

Management Based on Exhaled Nitric Oxide Levels Adjusted for Atopy Reduces Asthma Exacerbations in Children: A Dual Centre Randomized Controlled Trial

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Summary. While several randomized control trials (RCTs) have evaluated the use of fractional exhaled nitric oxide (FeNO) to improve asthma outcomes, none used FeNO cut-offs adjusted for atopy, a determinant of FeNO levels. In a dual center RCT, we assessed whether a treatment strategy based on FeNO levels, adjusted for atopy, reduces asthma exacerbations compared with the symptoms-based management (controls). Children with asthma from hospital clinics of two hospitals were randomly allocated to receive an a-priori determined treatment hierarchy based on symptoms or FeNO levels. There was a 2-week run-in period and they were then reviewed 10 times over 12-months. The primary outcome was the number of children with exacerbations over 12-months. Sixty-three children were randomized (FeNO = 31, controls = 32); 55 (86%) completed the study. Although we did achieve our planned sample size, significantly fewer children in the FeNO group (6 of 27) had an asthma exacerbation compared to controls (15 of 28), $P = 0.021$; number to treat for benefit = 4 (95% CI 3–24). There was no difference between groups for any secondary outcomes (quality of life, symptoms, FEV₁). The final daily inhaled corticosteroids (ICS) dose was significantly ($P = 0.037$) higher in the FeNO group (median 400 µg, IQR 250–600) compared to the controls (200, IQR 100–400). Taking atopy into account when using FeNO to tailor asthma medications is likely beneficial in reducing the number of children with severe exacerbations at the expense of increased ICS use. However, the strategy is unlikely beneficial for improving asthma control. A larger study is required to confirm or refute our findings. *Pediatr Pulmonol.* © 2014 Wiley Periodicals, Inc.

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INTRODUCTION

Asthma is one of the most common chronic disease in children, accounting for 12¹–21%² of hospitalizations worldwide.³ Preventing exacerbations, particularly severe exacerbations and hospitalizations, is one goal of good asthma management. The second component in asthma management is monitoring of asthma control (by subjective and objective measures).^{4–6} Subjective measures usually involve a series of questions used for clinical assessment, diary cards and quality of life (QoL) questionnaires. Traditional objective methods include peak flow, spirometry, and degree of airway hyper-responsiveness.⁷ Newer, and arguably more sensitive, methods include measurement of airway inflammation such as airway cellularity in induced sputum or fractional exhaled nitric oxide (FeNO).⁸

Induced sputum has been shown to be beneficial in adults⁹ but is relatively labor intensive and has limited availability, particularly in children. In contrast, FeNO is easily measured in children and confers some advantage

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over sputum eosinophils.⁷ Thus its universal use has been advocated by some.¹⁰ However, our Cochrane review found that the role of utilizing exhaled nitric oxide to tailor the dose of inhaled corticosteroids cannot be routinely recommended for clinical practice at this stage and its role in monitoring asthma remains uncertain.¹¹

There are seven published^{12–18} randomized controlled trials (four children/adolescents and three adults) that have assessed whether adjustment of asthma treatment in accordance to FeNO levels is superior to “usual management.” None of the four pediatric studies^{13–15,17} used asthma exacerbations as the primary outcome, while three adult papers did.^{12,16,18} Meta-analysis revealed there was no significant difference in exacerbations between the FeNO group compared to controls.¹¹ In adults, the daily dose of inhaled corticosteroids (ICS) at end of study was decreased in the FeNO group compared to controls (mean difference $-450\text{ }\mu\text{g}$ (95% CI -677 , -223 ; $P < 0.0001$). However in children, adjusting medications according to FeNO levels resulted in a significant increase of mean daily ICS dose (mean difference $140\text{ }\mu\text{g}$, 95% CI 29, 251; $P = 0.014$).

Thus, controversy remains of the benefit or otherwise on the benefits of use of FeNO for routine asthma management.¹⁹ Further, the appropriate FeNO cut-off remains elusive despite recent recommendations.²⁰ FeNO levels are dependent on atopy^{21,22} and none of the RCTs have considered atopic status in FeNO levels when medications were adjusted. We conducted a dual-center RCT with three unique features; exacerbation was our primary outcome, atopy was considered in the FeNO strategy when medications were tailored and lastly, only FeNO levels were used (discounting symptoms) in the FeNO strategy group.

