ICS was not included in the model where outcomes between ICS subgroups were analysed.

FIGURE 1 Kaplan-Meier curves showing time to first exacerbation for patients whose asthma treatment was guided by either exhaled nitric oxide fraction (F_{ENO}) or by symptoms only (standard) and stratified by leukotriene receptor antagonist (LTRA) treatment. a) Patients not treated with LTRA; b) patients treated with LTRA. The difference between treatment arms was significant for those not treated with LTRA ($p=0.048$), but not for the patients treated with LTRA ($p=0.292$).

However, there was an indication of reduced odds of loss of control in the F_{ENO} arm *versus* standard arm in those subgroups of participants who were not on LTRA at baseline, and in those who were not obese at baseline (supplementary table S3). The number of controlled participants needed to treat with F_{ENO} guided management to prevent one losing control among those not treated with LTRA was 11.

Time to loss of control

Within the subgroup who lost control ($n=344$) the median (IQR) time to loss of control was 17 (13–30) weeks with standard treatment and 22 (13–34) weeks with F_{ENO} -guided treatment. The interaction terms with treatment arm were not significant for ICS dose $\leq 400 \mu\text{g}$ *versus* $>400 \mu\text{g}$, atopy, LTRA treatment, white *versus* other race or obesity (yes or no) (table 5). There was borderline evidence of a longer time to first loss of control for F_{ENO} -guided compared to standard treatment within subgroups who were not treated with LTRA (HR 0.77, 95% CI 0.60–0.99) (figure 2), nonobese (HR 0.77, 95% CI 0.61–0.99) (figure 3) and atopic (HR 0.80, 95% CI 0.63–1.00) (table 5 and supplementary figure S1).

TABLE 5 Results from Cox regression models[#] analysing time to first loss of control for subgroups of participants, all of whom were controlled at baseline

	Time to first exacerbation for participants where treatment was guided by F_{ENO} compared to standard care		Interaction p-value
	HR (95% CI)	p-value	
LTRA treatment			
Yes	0.77 [0.60–0.99]	0.038	0.230
No	1.05 [0.68–1.64]	0.822	
ICS dose			
$\leq 400 \mu\text{g}$ BUD	0.82 [0.62–1.10]	0.182	0.899
$>400 \mu\text{g}$ BUD	0.84 [0.62–1.16]	0.293	
Obese			
Yes	0.77 [0.61–0.99]	0.042	0.130
No	1.15 [0.73–1.81]	0.538	
Atopic			
Yes	1.29 [0.54–3.08]	0.566	0.293
No	0.80 [0.63–1.00]	0.050	
Ethnic group			
White	0.85 [0.58–1.24]	0.396	0.970
Non-white	0.85 [0.64–1.14]	0.289	

F_{ENO} : exhaled nitric oxide fraction; HR: hazard ratio; LTRA: leukotriene receptor antagonist; ICS: inhaled corticosteroids; BUD: budesonide equivalent. [#]: these models are fitted as time = subgroup + treatment group + subgroup * treatment + age + study ID + baseline ICS. Baseline ICS was not included in the model where outcomes between ICS subgroups were analysed.

FIGURE 2 Kaplan-Meier curves showing time to loss of control for patients who were initially controlled and whose asthma treatment was guided by either exhaled nitric oxide fraction (F_{ENO}) or by symptoms only (standard) and stratified by leukotriene receptor antagonist (LTRA) treatment. a) Patients not treated with LTRA; b) patients treated with LTRA. The difference between treatment arms was significant for those not treated with LTRA ($p=0.038$), but not for the patients treated with LTRA ($p=0.822$).

FIGURE 3 Kaplan-Meier curves showing time to loss of control for patients who were initially controlled and whose asthma treatment was guided by either exhaled nitric oxide fraction (F_{ENO}) or by symptoms only (standard) and stratified by obesity status. a) Nonobese patients; b) obese patients. The difference between treatment arms was significant for those who were not obese ($p=0.042$), but not for the patients who were obese ($p=0.538$).

