

Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial

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Summary

Background Asthma exacerbations during pregnancy are common and can be associated with substantial maternal and fetal morbidity. Treatment decisions based on sputum eosinophil counts reduce exacerbations in non-pregnant women with asthma, but results with the fraction of exhaled nitric oxide ($F_{E}NO$) to guide management are equivocal. We tested the hypothesis that a management algorithm for asthma in pregnancy based on $F_{E}NO$ and symptoms would reduce asthma exacerbations.

Methods We undertook a double-blind, parallel-group, controlled trial in two antenatal clinics in Australia. 220 pregnant, non-smoking women with asthma were randomly assigned, by a computer-generated random number list, before 22 weeks' gestation to treatment adjustment at monthly visits by an algorithm using clinical symptoms (control group) or $F_{E}NO$ concentrations (active intervention group) used to uptitrate ($F_{E}NO > 29$ ppb) or downtitrate ($F_{E}NO < 16$ ppb) inhaled corticosteroid dose. Participants, caregivers, and outcome assessors were masked to group assignment. Longacting β_2 agonist and minimum dose inhaled corticosteroid were used to treat symptoms when $F_{E}NO$ was not increased. The primary outcome was total asthma exacerbations (moderate and severe). Analysis was by intention to treat. This study is registered with the Australian and New Zealand Clinical Trials Registry, number 12607000561482.

Findings 111 women were randomly assigned to the $F_{E}NO$ group (100 completed) and 109 to the control group (103 completed). The exacerbation rate was lower in the $F_{E}NO$ group than in the control group (0.288 vs 0.615 exacerbations per pregnancy; incidence rate ratio 0.496, 95% CI 0.325–0.755; $p=0.001$). The number needed to treat was 6. In the $F_{E}NO$ group, quality of life was improved (score on short form 12 mental summary was 56.9 [95% CI 50.2–59.3] in $F_{E}NO$ group vs 54.2 [46.1–57.6] in control group; $p=0.037$) and neonatal hospitalisations were reduced (eight [8%] vs 18 [17%]; $p=0.046$).

Interpretation Asthma exacerbations during pregnancy can be significantly reduced with a validated $F_{E}NO$ -based treatment algorithm.

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Introduction

Asthma is the most common chronic medical disorder to complicate pregnancy, and both mothers and health professionals expect asthma to be controlled with minimum drug exposure to the developing fetus.¹ Asthma exacerbations are frequent in pregnant women, even when the asthma is considered to be mild,² and can lead to low birthweight babies,² maternal distress, and increased health-care use.³

Maintenance treatment with inhaled corticosteroids can effectively reduce the frequency and severity of asthma exacerbations.^{4,5} Inhaled corticosteroid therapy is started and dose adjustments are made on the basis of measures of asthma control (the assessment of symptoms and lung function). Although inhaled corticosteroids treat airway inflammation, the relation between these measures of asthma control and airway inflammation is poor.⁶ However, when therapy is adjusted according to direct measures of airway inflammation, results improve.^{7–11}

Studies using the fraction of exhaled nitric oxide ($F_{E}NO$) to guide therapy have shown variable benefit,^{10–13} possibly

because of the complex design issues related to studies of asthma treatment algorithms.¹⁴ In the Managing Asthma in Pregnancy (MAP) study, we developed an improved $F_{E}NO$ -based treatment algorithm and tested its applicability for the adjustment of therapy for asthma during pregnancy. We tested the hypothesis that control of asthma in pregnancy would be improved when based on measures of $F_{E}NO$ compared with a clinical algorithm for the primary study outcome of asthma exacerbations.

Methods

Study design and participants

We undertook a double-blind, parallel, randomised controlled trial of $F_{E}NO$ -guided therapy in two antenatal clinics (John Hunter Hospital and Maitland Hospital; NSW, Australia) from June, 2007, to December, 2010. Non-smoking pregnant women (aged >18 years) with asthma attending the antenatal clinics were recruited between weeks 12 and 20 of gestation. Women had a doctor's diagnosis of asthma and were using inhaled therapy for asthma within the past year. The diagnosis



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was confirmed by a respiratory physician's diagnostic interview. Non-smoking status was validated by normal exhaled carbon monoxide (<10 ppm; piCO Smokerlyzer Breath CO Monitor, Bedford, UK), and urinary cotinine <level 5 (2840 nmol/L) (Nicalert: NYMOX, St-Laurent, QC, Canada). The study was approved by the Hunter New England and University of Newcastle ethics committees. All women provide written informed consent.

At visit 1 (baseline characterisation), F_eNO^{15} and spirometry were measured, and the asthma control questionnaire (ACQ) was administered. Atopy was defined as specific IgE to aeroallergen of 0.35 kUA/L or greater in venous blood. Asthma self-management skills including inhaler technique, knowledge, action plan, and adherence were assessed and optimised.¹⁶ Eligible women commenced a 2-week run-in period. Women using inhaled corticosteroids continued with their current dose, delivered as budesonide turbuhaler (Astra Zeneca, North Ryde, NSW, Australia), with dose equivalence determined from guidelines.¹ Women with uncontrolled asthma who were not using maintenance inhaled corticosteroids ($n=31$) were started on budesonide (200 µg twice per day).

At randomisation (visit 2), measurements included asthma symptoms, F_eNO , spirometry, ACQ score,¹⁷ and quality-of-life questionnaires.^{18,19} F_eNO was measured with online chemiluminescence analysers with 50 mL/s flow rate (ECOMEDICS, Duernten, Switzerland) according to published guidelines from the European Respiratory Society (ERS) and American Thoracic Society (ATS).¹⁵ Pregnancy has not been shown to change F_eNO .^{20–22}

Randomisation and masking

Eligible participants were randomly assigned before 22 weeks' gestation to a clinical guideline algorithm (control group) or an F_eNO algorithm to adjust therapy (active intervention group). A statistician used a computer-generated random number list for randomisation. Randomisation was computed in blocks of four with an equal treatment allocation ratio and stratified with maintenance budesonide dose at visit two (<800 µg per day or ≥800 µg per day). Allocation to treatment algorithm group was concealed from the participant, the research assistant, and investigators through the use of an algorithm keeper who was not directly involved in assessment or care of participants, but treatment with inhaled corticosteroids or longacting β₂ agonists was not masked. Investigators analysing outcomes were masked to group assignment.