Our aim was to determine if adjustment of asthma medications based on FeNO levels (compared to management based on clinical symptoms) reduces severe exacerbations in children with asthma. We also examined the effect on two asthma control measures (diary card and QoL). We hypothesized that a childhood asthma management strategy based on FeNO and atopy status reduces exacerbations requiring rescue oral corticosteroids and/or hospitalizations.

METHODS

Subjects

Inclusion criteria: Children aged >4 years with persistent asthma,⁴ prescribed anti-inflammatory asthma treatment, and receiving their care primarily through our clinical service at Royal Children's Hospital, Brisbane or Prince of Wales Hospital, Hong Kong. We excluded children who had underlying cardio-respiratory illness such as bronchiectasis or tracheomalacia, inability to take ICS or long acting beta-2-agonists (LABA) or had

previous poor adherence to medications (as documented in clinic notes).

The study was approved by the ethics committee at Royal Children's Hospital, Brisbane and Prince of Wales Hospital, Hong Kong. Informed and written consent was obtained from all parents of participants. The trial is registered with the Australia New Zealand Clinical Trials Registry (ACTRN012605000321640).

Protocol

Children and their parents were approached when they attended a routine clinic visit. After consent and recruitment, we recorded the child's demographics, run-in measurements and their technique of taking their medications checked by an asthma educator-nurse (HP and CA). A 2-week run-in period was undertaken to ensure stability. During this period, the children were maintained on their current treatment. If they were unstable (based on clinician review and diary cards) their medications were adjusted by their treating physician and a further run-in period was undertaken. At the end of the run-in, the child was randomized and initial measurements were obtained. These were spirometry, asthma QoL,^{23,24} FeNO, skin prick test, and commencement of asthma symptom diary.²⁵

The children were randomized (stratified by age [<6 or ≥ 6 years] and site [Brisbane or Hong Kong]) to one of two strategies (a) management based on clinical symptoms (control group) or (b) management based on FeNO levels (FeNO group). Randomization was done by an independent individual off-site through computer generation sequence list in permuted random blocks of 4–6. Allocation was fully concealed using opaque covers.

Patients were followed up for 12-months, with monthly visits for the first 4 months and every 2 months thereafter. Children attended at the same time of day on each occasion. At each visit we assessed patients with FeNO, spirometry before and after $400\text{ }\mu\text{g}$ inhaled salbutamol, the Paediatric Asthma Caregiver QoL Questionnaire (PACQLQ)²⁴ and Paediatric Asthma QoL Questionnaire (PAQLQ)²³ (in children aged ≥ 7 years), symptom diary cards²⁵ and review by pediatric respiratory physician. FeNO measurements were performed before spirometry. All investigations were standardized. Decisions to adjust therapy (in accordance to hierarchy of medication treatment) were made by investigators who were blinded to the participant's FeNO if randomized to clinical symptoms group or symptoms scores if randomized to FeNO group. The asthma management strategy was not revealed to the children and parents. Adherence was monitored by checking their medications (supplied for the entire study period). Cumulative doses of ICS for each child was calculated based on the child's daily dose over the study period and expressed per child-year.

Hierarchy of Medication Treatment

The hierarchy (Table 1) was modified from the Australian National Asthma Council guidelines⁴ and GINA guidelines.⁵ In the control group treatment decisions were made on symptoms as recorded on the asthma symptom diary card. Control was considered inadequate and treatment increased if scores increased by $\geq 15\%$ since the previous visit. Treatment was stepped down if the child's scores totalled < 10 in recent week. Reasons for using these cut offs are described below. In the FeNO group, adjustment of treatment was based on FeNO level and atopic status. If FeNO was elevated, therapy was stepped up according to the predetermined hierarchy of management (Table 1). If FeNO was low for two consecutive visits, medications were stepped down. Elevated FeNO was defined (based on a cohort study²⁶ in Perth, Australia) as ≥ 10 ppb in children with no positive skin prick test (SPT), ≥ 12 ppb in children with one positive SPT, and ≥ 20 ppb in children with ≥ 2 positive SPT.