Discussion

We analysed data collected in seven RCTs to test the hypothesis that there are subgroups of patients in whom F_{ENO} -guided treatment is more effective in improving asthma outcomes compared to standard treatment. The main finding was that within these RCTs, the odds for exacerbation and loss of control for those not treated with LTRA were 32% and 30% lower, respectively, in the F_{ENO} -guided arm compared to standard treatment. The significant interaction term for LTRA treatment and treatment for exacerbation indicated that F_{ENO} -driven management may have reduced exacerbations for those not treated with LTRA, but not among those treated with LTRA. A second finding was that outcomes were no different between groups stratified by ICS dose or ethnic group. Collectively, these findings support the hypothesis that F_{ENO} is more useful for guiding treatment compared to standard practice in children with asthma not treated with LTRA.

A further finding was that in nonobese participants (but not in obese participants), F_{ENO} -guided treatment was associated with a 31% reduction in odds for loss of control compared to standard treatment and when control was lost, time to loss of control was longer. Although the interaction term for obesity and treatment for loss of control was not significant, we believe that the improved outcomes for nonobese children merits further consideration. There was consistency in our results (*i.e.* an association with any loss of control and time to loss of control) and also there is biological plausibility whereby asthma associated with obesity may be a separate non-eosinophilic phenotype, especially in females [33]. A systematic review found no evidence of increased or reduced asthma control among children who were obese [34], and asthma guidelines do not recommend different treatment approaches for obese patients with asthma [4–6]. Further research is required to clarify whether F_{ENO} -guided treatment is equally effective in obese and nonobese children.

Our observation that time to loss of control was longer among children who were atopic receiving F_{ENO} -guided treatment compared to standard treatment deserves careful consideration. The number of nonatopic participants included in our analysis was relatively small, since atopy was an inclusion criterion for four cohorts [18, 19, 21, 23] and the atopic subgroup were no more or less likely to have an exacerbation or to lose control within the trials. Since F_{ENO} is considered to be a surrogate for allergic or eosinophilic airway inflammation [35], it is biologically plausible that F_{ENO} -guided treatment algorithms are more likely to suppress airway inflammation and improve asthma control. Further evidence of biological plausibility comes from an RCT whose data are included in our analysis [14], which found fewer days with maximal symptoms among those with elevated IgE and multiple positive skin-prick tests. Although nonatopic asthma is less common than atopic asthma, *e.g.* present in 18% of participants in the three trials which did not include only atopic participants [14, 20, 22], asthma is a very common condition and there are ~150 000–200 000 nonatopic asthmatic children in the UK [1]. There is a need to establish whether treatment and monitoring for atopic and nonatopic children should be the same.

The magnitude of significantly reduced risk for exacerbations and loss of control in the intervention compared to standard treatment was typically 25–30%, and this difference is clinically meaningful since it is consistent with the benefit seen from commonly used asthma treatments such as LTRA and ICS. KNORR *et al.* [36] report a 23% reduced incidence of exacerbations in young children treated with montelukast compared to placebo. The review by CALPIN *et al.* [37] reports a 32% reduced risk for oral steroid treatment for exacerbations among children treated with ICS compared to placebo.

The RCTs included in our study applied different inclusion criteria, F_{ENO} -guided treatment algorithms and asthma control scores, and these methodological differences will weaken any relationship between the intervention and asthma outcomes. The seven RCTs did apply a standard definition of exacerbation and apparatus for measuring F_{ENO} . Despite the differences between RCTs, we still observed differences in outcomes between some of the subgroups studied, and it is likely that the magnitude of difference that we report in outcomes between the subgroups stratified by LTRA treatment, obesity and atopy may be an underestimate of the true value.

Our study was not designed to determine why F_{ENO} -guided treatment was associated with improved asthma outcomes among those not treated with LTRA compared to participants receiving LTRA treatment. Treatment with LTRA is known to reduce F_{ENO} by ~25% in children with atopic asthma [31] and may plausibly confound F_{ENO} -guided treatment, especially since the RCT treatment algorithms did not consider the effect of LTRA on F_{ENO} . There is an alternative explanation for the differences in exacerbation outcomes associated with LTRA treatment in different RCT arms; those treated with LTRA were younger and had more severe asthma (including higher ICS dose, needing LABA treatment and almost twice the exacerbation prevalence) and F_{ENO} -guided asthma treatment may be less effective in more severe asthma rather than in children receiving LTRA treatment *per se*. Given that LTRA are commonly used in asthma treatment, there is a need to study the impact of LTRA treatment on F_{ENO} -guided asthma treatment.