Procedures

Women were reviewed monthly at the antenatal clinic until delivery. The research assistant collected data for the clinical symptoms, ACQ score, present treatment, F_eNO , and forced expiratory volume in 1 s (FEV₁). ACQ score, F_eNO concentration, and treatment were sent by facsimile to the algorithm keeper. This person applied the relevant algorithm, and sent the treatment recommendation to the research assistant in the antenatal clinic, who informed the participant. Participants were seen by the investigator in the antenatal clinic if their asthma was uncontrolled and they were at the maximum treatment level of the algorithm. Telephone assessments were done 2 weeks after each clinic visit to assess symptoms and to encourage drug adherence.

F_eNO algorithm

The F_eNO algorithm used a sequential process: first, the F_eNO concentration was used to adjust the dose of inhaled corticosteroids; and second, the ACQ score was used to adjust the dose of longacting β₂ agonist (table 1). The cutoff points for the F_eNO algorithm were derived from a prospective cohort study of asthma in pregnancy.²³ The cutoff used for dose reduction was 16 ppb, which was the upper 95% confidence limit of the mean F_eNO concentration in pregnant women with asthma that remained controlled (ACQ score <1.5) throughout pregnancy. It is also the cutoff that is associated with control of eosinophilic inflammation,²⁴ and at which reduction of inhaled corticosteroid dose is possible without compromising asthma control.^{25,26} The cutoff for dose increase was derived from pregnant asthmatic women with unstable eosinophilic asthma (ACQ score >1.5, F_eNO >16 ppb). In that group, the lower 95% CI for F_eNO was 29 ppb.

Table 2 shows the F_eNO algorithm treatment steps. Steroid-naïve patients who needed inhaled corticosteroids started with budesonide 100 µg twice per day.

	F_eNO concentration (ppb)	Symptoms (ACQ score)	ICS dose change	β ₂ -agonist dose change
Level 1	>29	NA	↑ ICS × 1 step	No change
Level 2	16–29	≤1.5	No change	No change
Level 3	16–29	>1.5	No change	↑ LABA × 1 step
Level 4	<16	≤1.5	↓ ICS × 1 step	No change
Level 5	<16	>1.5	↓ ICS × 1 step	↑ LABA × 1 step

F_eNO =fraction of exhaled nitric oxide. ACQ=asthma control questionnaire. ICS=inhaled corticosteroid. NA=not part of the assessment at this F_eNO level. LABA=longacting β₂ agonist.

Table 1: Dose changes based on F_eNO and ACQ results for the F_eNO intervention algorithm

	ICS step	β ₂ step
Step 1	0	Salbutamol as required
Step 2	Budesonide 100 µg twice per day	Formoterol 6 µg twice per day
Step 3	Budesonide 200 µg twice per day	Formoterol 12 µg twice per day
Step 4	Budesonide 400 µg twice per day	Formoterol 2 × 12 µg twice per day
Step 5	Budesonide 800 µg twice per day	Formoterol 2 × 12 µg twice per day

F_eNO =fraction of exhaled nitric oxide. ICS=inhaled corticosteroid.

Table 2: F_eNO algorithm treatment steps

If a participant had undergone two dose increments but the $F_{E}NO$ concentration remained greater than 29 ppb, the inhaled corticosteroid dose was not increased further. If such a participant was symptomatic (ACQ score >1.5), formoterol 6 μ g twice per day was added. When $F_{E}NO$ concentrations were between 16 ppb and 29 ppb, the inhaled corticosteroid dose was not changed (table 1; $F_{E}NO$ levels 2 and 3). Symptomatic patients (ACQ score >1.5) with $F_{E}NO$ in the range 16–29 ppb ($F_{E}NO$ level 3) were treated with an increase in the β_2 -agonist step, either with the addition of formoterol 6 μ g twice per day or an increase in formoterol dose (table 2; β_2 step). When $F_{E}NO$ concentrations were less than 16 ppb ($F_{E}NO$ levels 4 and 5), inhaled corticosteroid dose was reduced by 50% (inhaled corticosteroid step). If participants were simultaneously symptomatic, formoterol 6 μ g per day was added ($F_{E}NO$ level 5). For participants taking formoterol, the budesonide dose was not reduced to zero, but to 100 μ g twice per day. Participants who remained uncontrolled and were taking the maximum dose step (both inhaled corticosteroid and longacting β_2 agonist, $F_{E}NO$ treatment step 5) were assessed with subsequent treatment decided by the respiratory physician.

Clinical algorithm

The clinical algorithm was based on asthma control, which was assessed with the Juniper ACQ¹⁷ with cutoff points defined as: well controlled asthma (ACQ score <0.75), partially controlled asthma (0.75 – 1.50), and uncontrolled asthma (>1.5). After assessment of asthma control, a woman with uncontrolled asthma (table 3; clinical level 1) had her dose increased by one treatment step (table 4). Those with well controlled asthma (clinical level 3) had their inhaled corticosteroid dose reduced by one treatment step. The intermediate group represents partial loss of control, and no definite treatment change was undertaken. Participants who remained uncontrolled and were taking the maximum allowed dose (clinical treatment step 5) were assessed, and their subsequent treatment decided by the respiratory physician.

Study outcomes

The primary study outcome was total number of asthma exacerbations²⁷ (ie, moderate and severe exacerbations), which were defined as events for which the patient sought medical attention (an unscheduled visit to a doctor, presentation to the emergency room or admission to hospital, or when oral corticosteroids were used for treatment of asthma). Data for asthma exacerbation were collected at monthly visits, follow-up telephone calls, and by review of medical records. All exacerbations that occurred after randomisation were included. Exacerbation events separated by 7 days or more were counted as a second event. Additional reported outcome measures included quality of life,

asthma treatment, and fetal outcomes. Quality of life was assessed with validated generic (short form 12, version 1)¹⁹ and disease-specific (asthma quality of life questionnaire—Marks)¹⁸ questionnaires.

	ACQ score	Treatment adjustment
Level 1	>1.5	$\uparrow$ 1 step
Level 2	0.75 – 1.5	No change
Level 3	<0.75	$\downarrow$ 1 step

ACQ=asthma control questionnaire.