Details of Methods

Allergens used for SPT in Brisbane were *Alternaria* mould, cat hair, cockroach mix, dust mite DPT, couch grass, and grass mix #7 (Hollister-Stier, WA). Negative (diluent) and positive (histamine) controls were also used. The allergens used in Hong Kong were *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* house dust mites, cat and dog dander, mixed American and German cockroaches, mixed ragweed, grass pollens, and tree pollens, and mixed moulds (*Penicillium notatum*, *Alternaria tenuis*, *Aspergillus fumigatus*, and *Hormodendrum cladosporioides*).

Atopy was defined as wheal ≥ 3 mm larger than the negative control and larger than the histamine.

FeNO was measured with a chemiluminescence analyser (Sievers NOA 280i, Colorado, USA) with children exhaling at 0.05 L/sec for > 4 sec in order to obtain a stable NO value for > 2 sec, in accordance to ATS/ERS guidelines.²⁷ Exhalations were repeated until three measurements were within 5% of the mean. Spirometry was performed using ATS criteria and % predicted based on local age and sex matched reference values in Hong Kong²⁸ and Eigen²⁹ from Australian data (Hibbert³⁰ (children ≥ 8 years) in Brisbane.

As multiple clinicians were involved in the on-going clinical care of the children, it was necessary to standardize clinical management. Thus, we utilized a validated daily diary asthma card.²⁵ The diary (completed every day) consisted of four questions (Table 2) with a 6-point scale, with a score of six reflecting worse symptoms. To obtain the composite scale, the score per question is averaged thus providing a score of 0–6 per day. The asthma scores were quantified by entering the numerical answer into a spreadsheet and average obtained for the previous month. The cut offs used for altering medications are based on the following: Santanello et al.'s paper³¹ had described that children had well-controlled asthma if their scores per day was < 1 /day (mean 0.56, SD 0.67) per week. For the week's total score taking 1.96 times the SD, the upper limit equates to 9.2/week. Hence, we considered children were well controlled if their total weekly score was < 10 . Our previous paper³² on asthma had also similar results with respect to the scores when well. For the 15% change representing instability, this was

TABLE 1—Hierarchy of Management (Modified From NAC, Australian Position Statement and GINA Guidelines)

Step	All MDI and spacer	Total Fluticasone dose, $\mu\text{m}/\text{day}$
1	Fluticasone 50 μm , once daily	50
2	Fluticasone 50 μm , one bd	100
3	Fluticasone 50 μm , two bd	200
4	Fluticasone 125 μm salmeterol 25 μm , one bd	250 (LABA 50 $\mu\text{m}/\text{day}$)
5	Fluticasone 125 μm salmeterol 25 μm , one bd plus fluticasone 50 μm , one bd	350 one bd (LABA 50 $\mu\text{m}/\text{day}$)
6	Fluticasone 125 μm salmeterol 25 μm , two bd	500 (LABA 100 $\mu\text{m}/\text{day}$)
7	Fluticasone 125 μm salmeterol 25 μm , two bd plus fluticasone 50, one bd	600 (LABA 100 $\mu\text{m}/\text{day}$)
Step	(If > 7 years old & on turbuhaler)	Total budesonide dose, $\mu\text{gm}/\text{day}$
1	Budesonide 100 μm , one daily	100
2	Budesonide 100 μm , one bd	200
3	Budesonide 200 μm , one bd	400
4	Budesonide 200 μm Formoterol 6 μm , one bd	400 (LABA 12 $\mu\text{m}/\text{day}$)
5	Budesonide 200 μm Formoterol 6 μm , one bd plus Budesonide 100 μm , one bd	600 (LABA 12 $\mu\text{m}/\text{day}$)
6	Budesonide 400 μm Formoterol 12 μm , one bd	800 (LABA 24 $\mu\text{m}/\text{day}$)
7	Budesonide 400 μm Formoterol 12 μm , one bd plus Budesonide 100 μm , one bd	1,000 (LABA 24 $\mu\text{m}/\text{day}$)

NAC, National Asthma Council; GINA, Global Initiative for asthma; MDI, metered dose inhaler; bd, twice a day; LABA, long acting beta-2-agonist; μgm , micrograms.

NB. If child already on QVAR, it was changed to fluticasone equiv. dose.