We observed that when data from the RCTs were combined, F_{ENO} -guided asthma treatment was associated with reduced risk for loss of control and time to loss of control among nonobese children. This contrasts with the findings of an RCT whose data are included in the present analysis [14], which reported fewer symptoms among obese participants (*i.e.* BMI >30 kg·m⁻²) receiving F_{ENO} -guided treatment. This apparent inconsistency may be due to several factors. First, the outcome in the study by SZEFLER *et al.* [14] was days of maximal symptoms, but this variable was not available in all the RCTs included in the present article and therefore loss of control was the outcome analysed here. Second, participants were all of African American or Hispanic ethnic origin, on higher ICS dose and had a considerably higher obesity prevalence [14], and some or all of these difference characteristics could explain different outcomes compared to the remaining six RCT participants. In our study, the reduced odds for loss of control and time to loss of control for nonobese children receiving F_{ENO} -guided treatment compared to standard treatment is likely to be underestimated due to inclusion of F_{ENO} and asthma control data from the RCT of SZEFLER *et al.* [14].

There are some limitations to our study. First, the time to loss of control or first exacerbation was restricted to the predetermined assessment periods and this lack of precision will weaken the reported differences in these outcomes between subgroups. Second, the RCTs had different study designs with different step-up/step-down criteria and management regimes. Third, ethnicity data was only available for four of the seven RCTs and was therefore not included as a covariate in the models, but ideally we would have included ethnicity in our model since ethnicity was associated with differences between the other subgroups analysed (supplementary table S2). Fourth, ideally we would have performed a sensitivity analysis by excluding participants in the RCT by SZEFLER *et al.* [14], since their characteristics were

different to the remaining RCTs for age, ethnicity and obesity, but this would have resulted in a 50% smaller sample size and the analysis would have been underpowered. A final limitation is that self-reported ICS adherence was available in only three RCTs included in our study [14, 22, 23], so we were not able to compare outcomes between treatment arms between adherent and nonadherent participants. Future research could test the hypothesis that asthma outcomes are improved by F_{ENO} -guided treatment in adherent compared to nonadherent patients.

In summary, we have used data from >1000 asthmatic children and report that F_{ENO} -guided treatment lead to better asthma outcomes among those not treated with LTRA.

Data availability: Data used in this study are available on request to the data custodians of the individual trials.

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References

- 1 Asthma UK. Asthma Facts and FAQs. www.asthma.org.uk/asthma-facts-and-statistics Date last accessed: August 31, 2017.
- 2 Centers for Disease Control and Prevention. Asthma: Most Recent Data. www.cdc.gov/asthma/most_recent_data.htm 2016 Date last accessed: August 31, 2017. Date last updated: March 25, 2019.
- 3 World Health Organization. Asthma. www.who.int/respiratory/asthma/en/ Date last accessed: December 7, 2018.
- 4 Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. <https://ginasthma.org/gina-reports/> Date last accessed: July 26, 2019.
- 5 British Thoracic Society and Scottish Intercollegiate Guidelines Network. SIGN 158. The British Guideline on the Management of Asthma. www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/ Date last accessed: July 27, 2019.
- 6 National Institute for Health and Care Excellence. Asthma: Diagnosis, Monitoring and Chronic Asthma Management. www.nice.org.uk/guidance/ng80 Date last accessed: January 28, 2018.
- 7 Pavord ID, Beasley R, Agusti A, *et al.* After asthma: redefining airways diseases. *Lancet* 2018; 391: 350–400.
- 8 Pijnenburg MW, Hofhuis W, Hop WC, *et al.* Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. *Thorax* 2005; 60: 215–218.
- 9 Zacharasiewicz A, Wilson N, Lex C, *et al.* Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med* 2005; 171: 1077–1082.
- 10 Beck-Ripp J, Griesse M, Arenz S, *et al.* Changes of exhaled nitric oxide during steroid treatment of childhood asthma. *Eur Respir J* 2002; 19: 1015–1019.
- 11 Baraldi E, Azzolin NM, Zanconato S, *et al.* Corticosteroids decrease exhaled nitric oxide in children with acute asthma. *J Pediatr* 1997; 131: 381–385.
- 12 Silkoff PE, Carlson M, Bourke T, *et al.* The Aerocrine exhaled nitric oxide monitoring system NIOX is cleared by the US Food and Drug Administration for monitoring therapy in asthma. *J Allergy Clin Immunol* 2004; 114: 1241–1256.
- 13 Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. *Cochrane Database Syst Rev* 2016; 11: CD011439.
- 14 Szeffler SJ, Mitchell H, Sorkness CA, *et al.* Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet* 2008; 372: 1065–1072.
- 15 Voorend-van Bergen S, Vaessen-Verberne AA, Landstra AM, *et al.* Fractional exhaled nitric oxide monitoring does not improve asthma management in children with concordant and discordant asthma phenotypes. *Am J Respir Crit Care Med* 2015; 192: 1016–1018.
- 16 Fielding S, Pijnenburg M, de Jongste JC, *et al.* Change in FEV₁ and F_{ENO} measurements as predictors of future asthma outcomes in children. *Chest* 2019; 155: 331–341.
- 17 Turner S. Exhaled nitric oxide and the management of childhood asthma – yet another promising biomarker “has been” or a misunderstood gem. *Paediatr Respir Rev* 2015; 16: 88–96.
- 18 Fritsch M, Uxa S, Horak FJ, *et al.* Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study. *Pediatr Pulmonol* 2006; 41: 855–862.
- 19 Peirsman EJ, Carvelli TJ, Hage PY, *et al.* Exhaled nitric oxide in childhood allergic asthma management: a randomised controlled trial. *Pediatr Pulmonol* 2014; 49: 624–631.
- 20 Petsky HL, Li AM, Au CT, *et al.* Management based on exhaled nitric oxide levels adjusted for atopy reduces asthma exacerbations in children: a dual centre randomized controlled trial. *Pediatr Pulmonol* 2015; 50: 535–543.
- 21 Pijnenburg MW, Bakker EM, Hop WC, *et al.* Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2005; 172: 831–836.
- 22 Pike K, Selby A, Price S, *et al.* Exhaled nitric oxide monitoring does not reduce exacerbation frequency or inhaled corticosteroid dose in paediatric asthma: a randomised controlled trial. *Clin Respir J* 2013; 7: 204–213.
- 23 Voorend-van Bergen S, Vaessen-Verberne AA, Brackel HJ, *et al.* Monitoring strategies in children with asthma: a randomised controlled trial. *Thorax* 2015; 70: 543–550.
- 24 Schatz M, Sorkness CA, Li JT, *et al.* Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006; 117: 549–556.