Table 3: Dose changes based on clinical assessment for the clinical algorithm (control)

	Treatment
Step 1	Salbutamol as required
Step 2	Budesonide 200 μ g twice per day
Step 3	Budesonide 400 μ g twice per day
Step 4	Budesonide 400 μ g and formoterol 12 μ g twice per day
Step 5	Budesonide 800 μ g and formoterol 24 μ g twice per day

Table 4: Clinical algorithm treatment steps

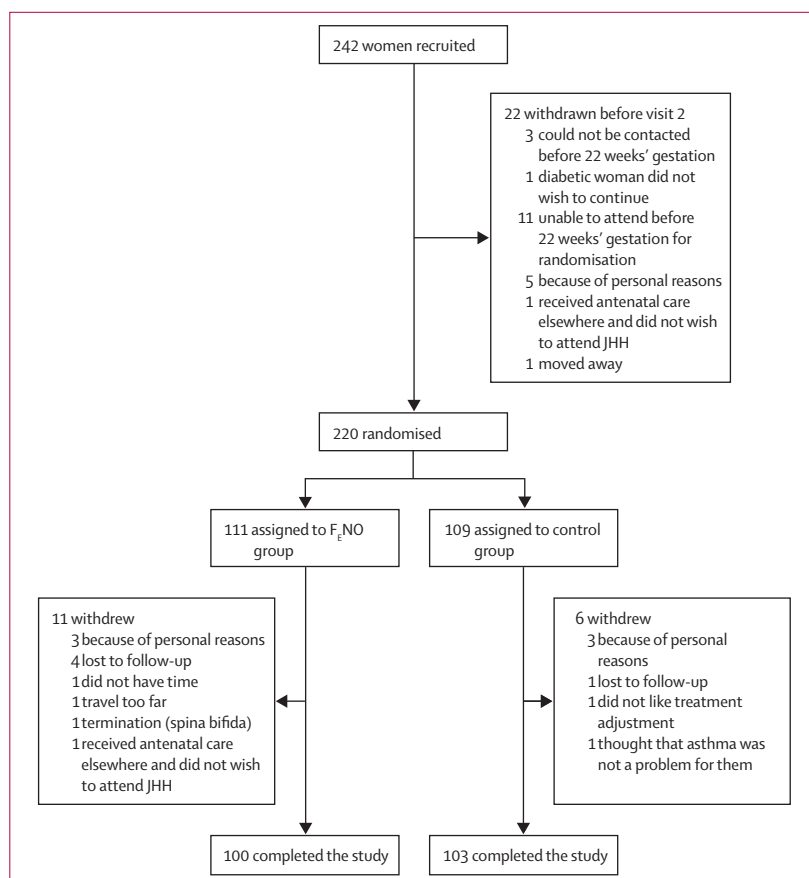


Figure 1: Trial profile

JHH=John Hunter Hospital. $F_{E}NO$ =fraction of exhaled nitric oxide.

Statistical analysis

Data were analysed on an intention-to-treat basis. All participants randomly assigned were included in the final analyses, with the final visit for those who dropped out counted as the end of study visit. Two-sided tests with *p* values less than 0·05 were regarded as significant. The exacerbation rate difference between the two groups was compared with a Poisson regression model. We analysed the time to first asthma exacerbation with Kaplan-Meier plots, with analysis of instantaneous risk described with a Cox proportional hazards model. The proportion of

participants with one or more exacerbations was compared with a χ^2 test.

ANCOVA was undertaken on quality-of-life variables at the end of the study, with adjustment for baseline values. Other continuous variables such as inhaled corticosteroid dose, β_2 -agonist use, and questionnaire results were analysed with a generalised linear mixed model (GLMM) with a random intercept for individuals to account for the repeated measurements on individuals. Student's *t* test and Wilcoxon rank tests were used for remaining variables at the end of the study. Sample size was calculated with power of 80%, and the type I error rate of 0·05. To detect a 40% reduction in the proportion of participants having an exacerbation from 55% to 33%, 176 women were needed and 210 randomly assigned to allow for a 20% dropout rate.

This study is registered with the Australian and New Zealand Clinical Trials Registry, number 12607000561482.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or

	Control group (n=109)	F _e NO group (n=111)
Demographic details		
Mean age ([95% CI]; years)	28·8 (27·72–29·84)	28·1 (27·12–29·09)
Atopy	77/101 (76·2%)	79/105 (75·2%)
Ex-smoker	39/97 (40·2%)	41/108 (37·9%)
Smoking history (pack-years)	3·4 (1·1–7·0)	3·0 (1·0–5·6)
Parity	1 (0–1)	1 (0–1)
Weight (kg)	78·4 (65·1–91·0)	78·2 (68·0–89·6)
BMI (kg/m ²)	28·7 (24·1–32·8)	27·9 (24·1–32·4)
Employed	72/103 (69·9%)	56/103 (54·4%)
Australian born	94/103 (91·3%)	96/103 (93·2%)
Quality of life		
n	105	106
SF12 physical summary score*	49·1 (42·0–53·4)	49·4 (43·4–52·8)
SF12 mental summary score*	53·3 (47·1–58·2)	56·0 (49·1–58·9)
AQLQ–M: total score†	1·0 (0·5–1·6)	0·8 (0·4–1·5)
Asthma history		
n	109	111
Mean number of ER visits in past 2 years (95% CI)	0·19 (0·09–0·30)	0·22 (0·01–0·42)
Mean number of hospital admissions in past 2 years (95% CI)	0·06 (0·004–0·12)	0·03 (–0·03–0·08)
Mean OCS use in past 2 years (95% CI)	0·43 (0·22–0·64)	0·28 (0·15–0·41)
Spirometry		
Mean FEV ₁ ([95% CI]; L)	3·06 (2·96–3·15)	3·05 (2·96–3·14)
Mean FEV ₁ ([95% CI]; %)	96·12% (93·49–98·73)	95·10% (92·76–97·44)
Mean FVC ([95% CI]; L)	3·80 (3·69–3·91)	3·84 (3·73–3·95)
Mean FEV ₁ /FVC ([95% CI]; %)	80·63% (79·30–81·96)	79·73% (75·43–78·03)
F _e NO (ppb)	13·1 (7·5–24·0)	13·9 (6·6–32·0)
Present treatment		
β_2 -agonist use in past week (days)	2 (0–6)	1 (0–5)
ICS	47/109 (43·1%)	46/111 (41·4%)
BDP equivalent ICS dose (μ g per day)	800 (400–1600)	800 (400–800)
Asthma skills		
pMDI: adequate	84/98 (85·7%)	71/96 (74·0%)
Turbuhaler: adequate	52/54 (96·3%)	47/48 (97·9%)
Correct knowledge of maintenance ICS	48/98 (49·0%)	40/98 (40·8%)
Correct knowledge of rescue β_2 -agonist use	73/101 (72·3%)	60/103 (58·3%)

Data are n/N (%) or median (IQR), unless otherwise indicated. BMI=body-mass index. SF12=short form 12 health survey. AQLQ–M=asthma quality of life questionnaire—Marks. ER=emergency room. OCS=oral corticosteroid. FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity. F_eNO=fraction of exhaled nitric oxide. ICS=inhaled corticosteroid. BDP=beclomethasone dipropionate. pMDI=pressurised metered dose inhaler. *Low=0, high=100. †Good=0, poor=10.