TABLE 2—Daytime Daily Symptom Score

Q1	How often did you experience asthma symptoms?						
	Score:	0	1	2	3	4	5
	(0 = none of the time)						6
							(6 = all the time)
Q2	How much did your asthma symptoms bother you today?						
	Score:	0	1	2	3	4	5
	(0 = not bothered at all)						6
							(6 = extremely bothered)
Q3	How much activity could you do today?						
	Score:	0	1	2	3	4	5
	(0 = usual activity)						6
							(6 = less than usual)
Q4	How often did your asthma affect your usual activities today?						
	Score:	0	1	2	3	4	5
	(0 = none of the time)						6
							(6 = all the time)

Parent/guardian or child completed every day for the duration of the study.

based on 1.96 times the standard deviation of the median change in the children with unstable asthma, as described by the authors of the asthma diary scale in their paper for discriminant validity between stable and unstable children.³¹

Outcome Measures

The primary outcome (stated a-priori in our trial registration) was number of children with severe exacerbation defined as respiratory events requiring a course of oral corticosteroids with or without hospitalization. Exacerbation treatment was determined by the primary pediatrician or respiratory physician that was blinded to the child's allocated group. In accordance to as ATS guidelines³³ (that was not available at time of study design), requirement for oral corticosteroids or hospitalisation represents a severe exacerbation. Secondary outcomes were: FEV₁ %predicted, asthma QoL, symptom scores and dose of ICS at end of study. ICS dose was expressed as budesonide-equivalent dose, with fluticasone considered twice the dose of budesonide.

Statistical Analysis

Sample size was calculated based on Green et al.⁹ study, which was the only study available at the time the study commenced. In Green et al.'s⁹ study the reduction in exacerbation in sputum-managed group was 31% less than the control arm (109 exacerbations in 26 subjects). To obtain a 30% reduction in exacerbations in the FeNO group compared to controls (three per person year), a sample size of 43 per group was required for 90.5% power at 0.05 significance level. We planned to recalculate sample size based on findings on the first 60 children recruited. However, as the first preliminary analysis showed a difference between groups, the study was terminated prior to reaching the sample size.

Descriptive statistics were used to summarize the demographic characteristics of the patients. Data that had a normal distribution were described using means and SD;

medians and inter-quartile ranges (IQR) were used otherwise. Fisher's exact tests were employed for categorical data. Kruskal–Wallis analyses were used for group comparisons. Two-tailed *P*-values of <0.05 were considered significant. All statistical calculations were analyzed using SPSS Version 13. Intention to treat analyses was used, and children who dropped out were assumed to have no exacerbations.

RESULTS

We recruited 65 children between February 2006 to April 2008; of whom 63 were randomized. Two children were not randomized; one child could not be stabilized during the run-in despite three visits, and one withdrew due to family circumstances. Of the 63 children who were randomized, only two children required adjustment of their medications during the run-in period to stabilize their asthma and therefore the 2-week run-in was repeated. By chance, both were randomized to the FeNO arm. During the follow-up period, 8 children withdrew (4 from each arm), leaving 27 children in FeNO management group and 28 in clinical symptom group (Fig. 1). No participant withdrew because of poor asthma control. The two groups were well matched at baseline (Table 3) for demographic and clinical features, other than symptom score that was significantly higher in the controls.

Exacerbations

None of the children were hospitalized during the study period. Compared to the control group, significantly less children in the FeNO group had ≥ 1 exacerbation over the study period (6 children in FeNO group vs. 15 in controls, *P* = 0.017) (Fig. 2). The number needed to treat (NNT) to prevent one child from having any exacerbation in 12 months was 4 (95% CI 3, 24). However, although the rate of exacerbations was lower in the FeNO group (0.39 per person-year) compared to controls (0.78 per person-year), the difference did not reach statistical