- 25 Santanello NC, Barber BL, Reiss TF, *et al.* Measurement characteristics of two asthma symptom diary scales for use in clinical trials. *Eur Respir J* 1997; 10: 646–651.
- 26 Verberne AA, Frost C, Roorda RJ, *et al.* One year treatment with salmeterol compared with beclomethasone in children with asthma. The Dutch Paediatric Asthma Study Group. *Am J Respir Crit Care Med* 1997; 156: 688–695.
- 27 Wasserfallen JB, Gold K, Schulman KA, *et al.* Development and validation of a rhinoconjunctivitis and asthma symptom score for use as an outcome measure in clinical trials. *J Allergy Clin Immunol* 1997; 100: 16–22.
- 28 Cole TJ, Bellizzi MC, Flegal KM, *et al.* Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000; 320: 1240–1243.
- 29 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
- 30 American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005; 171: 912–930.
- 31 Montuschi P, Mondino C, Koch P, *et al.* Effects of a leukotriene receptor antagonist on exhaled leukotriene E4 and prostanoids in children with asthma. *J Allergy Clin Immunol* 2006; 118: 347–353.
- 32 Koo S, Gupta A, Fainardi V, *et al.* Ethnic variation in response to IM triamcinolone in children with severe therapy-resistant asthma. *Chest* 2016; 149: 98–105.
- 33 Jensen ME, Gibson PG, Collins CE, *et al.* Airway and systemic inflammation in obese children with asthma. *Eur Respir J* 2013; 42: 1012–1019.
- 34 Ahmadizar F, Vijverberg SJH, Arets HGM, *et al.* Childhood obesity in relation to poor asthma control and exacerbation: a meta-analysis. *Eur Respir J* 2016; 48: 1063–1073.
- 35 Payne DN, Adcock IM, Wilson NM, *et al.* Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. *Am J Respir Crit Care Med* 2001; 164: 1376–1381.
- 36 Knorr B, Franchi LM, Bisgaard H, *et al.* Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. *Pediatrics* 2001; 108: E48.
- 37 Calpin C, Macarthur C, Stephens D, *et al.* Effectiveness of prophylactic inhaled steroids in childhood asthma: a systemic review of the literature. *J Allergy Clin Immunol* 1997; 100: 452–457.