Table 5: Participant data at randomisation

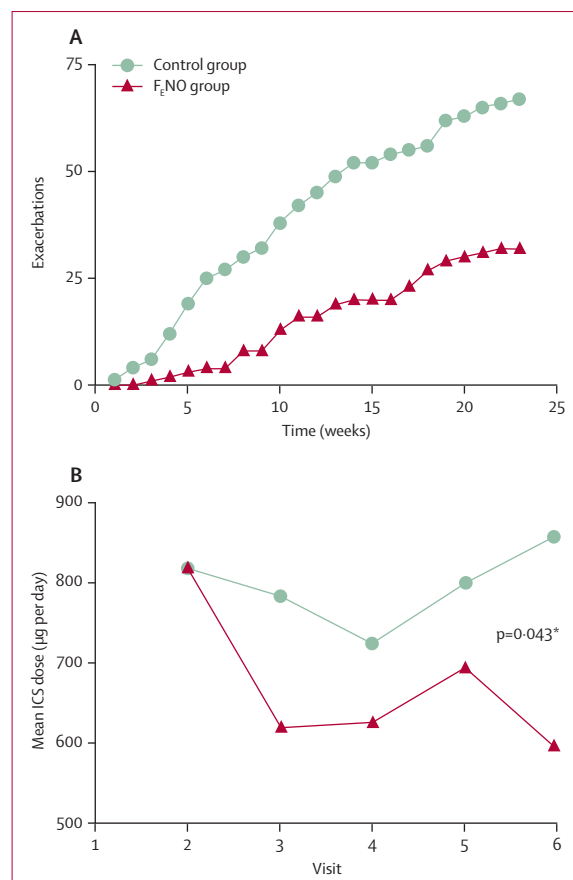


Figure 2: Effect of F_eNO-guided asthma management during pregnancy on number of asthma exacerbations (A) and maintenance mean daily ICS dose (B) ICS=inhaled corticosteroids. F_eNO=fraction of exhaled nitric oxide. *From generalised linear mixed model analysis.

writing of the report. HP and PGG had full access to all the data in the study and PGG had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. We recruited 242 women and randomly assigned 220, of whom 203 completed the study. Women had a mean age of 28 years (SD 5.4), 80 (39%) were past smokers with a mean smoking history of 4.5 pack-years (SD 5.2), 156 of 206 (76%) were atopic, and the mean gestational age was 16.1 weeks (SD 2.6). At enrolment, mean FEV₁ was 95.1% (13.9) predicted, the ratio of FEV₁ to forced vital capacity (FVC) was 79.6% (7.4), and median ACQ score was 0.85 (IQR 0.29–1.14). In the 2 years before study enrolment, 42 (19%) women had asthma exacerbations needing oral corticosteroids and 24 (11%) visited the emergency room. At randomisation the characteristics of the two treatment groups were well balanced (table 5). Inhaled corticosteroids were used by 93 (42%) women, at a median daily dose of 800 µg (IQR 500–1000) beclometasone dipropionate equivalents daily. The mean study treatment period was 17.8 weeks (SD 5.5) in the F_ENO group and 18.8 weeks (3.8) in the control group (p=0.11).

With F_ENO-guided asthma management we recorded a significant reduction in asthma exacerbations during pregnancy (figure 2A). The exacerbation rate was significantly lower in the F_ENO group (0.288 exacerbations per pregnancy) than in the control group (0.615 exacerbations; incidence rate ratio 0.496, 95% CI 0.325–0.755; p=0.001). The F_ENO group had a longer exacerbation-free interval than did the control group (hazard ratio 0.565, 95% CI 0.352–0.905, p=0.018; webappendix p 6). 28 (25%) women in the F_ENO group had an exacerbation compared with 45 (41%) in the control group (p=0.011). For every six women receiving treatment adjustment by the F_ENO-based algorithm, one woman was prevented from having an exacerbation (number needed to treat [NNT] 6). The masking process was successful, with most participants not aware of the group to which they were randomly assigned (table 6).

Most exacerbations were of moderate severity; mean ACQ score at exacerbation was 2.02 (SD 0.79) in the F_ENO group and 1.97 (0.95) in the control group, indicating significant asthma symptoms and increased use of shortacting β₂ agonist (figure 3). We noted a significant reduction in the rate of unscheduled doctor visits for asthma and in oral corticosteroid courses in the F_ENO group (table 6). The mean ACQ score at unscheduled doctor visits was 2.03 (SD 0.76) in the F_ENO group and 2.01 (0.97) in the control group (p=0.947). A treatment change occurred in 23 (72%) exacerbations in the F_ENO group and 53 (79%) in the control group. The rates of admission or emergency room visit for an asthma exacerbation were low in both groups (table 6).

	Control group (n=109)	F _E NO group (n=111)	p value
Exacerbation types (mean [95% CI])			
Unplanned or unscheduled doctors visits*	0.56 (0.40 to 0.72)	0.26 (0.16 to 0.36)	0.002
OCS use*	0.19 (0.08 to 0.31)	0.08 (0.03 to 0.133)	0.042
Hospital admission*	0.03 (−0.004 to 0.06)	0 (0 to 0)	1.0
ER/labour ward visits*	0.02 (−0.01 to 0.04)	0.04 (0.001 to 0.07)	0.399
Health-related quality of life†			
SF12 physical summary‡	46.9 (38.2 to 51.8)	47.7 (40.8 to 52.0)	0.89
SF12 mental summary‡	54.2 (46.1 to 57.6)	56.9 (50.2 to 59.3)	0.037
AQLQ-M: total score§	0.81 (0.38 to 1.63)	0.75 (0.38 to 1.25)	0.54
Lung function (mean [95% CI])			
F _E NO (ppb)¶	11.0 (5.9 to 21.4)	10.55 (5.95 to 19.3)	0.732
FEV ₁ (L)	3.01 (2.91 to 3.10)	3.09 (3.0 to 3.17)	0.221
FEV ₁ (%)	94.4% (91.84 to 96.96)	96.4% (94.31 to 98.46)	0.235
Current treatment			
β ₂ -agonist use in past week (days)¶	1 (0 to 5)	0 (0 to 3)	0.024
ICS (n [%])**	46 (42.2%)	76 (68.5%)	<0.0001
BDP equivalent ICS dose (µg/day),¶ all women	0 (0 to 800)	200 (0 to 400)	0.079
Longacting β ₂ agonist (n [%])**	19 (17.4%)	45 (40.5%)	<0.0001
Symptom-free days (past week)¶	6 (2 to 7)	7 (4 to 7)	0.058
What management group? (n [%])**			
Control	19 (20.7%)	11 (12.9%)	0.387
F _E NO	13 (14.1%)	14 (16.5%)	..
Do not know	60 (65.2%)	60 (70.6%)	..