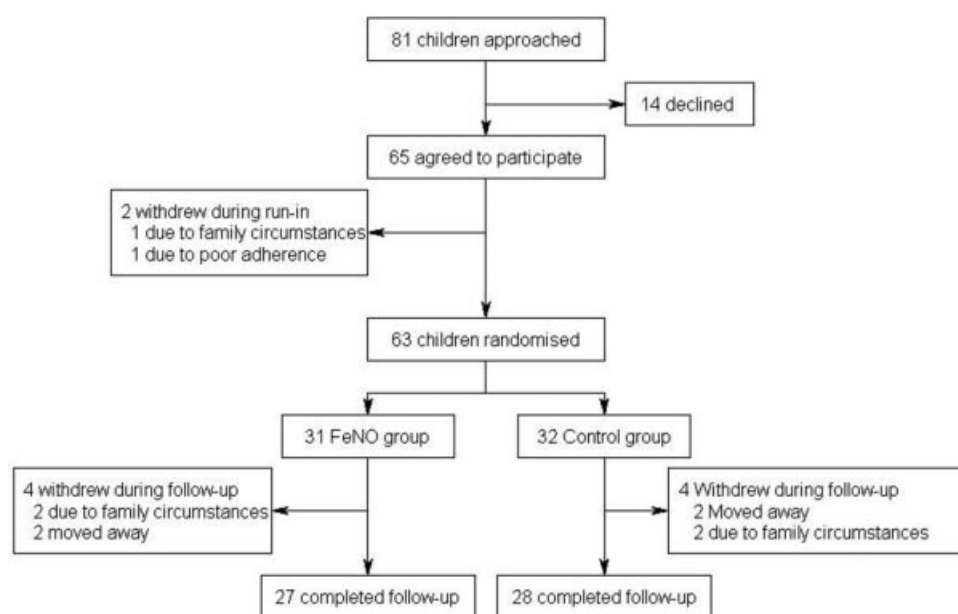


Fig. 1. Consort flow chart.

significance ($P = 0.102$). When the groups were sub-analyzed into those with ≥ 2 exacerbations per year, we also found no significant difference between the groups (three children in FeNO group vs. five children in control group, $P = 0.251$).

Other Outcome Measures

Asthma QoL scores, FEV₁ %predicted and FeNO values were not significantly different between the groups at the end of, or at any time point of the study (P range

from 0.08 to 0.829) (Figs. 3–5). Asthma diary scores were also similar between the groups (P -value range 0.06–0.928). Asthma symptom scores at final visit were: FeNO group (median 0, IQR 0, 8.75) and controls (median 2.5, IQR 0, 17.25, $P = 0.394$).

Inhaled Corticosteroid (ICS) Dose

At end of study (12-months), the final daily ICS dose was significantly ($P = 0.037$) higher in the FeNO group (median 400 μg , IQR 250, 600) compared to the control

TABLE 3—Initial Data (i.e., Collected Post the Run-In Phase But Just Before Start of Intervention)

Demographics	FeNO group (n = 31)	Control group (n = 32)
Boys: girls	18: 13	13: 19
Age in years, median (IQR)	10.17 (6.56, 12.69)	10.08 (6.25, 12.44)
<6 years old, n (%)	4 (12.9)	4 (12.5)
≥ 6 years old, n (%)	27 (87.1)	28 (87.5)
Atopy present, n (%)	23 (74%)	28 (87.1%)
Positive SPT: 1 allergen, n (%)	13 (41.9)	11 (34.4)
≥ 2 allergen, n (%)	10 (31.3)	17 (53.1)
History		
No. rescue corticosteroid courses in previous year, mean (SD)	1.86 (2.75)	1.81 (2.53)
No. of asthma admissions in previous year, mean (SD)	0.50 (0.79)	0.23 (0.43)
Dose inhaled steroid ¹ (median, IQR)	400 (250, 400)	400 (125, 200)
Asthma score, (median, IQR)	3.0 (0, 13.38)	6.75 (1.13, 23.0)
Investigations		
FEV ₁ %Predicted, median (IQR)		
Pre-bronchodilation	92.10 (85.20, 102.90)	88.00 (83.65, 104.15)
Post-bronchodilation	97.30 (88.90, 101.35)	91.50 (82.30, 105.4)
FeNO (ppb), median (IQR)—all	24.00 (10.92, 48.45)	25.60 (13.40, 53.70)
Atopy present	29.6 (14.15, 49.4)	29.7 (18.40, 56.10)
Atopy absent	11.7 (5.45, 28.55)	7.35 (6.40, 13.35)

¹Budesonide equivalent doses.