OCS=oral corticosteroid. ER=emergency room. SF12=short form 12 health survey. AQLQ-M=asthma quality of life questionnaire—Marks. F_ENO=fraction of exhaled nitric oxide. FEV₁=forced expiratory volume in 1 s. ICS=inhaled corticosteroid. BDP=beclometasone dipropionate. *Poisson regression. †Median (IQR), ANCOVA. ‡Low=0, high=100. §Good=0, poor=10. ¶||Median (IQR), Wilcoxon rank sum test. ||Student's t test. **χ² test.

Table 6: Efficacy results at end of study

Both groups had good symptom control at the end of the study. Shortacting β₂-agonist use was significantly less in the F_ENO group than in the control group (table 6). The number of symptom-free days did not differ significantly between groups (table 6). Mean ACQ scores were 0.56 (SD 0.67) in the F_ENO group and 0.72 (0.80) in the control group (GLMM repeated measures p=0.046; webappendix p 7).

At the end of the study, the generic quality of life (short form 12) mental component domain was significantly higher with F_ENO management than in the control group (table 6, p=0.008), and remained significantly different after adjustment for baseline values (p=0.037, effect size 0.3). Asthma-specific quality-of-life scores were low at completion of the study, and we noted no difference between treatment groups (table 6).

The F_ENO algorithm resulted in a substantially different asthma treatment profile. Overall, 76 (68%) women in the F_ENO group were being treated with inhaled corticosteroids at the end of the study compared with 46 (42%) in the control group (table 4). Throughout the study, the mean daily inhaled corticosteroid dose was

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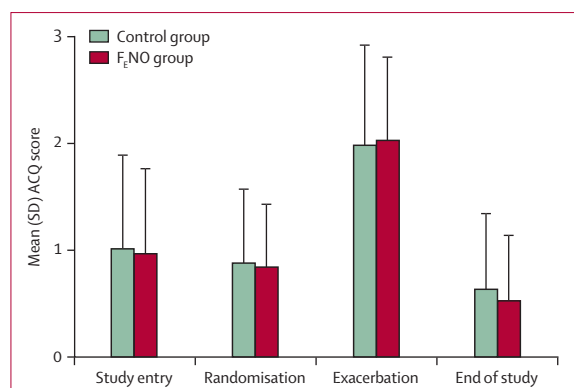


Figure 3: ACQ score at study entry, randomisation, during an exacerbation, and at end of study

ACQ=asthma control questionnaire. F_eNO=fraction of exhaled nitric oxide.

lower in the F_eNO group than in the control group (figure 2B). More women received longacting β_2 agonist in the F_eNO group than in the control group (table 6).

Perinatal outcomes tended to be improved in the F_eNO group compared with the control group, with higher median birthweight (F_eNO group 3520 g [IQR 3060–3920] vs control group 3460 g [3040–3730]; $p=0.233$), a reduction in preterm deliveries (six [6%] vs nine [8%]; $p=0.466$), and significantly reduced neonatal hospitalisation (eight [8%] vs 18 [17%], $p=0.046$; webappendix p 5). The groups had similar numbers of low birthweight (<2500 g) babies (five [5%] vs five [5%]) and babies with a birthweight less than the tenth percentile (14 [14%] vs 16 [15%]).

Discussion

In this randomised controlled trial of inflammatory marker-based management of asthma in pregnancy, we have shown that a treatment algorithm based on F_eNO and ACQ score led to a significant reduction in asthma exacerbations and less use of β_2 agonist compared with a clinical algorithm. These benefits occurred because the F_eNO treatment algorithm was associated with a different profile of maintenance asthma treatment, with inhaled corticosteroids being used by more women, but at a lower average dose, and more often in combination with a longacting β_2 agonist than in the control group. This different treatment profile is consistent with present advice in asthma management guidelines that promote greater use of inhaled corticosteroid, at lower doses, and the earlier introduction of a longacting β_2 agonist. Our results show that with addition of F_eNO to clinical assessment, these treatment principles can be extended to more participants, with associated improvements in asthma outcomes (panel).

The women in this study predominantly had mild asthma. However, they were at high risk of an exacerbation during pregnancy that could be reduced with an F_eNO algorithm to guide treatment. This beneficial effect could have occurred because an increased F_eNO concentration is a marker of uncontrolled eosinophilic inflammation in

mild asthma that could be clinically silent²⁸ but could be associated with future exacerbation risk.²⁹ The consequence of this approach was that about 26% more women received inhaled corticosteroids as a result of F_eNO assessment than with clinical assessment alone. A second mechanism of benefit arose because longacting β_2 agonists were started when women were symptomatic but F_eNO was suppressed. At the end of the study, an additional 23% of women were using a longacting β_2 agonist as a result of the F_eNO algorithm compared with the clinical assessment algorithm. Longacting β_2 -agonist use is associated with reduced asthma exacerbations,^{4,5} and by use of the F_eNO algorithm we were able to target longacting β_2 agonist to symptomatic non-eosinophilic asthma, for which symptoms were increased but F_eNO was suppressed.

The algorithm gave different treatment recommendations from the clinical protocol, which is a necessary feature of methodologically sound algorithm studies.¹⁴ To achieve this difference, we selected two discrete cutoffs, one for a dose increase and a second for a dose decrease. The cutoff values were specifically not based on the normal range. Rather, the dose increase cutoff was that associated with uncontrolled eosinophilic asthma, and also had been associated with a favourable response to ICS.^{14,26} The dose decrease cutoff was based on F_eNO values from well controlled asthma and on an F_eNO concentration at which ICS dose decrease was not associated with deterioration of asthma control.^{14,26} The dose increments were chosen to be in the responsive range for the outcome of asthma exacerbations.^{4,5} Finally, the algorithm was pilot tested with data from a prospective cohort study of asthma in pregnancy.