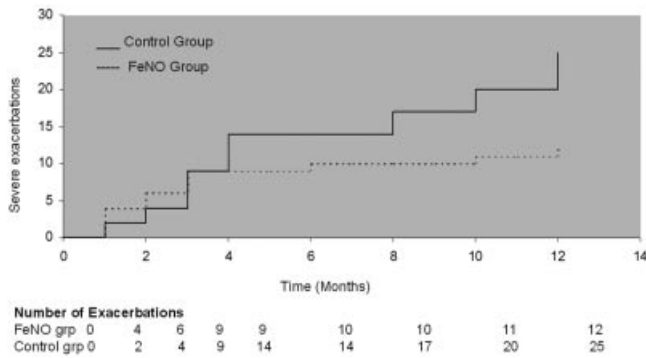


Fig. 2. Cumulative asthma exacerbations in Clinical Symptoms group (controls) and FeNO group. Graph shows FeNO group had smaller cumulative number of asthma exacerbations over study period when compared to clinical symptoms group.

group (median 200 μg , IQR 100, 400). However, when the difference between final and baseline dose was considered, there was no difference ($P = 0.139$) between the groups (FeNO group: median 0, IQR (-175, 100); control group: median of -200, (IQR -300, 100). With respect to the cumulative dose per child-year, the total median dose was significantly higher in the FeNO group (168,000 μg , IQR 93,000, 210,000) compared to the control group (105,000 μg , IQR 73,500, 156,000), $P = 0.016$.

DISCUSSION

Our dual center RCT evaluated an asthma management strategy based on FeNO (with atopy considered) compared to usual treatment (controls, based on asthma guidelines). We found that significantly fewer children in the FeNO group had severe asthma exacerbations compared to children managed by symptom control (diary). However, while the exacerbation rate was lower

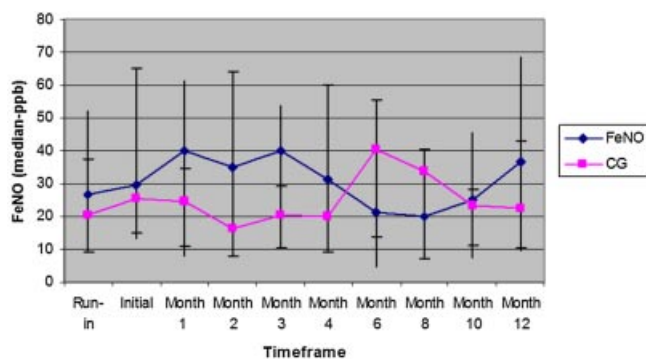


Fig. 3. FeNO in ppb of the two groups during the study period. Figure shows FeNO levels in ppb (median, IQR) over the study period between the two strategies (Run-in measurement is prior to commencing run-in period and initial measurement after run-in). There was no statistical significance between the groups at each time point.

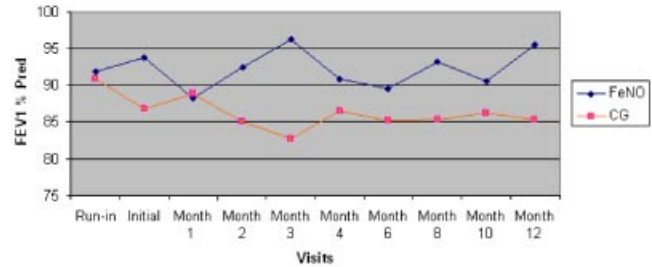


Fig. 4. FEV₁ % predicted pre-bronchodilator in the two groups during the study period. There was no statistical significance between the groups at each time point.

in the FeNO group (compared to controls), this did not reach statistical significance (which is likely related to the lack of power). Children in the FeNO group had significantly higher ICS use (daily dose by the end of the 12 months and accumulative dose) compared to the control group, but the difference between end and start of trial was not significantly different between groups. Also asthma control factors (asthma and cough diary scores, QoL) were similar between groups.

While there are now several published RCTs^{13–15,17} that evaluated whether using FeNO to adjust asthma medications is superior to using symptoms alone, our study has three features that likely accounts (at least in part) for our different results differ from previous published RCTs in children/adolescent. These features are (a) our study is the sole study that adjusted FeNO cut-offs based on atopy, (b) none of the previous pediatric studies used asthma exacerbations as the primary outcome, and (c) the FeNO strategy only utilized FeNO levels to adjust treatment.

There are four published RCTs in children that have evaluated the benefit of a FeNO-based strategy in adjusting medications for asthma.^{13–15,17} None had shown any significant benefit of using FeNO compared to controls with respect to exacerbations but none of the studies used exacerbation as their primary end-point, used FeNO levels solely in intervention arm or adjusted according to atopy status. In contrast, the adult-based studies^{12,16,18} used exacerbations as their primary

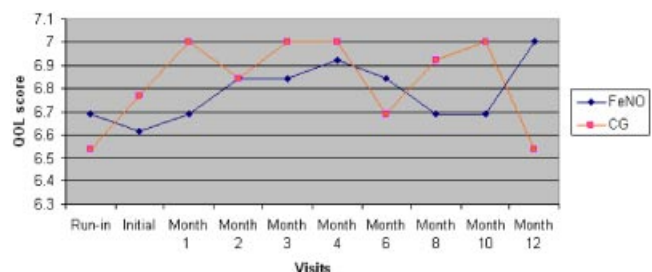


Fig. 5. Asthma Quality of Life scores in the two groups during the study period. There was no statistical significance between the groups at each time point.

outcome, but none showed any benefit in reducing asthma exacerbation. Also, none of these adult studies adjusted FeNO based on atopy. De Jongste et al.¹⁵ assessed daily FeNO telemonitoring in 151 children with atopic asthma over 30 weeks with treatment (adjusted every 3 weeks). Both control and FeNO groups showed an increase in symptom-free days, improvement of FEV₁ and QoL, and a reduction in ICS dose, with no significant difference between the groups. Fritsch et al.¹³ concluded that therapy aimed at lowering FeNO in 47 children with asthma, improved parameters of small airway function but was did not improve clinical markers of asthma control. At the end of the study (6 months) children in the FeNO group had higher median daily doses of ICS in comparison to the control group (316 µg vs. 241 µg) but reported as not significant.¹³ Pijnenburg et al.¹⁷ showed that titrating steroids based on FeNO levels in children did not result in higher steroid doses and improves airway hyper-responsiveness and markers of airway inflammation, but there was no difference in exacerbations or asthma symptoms between groups. In Szeffler et al.'s study¹⁴ (n = 546 adolescents), the mean number of days with asthma symptoms (primary outcome), pulmonary function and asthma exacerbations also did not differ between the groups. Participants in the FeNO group received higher doses of ICS (difference 119 µgm per day, 95% CI 49, 189) than controls. All but one study¹⁷ reported no difference in FeNO levels between the groups at end point. Pijnenburg et al.¹⁷ reported no change from baseline in the FeNO group, but the symptom group had an increase of 32% from baseline levels.

Our study is the first RCT on FeNO-based asthma management evaluation that have considered the presence or severity of atopy in their algorithm of management. Our FeNO cut-off levels were adjusted in accordance to severity of atopy defined on SPT. We speculate that this is one of the reasons why our study showed a benefit compared to the others which did not show a difference in exacerbations between groups. Raised FeNO in children has been associated with atopy with or without respiratory symptoms.^{21,22} FeNO values in people with atopy can be as high as 54 ppb compared to non-atopic people even in the absence of any disease.³⁴ However our inclusion criteria was different as not all the children in our study was atopic whereas "Atopic asthma" was an inclusion criterion for Pijnenburg et al.¹⁷ as defined as RAST class 2 or higher for at least one airborne allergen ever. Similarly all children in Fritsch et al.¹³ and de Jongste¹⁵ had an inclusion criteria of positive skin prick test or RAST. Szeffler et al.¹⁴ attended to skin prick tests with 88% testing positive to at least 1 of 15 allergens. Of the adult studies, Shaw et al.¹⁶ reported that some of their participants were atopic (62% in FeNO group, 70% in control group). Powell et al.¹⁸ also reported participants being atopic (75.2% in FeNO

group, 76.2% in control group). Whereas Smith et al.¹² did not describe whether their subjects were atopic or not. The cut-offs we used for adjustment was low but this was intended in the context that children already on ICS would have low FeNO levels and we were guided by the sole paper that reported FeNO levels and atopy in children at the time our study commenced. It could be argued that adjustment for age, gender, size, and ethnicity should also be taken into account. However we considered this unnecessary as it would have been not feasible to adjust for so many factors. Further age and ethnicity are lesser predictors for FeNO levels (compared to atopy)³⁵ and our study was a RCT and groups were well matched (Table 3).