Both treatment approaches were associated with good asthma control and pregnancy outcomes. The main benefits of an F_eNO-guided approach were in reduction of exacerbations, mainly unscheduled doctor visits. These events were episodes of significantly symptomatic asthma, as indicated by increased ACQ score at the exacerbation, and met the ATS/ERS Task Force definition of moderate asthma exacerbations. The rate of oral corticosteroid use for exacerbations was also reduced, whereas the rate of admission and emergency room visits for exacerbations was low in both groups. The women in the study were assessed early and given a written action plan, which led to earlier presentation and treatment of exacerbations. In previous studies from the same clinic, we showed that the effect of nurse monitoring of asthma led to a reduction in asthma admissions from 8.2%³⁰ to 3.8%³¹ of patients. Further, in this study, women in both groups were provided with their asthma therapy free of charge and had regular visits and telephone calls to enhance adherence. These interventions were applied to both treatment groups, with the expectation that the rate of severe exacerbations would be reduced in both groups. In our antenatal clinic, the addition of prospective monitoring of exacerbations by fortnightly phone calls and additional clinic visits (monthly rather than two to three times during

Panel: Research in context**Systematic review**

We searched PubMed and Medline for articles of the use of fraction of exhaled nitric oxide ($F_{\text{e}}\text{NO}$) to guide asthma management in adults and children, up to December, 2010. We also searched the reference lists of relevant articles, review articles, and non-randomised studies that examined $F_{\text{e}}\text{NO}$ use in asthma. We selected studies that were relevant to our discussion, and used the Cochrane systematic review by Petsky and colleagues³² as the best synthesis of available randomised trials of $F_{\text{e}}\text{NO}$ guided therapy in non-pregnant women with asthma. We identified no previous randomised trials that used $F_{\text{e}}\text{NO}$ to guide asthma therapy in pregnancy.

Interpretation

The Managing Asthma in Pregnancy (MAP) study is the first randomised study of its type in pregnancy, and the second largest trial of $F_{\text{e}}\text{NO}$ guided asthma management in general. We used an improved algorithm that incorporated $F_{\text{e}}\text{NO}$ to adjust inhaled corticosteroid dose and asthma symptoms to adjust β_2 -agonist doses. Findings from the study showed that our algorithm based on $F_{\text{e}}\text{NO}$ and symptoms led to significant reductions in asthma exacerbations during pregnancy, with a 50% reduction in incidence. This reduction was accompanied by important changes in maintenance asthma pharmacotherapy, including more frequent use of inhaled corticosteroid, but at a lower total daily dose, and earlier introduction of longacting β_2 agonist. Asthma management during pregnancy can be improved by the use of measuring $F_{\text{e}}\text{NO}$ concentration, and symptoms to adjust treatment. This algorithmic approach might also be beneficial for non-pregnant women with asthma.

pregnancy) resulted in a reduction in hospital admissions for exacerbation (2·8% vs 8·2%) and a greater percentage of women being assessed by a physician at exacerbation (39·5% vs 26%).³⁰ However, an additional treatment benefit could be detected with $F_{\text{e}}\text{NO}$ -guided therapy.

There is a general consensus that the gains associated with use of $F_{\text{e}}\text{NO}$ measurements to guide inhaled corticosteroid treatment in asthma are small, and on the basis of studies done so far, routine use is not recommended.¹² However, in these studies the algorithm for $F_{\text{e}}\text{NO}$ -guided treatment might have been sub-optimum.¹⁴ In our study an improved $F_{\text{e}}\text{NO}$ algorithm was applied on the basis of a review of the weaknesses of the methods used in previous studies. Furthermore, we adequately powered the study to assess asthma exacerbations as an outcome.

The control algorithm was not identical to present guidelines in two ways. First, a step-down in inhaled corticosteroid dose was possible after 1 month of treatment, which differs from present guidelines that recommend step-down after 3 months. However, we

recorded no apparent excess of exacerbations because of this approach. Second, at guideline step 3, when asthma is uncontrolled on low-dose inhaled corticosteroids, the options are to increase the dose of inhaled corticosteroid in addition of a longacting β_2 agonist. In this study we used increased inhaled corticosteroids in the control group because we considered further randomisation to increased inhaled corticosteroids or added longacting β_2 agonists to be too complex.

Although the study was not specifically powered to assess perinatal outcomes, we did detect some benefits in the $F_{\text{e}}\text{NO}$ group that could be associated with fewer exacerbations, and are consistent with the known adverse effects of asthma on pregnancy and the fetus. Asthma is associated with a reduction in birthweight of 93 g.³² We noted that with $F_{\text{e}}\text{NO}$ -guided management babies' birthweights normalised, although this finding was not significant. Similarly, the rate of preterm delivery, which is increased in asthmatic pregnancies, was reduced by almost a third with $F_{\text{e}}\text{NO}$ -guided therapy. Asthma in pregnancy is also associated with an increased risk of neonatal admission,³² which in this study was reduced by $F_{\text{e}}\text{NO}$ -guided management. These results lend support to the hypothesis that $F_{\text{e}}\text{NO}$ -guided therapy for asthma in pregnancy could lead to beneficial fetal outcomes; however, this notion needs to be confirmed by further study. Future work should investigate the application of this algorithm in routine antenatal care and other settings.

Contributors

HP analysed and interpreted data and co-wrote the report. VEM was responsible for study design, algorithm development, and editing of the report. DRT was responsible for the study concept, study design, algorithm development, and editing of the report. MJH, KMcC, WG, and VLC contributed to study design and editing of the report. PGG was responsible for study concept, study design, algorithm development, data interpretation, and writing and editing of the report.

Conflicts of interest

PGG has received payment for reimbursement of meeting/travel expenses from GlaxoSmithKline, AstraZeneca, Novartis, and Boehringer Ingelheim. DRT has received lecture fees from Aerocrine AB. MJH, KMcC, WG, HP, VEM, and VLC declare that they have no conflicts of interest.

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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Powell H, Murphy VE, Taylor DR, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet* 2011; **378**: 983–90.

Web Appendix

Management of asthma in pregnancy using exhaled nitric oxide based inflammometry: a Randomized Controlled Trial

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Additional Methods

Exclusion criteria

Exclusion criteria were inability to attend antenatal clinic visits during pregnancy, inability to perform manoeuvres required for spirometry and FENO, requirement for >3 courses of oral corticosteroid in the previous 12 months, admission to hospital for asthma exacerbation in the previous three months; maintenance oral corticosteroids, maintenance oral theophylline, current (past six weeks) smoking, concomitant chronic medical illness, chronic lung disease (other than asthma), and drug or alcohol dependence.

Baseline assessment

We recorded current asthma therapy and asthma control¹, current asthma triggers and co-morbidity, past asthma history, and frequency of oral corticosteroid use and health care utilization over the prior two years.

Action Plan

Each subject received instruction in asthma self-management and a personalised written asthma self-management plan instructing them to increase β_2 -agonist in the face of deteriorating asthma and to seek medical assistance if there was no response to treatment.