In our study, children in the FeNO group had significantly higher ICS doses than controls. This is similar to two other published pediatric studies^{13,14} but dissimilar to two others.^{15,17} Although, there was no significant difference between groups for ICS dose in the Pijnenburg et al.¹⁷ study, children in that study had a high mean daily dose of ICS at the final visit (FeNO group = 935 µg (SD 656); control group = 910 µg (SD 678)). The cumulative dose of ICS at end of study was also significantly higher in the FeNO group.

The cut offs of FeNO utilized for stepping up or down therapy also differed among previous published studies (ranging from 15 to 30 ppb). Recently published ATS guidelines²⁰ suggests that FeNO levels in children <20 ppb is less likely to respond to corticosteroids (CS) and levels >35 ppb in children will be responsive to CS. These guidelines also recommend that cut points are utilized rather than reference values.²⁰ Furthermore, in the RCT's conducted to date the algorithms used are not based on Asthma Treatment ALgorithm (ASTRAL) studies.³⁶ Jacinto et al.³⁷ conducted a systematic review examining the reference/normative values and individual factors effecting FeNO levels. They concluded that the formulation of reference values should be "based on a preset physiological model with endogenous and stable factors."³⁷

We used a cut-off that was very low as, when our protocol was designed in 2005, there was little data to guide and we based our cut off values on the only data available in large healthy Australian cohort.²¹ Despite this limitation, we believe that the concept of atopy adjustment for FeNO levels is important given that our study was dual-centered with significant differences found between the two treatment strategies. Recently, "personal best" has been suggested as the cut-off point³⁸ but defining this level may not be straightforward.

Current asthma guidelines differ with respect to steps in therapy and none of the current guidelines currently recommend using FeNO. In designing our hierarchy of treatment we considered feasibility, the Australian approach and health system (at the time the study was

designed). Thus the steps used in our study are neither aligned to steps in the BTS or USA guidelines.^{5,6} Also, we used a validated symptom score diary to assure a consistent interpretation of symptoms, that is, to semi-objectively quantify asthma symptoms as opposed to true “usual care.” The change of scores to up and down-tailor medications is beyond the realms of “usual care” but arguably our method was more robust as usual care would be difficult to define when several physicians across two centers were involved in the care of the children. Further use of a symptom scoring system allowed blinding of the physician. Nevertheless, our “control” strategy did not represent “placebo” as the children were still actively managed. This possibly dilutes the effect of the utility of using FeNO.

Further to the above, our study has several additional limitations. Firstly, we ceased recruitment after 2.3 years for feasibility reasons, before reaching our planned sample size, as preliminary analysis had shown a difference between the groups. This is a major limitation as we did not pre-specify stopping rules in our trial register. We did not perform post-hoc power analyses for equivalence for the outcomes where there were no difference between groups, in line with current recommendations on post hoc analyses.³⁹

Secondly, although the children, parents and physician were unaware of the group allocation, the authors (HP & CA) who performed the FeNO measurements and calculated the scores from the parents' dairy cards were not blinded. Thirdly, we did not ask the parents or children after the trial which group they thought they were in, so we were unable to test participant masking. Fourthly, although the randomization sequence was externally generated and different block sizes were used, there is small chance of selection bias in our study. Routinely in practice decisions regarding treatment are certainly more complex than our simple algorithm, consequently our study did not compare “usual care.”

Despite the favorable results in number of patients experiencing asthma exacerbations in the 12-month follow-up period, the other asthma outcomes measured that reflect asthma control asthma QoL and symptoms) showed no difference between groups. A decrease in exacerbation rates from baseline in both groups could be possibly explained by the Hawthorne effect. The discordance between asthma control and exacerbations is increasingly appreciated.^{40,41} While exacerbations are an important outcome, arguably subjective measures of asthma control are also important. Thus, although our findings demonstrate that monitoring FeNO is useful in reducing exacerbations, it is likely not beneficial in all children. It is possible that it is most beneficial to children who have frequent exacerbations. The non-beneficial effect on asthma control is consistent in all published pediatric studies to date.^{13–15,17}

In spite of the limitations of our study, we believe that our study is important as this is the first RCT on FeNO that has taken atopy status into account. We conclude that taking atopy into account when using FeNO to tailor asthma medications is likely beneficial in reducing the number of children with severe exacerbations. This occurred at the expense of significantly higher ICS doses. However, the strategy is unlikely beneficial for improving asthma control and a larger study that addresses the limitations presented above, is required to confirm or refute our findings.

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