Medications used

ICS was administered as budesonide by Turbuhaler (Pulmicort, AstraZeneca, North Ryde, NSW, Australia). Long-acting β_2 -agonist was administered as formoterol 6 μ g bd by Turbuhaler (AstraZeneca, North Ryde, NSW, Australia). Subjects allocated to inhaled corticosteroid and long-acting β_2 -agonist were treated with budesonide/formoterol (Symbicort) Turbuhaler (AstraZeneca, North Ryde, NSW, Australia). No subject received formoterol as monotherapy, and subjects allocated to this therapy received formoterol 6 μ g/budesonide 100 μ g as Symbicort Turbuhaler. In order to maintain blinding, subjects allocated to budesonide 400 μ g and long-acting β_2 -agonist received budesonide 400 μ g/formoterol 12 μ g as Symbicort Turbuhaler. Subjects were permitted to use salbutamol pMDI 100 μ g prn for symptom relief throughout the trial.

FENO measurement

The NO detection limit was 1.5 ppb, with a response time of <0.7sec for 90% full scale. Data were collected via a computerised data collection program. The analyser underwent regular two point calibration (0ppb, 200ppb) using calibration gas (NIOX calibration gas, AGA Linde Healthcare) consisting of 100% nitrogen containing <1 ppb NO, and NO in N₂ at 200 (+/-20) ppb. For the measurement of FENO, we used a restricted breath technique, with exhalation via a high resistance, and positive mouth pressure to close the velum, thus excluding nasal NO. Subjects inhaled medical-grade compressed air that contained <2 ppb NO and then exhaled via a high expiratory resistance while

targeting a mouth pressure of 20 mm Hg. This produces an expiratory flow rate of 50 mL/s (including analyser sampling rate). Exhalations were repeated until three plateau FENO values that vary by <5% were obtained. The mean of the three replicate FENO values was used. We found no difference in FENO during pregnancy ($p>0.05$). FENO (ppb NIOX, Aerocrine, Sweden; median [IQR]) was measured in non-pregnant control women ($n=17$; FENO 15.7 [12-26.9] ppb), and nonasthmatic women during pregnancy ($n=21$) at 18 weeks (12.1 [9.1-20.6]), at 30 weeks (14.9 [9.1-20.6]) and at 36 weeks (14.2 [11-18.1])²

Sample size

Previously, we observed a mean (SD) asthma exacerbation rate in pregnant women attending our hospital of 1.92 (1.63)/person/pregnancy. An *a priori* sample size calculation was performed. Power was set at 80%, and the type I error rate set at 0.05. The study was powered to detect a reduction in exacerbation rate of 50%, which is both clinically important and feasible based on prior evidence. Previous non-invasive marker studies are consistent in showing a reduction in exacerbations of approximately 50% (Sont 47%³, Green 68%⁴, Smith 45%⁵, Jayaram 49%⁶ using an inflammometry based algorithm. To detect a reduction in the proportion of subjects experiencing an asthma exacerbation from 33% to 16%, we estimated we would need to randomise 176 subjects. We planned to enrol 220 subjects to allow for withdrawals.

Additional Results

The demographic characteristics of the study population at enrolment are shown in web appendix table 1.

In order to assess for any trial run-in effect, the data at study entry and at randomization visits were compared (web appendix table 2), and show no obvious differences between parameters upon study entry.

The FENO group had a longer period free of an asthma exacerbation compared to the Control group (hazard ratio (95%CI) = 0.565 (0.352, 0.905), $p=0.018$; web appendix figure 1). The changes in ACQ score, symptom-free days and FENO, are shown in web appendix figure 2. There was a trend to more symptom-free days and lower ACQ in the FENO group ($p=0.058$, GLMM repeated measures $p=0.046$, web appendix figure 2). The mean ACQ at exacerbation was 2.01 (SD 0.86) indicating significant asthma symptoms were experienced by the women at exacerbation. The perinatal outcomes are shown in web appendix Table 3.

Web Appendix Table 1: Demographic Details and quality of life at study entry (n=220)

Visit 1	
Age, yrs	28·4 (5·4)
Atopy, n(%)	156 (75·7)
Ex smoker, n(%)	80 (39·0)
Smoking history, Pack years	4·5 (5·2)
Parity	1 (0,1)
Weight, kg	80·5 (21·1)
BMI, kg/m ²	29·5 (7·3)
Employed, n(%)	128 (62·1)
Australian born, n(%)	190 (92·2)
SF12 Physical summary+	49·2 (42·6, 53·2)
SF12 Mental summary+	55·5 (47·7, 58·4)
AQLQ-M: Breathlessness Domain+	1·0 (0·5, 2·0)
Mood Domain+	1·5 (1·0, 2·5)
Concerns Domain+	0·4 (0, 0·7)
Social Domain+	0 (0, 0·7)
AQLQ-M: Total score+	0·88 (0·38, 1·63)

All values are mean(SD) or where stated (+) median (IQR)

Web Appendix Table 2: Symptom data for stable subjects at visit 1 & 2

	Visit1		Randomisation	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
ICS, BDP equivalent dose (ug/day)	1011.5 (675.8)	800 (500, 1000)	818.8 (457.3)	800 (400, 800)
ACQ score	0.93 (0.78)	0.71 (0.28, 1.29)	0.85 (0.65)	0.85 (0.29, 1.14)
FEV ₁ %	95.42 (13.65)	96.17 (86.47, 103.85)	95.87 (12.94)	95.64 (87.91, 104.46)
Symptom free days per wk	3.90 (2.85)	5 (0, 7)	3.76 (2.69)	4 (1, 6)
FENO, ppb	26.98 (35.99)	16.2 (7.1, 31.5)	22.56 (30.35)	13.7 (7.45, 26.05)

ICS: inhaled corticosteroid

BDP: beclomethasone dipropionate

ACQ: asthma control questionnaire

Web Appendix Table 3: Perinatal outcome variables by asthma management group

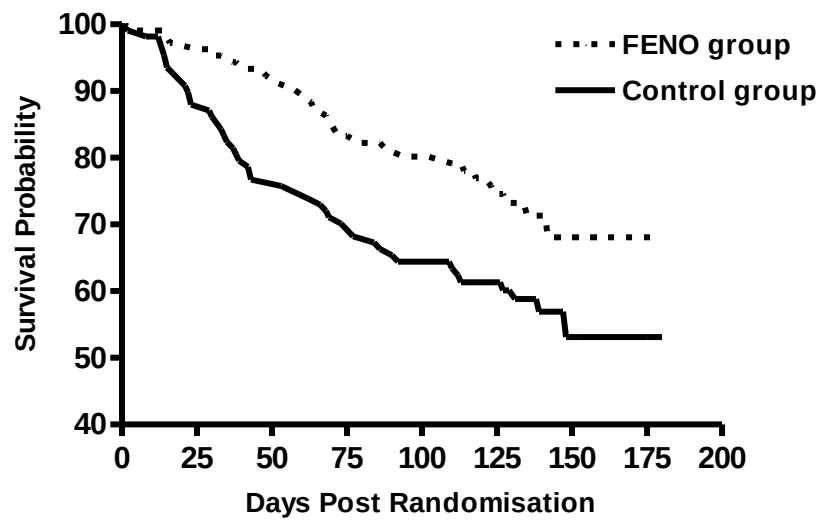
	Clinical group	FENO group	P value
Number of MAP subjects/number of babies	106/109	104/105	
Gestational age*	39·6 (38·4, 40·6)	39·9 (38·7, 40·7)	0·224
Baby's gender, M/F	54/55	45/60	0·327
Birth weight, g*	3460 (3040, 3730)	3520 (3060, 3920)	0·233
Birth length, cm*	51·5 (49·5, 53·0)	51·3 (50·0, 54·0)	0·408
Birth head circumference, cm*	34·5 (34·0, 35·8)	34·5 (34·0, 36·0)	0·807
<i>Labour</i>	N=106	N=104	
Spontaneous	54 (50·9)	63 (60·6)	0·160
Induced	33 (31·2)	27 (26·0)	0·407
No labour	15 (14·2)	12 (11·5)	0·572
Spontaneous & augmented #	3 (2·8)	2 (1·9)	1·0
<i>Delivery</i>	N=109	N=105	
Vaginal	72 (66·1)	78 (74·3)	0·189
Forceps	7 (6·4)	9 (8·6)	0·550
Vacuum #	4 (3·7)	3 (2·9)	1·0
C section elective	16 (14·7)	13 (12·4)	0·623
C section non-elective	15 (13·8)	11 (10·5)	0·462
<i>Maternal complications</i>	N=106	N=104	
Preeclampsia#	5 (4·7)	3 (2·9)	0·721
Gestational diabetes	11 (10·4)	8 (7·7)	0·498
Pregnancy induced hypertension	11 (10·4)	7 (6·7)	0·345
Antepartum haemorrhage#	1 (0·9)	1 (0·96)	1·0
Post partum haemorrhage#	4 (3·8)	5 (4·8)	0·747
Ruptured membranes	9 (8·5)	12 (11·5)	0·462
Hyperemesis	0	0	
Multiple pregnancy	2 (1·9)	1 (0·96)	1·0
Proteinuria#	0	3 (2·9)	0·120
<i>Fetal Complications</i>	N=109	N=105	
Still birth#	1 (0·9)	1 (0·95)	1·0
Termination of pregnancy#	0	1 (0·95)	0·491
Preterm delivery#	9 (8·3)	6 (5·7)	0·466
IUGR#	3 (2·8)	1 (0·95)	0·622
Jaundice#	3 (2·8)	3 (2·9)	1·0
Neonatal hospitalization	18 (16·5)	8 (7·6)	0·046
Congenital malformation	0	1 (0·95)	0·491

Numbers are n (%), Chi square test

*Median (IQR), Wilcoxon rank sum test; # Fisher's exact test

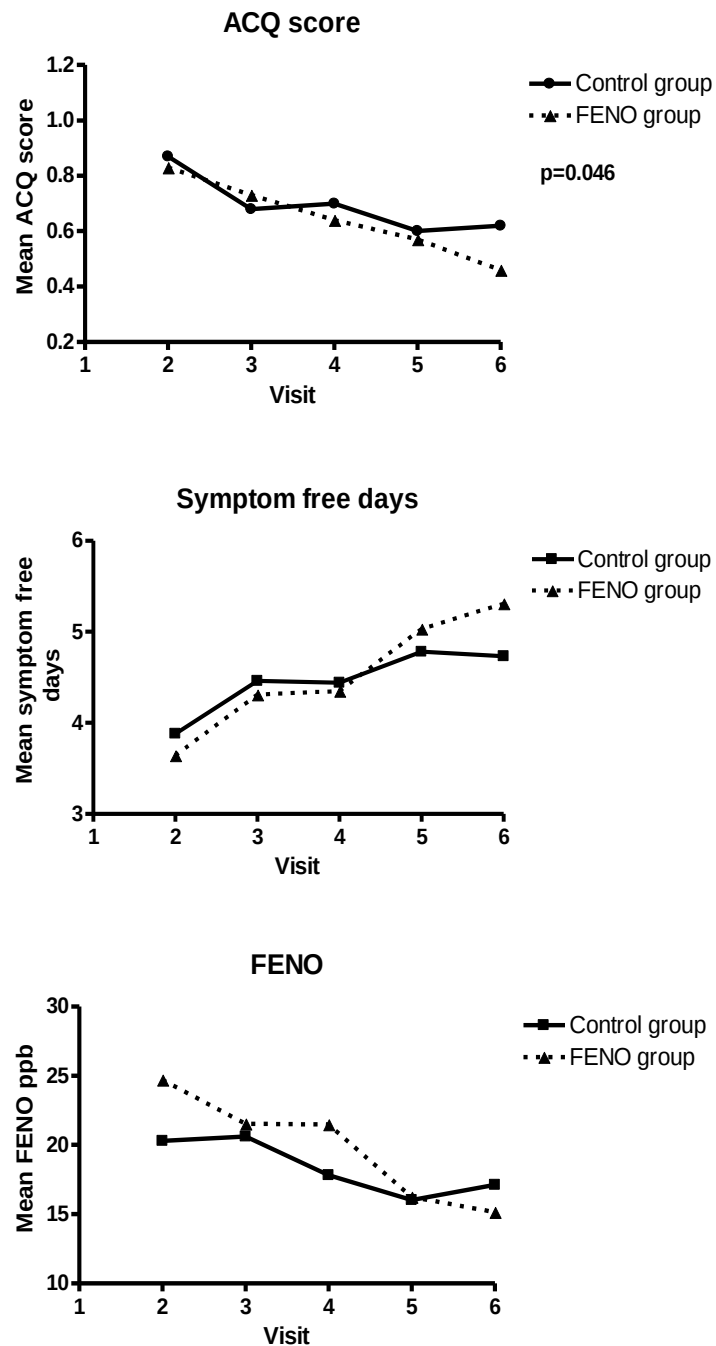
Web Appendix Figures

Web Appendix Figure 1: Time to first exacerbation.



The FENO group had a longer period free of an asthma exacerbation compared to the Control group (hazard ratio (95%CI) = 0·565 (0·352, 0·905), $p=0·018$)

Web Appendix Figure 2: Differences in ACQ score, symptom-free days and FENO in the FENO managed group and Control group during the study.



There was a trend to more symptom-free days and lower ACQ in the FENO group ($p=0.058$, GLMM repeated measures $p=0.046$)

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