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

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Summary

Background **Preliminary evidence is equivocal about the role of exhaled nitric oxide (NO) in clinical asthma management. We aimed to assess whether measurement of exhaled NO, as a biomarker of airway inflammation, could increase the effectiveness of asthma treatment, when used as an adjunct to clinical care based on asthma guidelines for inner-city adolescents and young adults.**

Methods **We did a randomised, double-blind, parallel-group trial at ten centres in the USA. We screened 780 inner-city patients, aged 12–20 years, who had persistent asthma. All patients completed a run-in period of 3 weeks on a regimen based on standard treatment. 546 eligible participants who adhered to treatment during this run-in period were then randomly assigned to 46 weeks of either standard treatment, based on the guidelines of the National Asthma Education and Prevention Program (NAEPP), or standard treatment modified on the basis of measurements of fraction of exhaled NO. The primary outcome was the number of days with asthma symptoms. We analysed patients on an intention-to-treat basis. This trial is registered with clinicaltrials.gov, number NCT00114413.**

Findings **During the 46-week treatment period, the mean number of days with asthma symptoms did not differ between the treatment groups (1·93 [95% CI 1·74 to 2·11] in the NO monitoring group *vs* 1·89 [1·71 to 2·07] in the control group; difference 0·04 [–0·22 to 0·29], p=0·780). Other symptoms, pulmonary function, and asthma exacerbations did not differ between groups. Patients in the NO monitoring group received higher doses of inhaled corticosteroids (difference 119 µg per day, 95% CI 49 to 189, p=0·001) than controls. Adverse events did not differ between treatment groups (p>0·1 for all adverse events).**

Interpretation **Conventional asthma management resulted in good control of symptoms in most participants. The addition of fraction of exhaled NO as an indicator of control of asthma resulted in higher doses of inhaled corticosteroids, without clinically important improvements in symptomatic asthma control.**

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Introduction

Asthma is a complex respiratory disorder that is characterised by variable and recurring symptoms, airflow obstruction, and underlying airway inflammation. In 2007, the US National Heart, Lung and Blood Institute (NHLBI) updated its Guidelines for the Diagnosis and Management of Asthma,[1,2] and proposed that treatment to achieve asthma control should aim both to regulate the manifestations of impairment (ie, symptoms, need for rescue treatment, limitations of activity, and pulmonary function) and to reduce future risk.

Asthma symptoms and exacerbations are theoretically linked to underlying inflammation of airways, but are not direct indicators of inflammation. Measurement of biomarkers that are more closely associated with airway inflammation could improve asthma control by enabling treatment to be better directed. One such marker of airway inflammation is the fraction of exhaled nitric oxide (NO),[3] which has been shown to increase during periods of uncontrolled asthma[4–12] and decrease during treatment with anti-inflammatory agents.[13–21] Previous trials have assessed the use of fraction of exhaled NO as an alternative to conventional modification of treatment based on symptoms and pulmonary function.[22–25] However, in practice, clinicians would be more likely to monitor exhaled NO as an additional way to monitor airway inflammation, rather than as a replacement. Therefore, we believe that a clinically more relevant question is whether the addition of NO monitoring to guideline-based management can improve management of asthma. We aimed to assess the effectiveness of measurement of fraction of exhaled NO as an adjunct to guideline-directed management of asthma in a population of inner-city adolescents and young adults who were characterised by high levels of atopy, allergen exposure, and poor asthma control.[26–30]

Methods

Participants

We designed a randomised, double-blind, parallel-group trial at ten centres in cities across the USA. We initially

	Days of symptoms†	Nights of symptoms‡	Proportion of best FEV_1§	Fraction of exhaled NO (ppb)
Level 1	0–3	0–1	≥80%	0–20
Level 2	4–9	2	≥80%	20·1–30
Level 3	10–13	3–4	70–79%	30·1–40
Level 4	14	5–14	<70%	>40

FEV_1=forced expiratory volume in 1 second. NO=nitric oxide. *Control level for each patient was determined from the highest value of: days of symptoms, nights of symptoms, and proportion of best FEV_1. †Participant recall of either the number of days with asthma symptoms in the 2 weeks directly before the visit, or the number of days of rescue treatment with salbutamol in that period—whichever number was higher. ‡Participant recall of either the number of nights of awakenings due to asthma sleep disruptions in the 2 weeks directly before the visit, or the number of nights of rescue treatment with salbutamol after awakening due to asthma in that period—whichever number was higher. §Calculated by dividing FEV_1 by the highest FEV_1 at any previous visit.

Table 1: **Control levels* for asthma assessment**

Panel: **Treatment to control asthma symptoms**

- Step 0 No controller medication; rescue treatment with salbutamol as needed
- Step 1 Fluticasone by dry powder inhaler 100 µg per day
- Step 2 Fluticasone by dry powder inhaler 100 µg twice a day
- Step 3 Fluticasone 100 µg and salmeterol 50 µg twice a day
- Step 4 Fluticasone 250 µg and salmeterol 50 µg twice a day
- Step 5 Fluticasone 500 µg and salmeterol 50 µg twice a day
- Step 6 Fluticasone 500 µg and salmeterol 50 µg twice a day, plus either low-dose theophylline or montelukast every day

screened participants on the basis of census tracts. Each census tract had between 2500 and 8000 people and was designed to be homogeneous with respect to population characteristics, economic status, and living conditions. We restricted eligibility to residents of urban census tracts in which at least 20% of households had incomes below the federal poverty threshold. Eligible participants were aged between 12 and 20 years, and had been diagnosed to have asthma by physicians. We specified that those on long-term control treatment must have symptoms of persistent asthma or evidence of uncontrolled disease, and that all others must have both symptoms of persistent asthma and evidence of uncontrolled disease, as defined by National Asthma Education and Prevention Program (NAEPP) guidelines.[1,2] The protocol was approved by ethical review boards at all participating institutions. Written informed consent was obtained from each participant, or their parent or legal guardian. In addition to the written consent of their parents, we obtained written assent from adolescents aged 12 to 17 years.

See Online for webappendix

At the initial visit, we assessed each patient's asthma symptoms, pulmonary function, skin-test sensitivity, adherence to prescribed drug regimen, and level of asthma control, according to four levels derived from the NHLBI guidelines (table 1). Control levels were assessed on the basis of the highest days and nights with symptoms, the lowest pulmonary function (forced expiratory volume in 1 second [FEV_1]), the highest fraction of exhaled NO, and adherence to drug regimen. Level 1 denoted good control, whereas level 4 denoted poor control. We also used a 22-item assessment of asthma control, with a score from 5 to 25, in which a score of 19 or lower denotes poor control.[31]

All eligible participants then underwent a 3-week run-in period, on a regimen based on standard treatment. The aim was to create a transition to the study medication. Physicians selected a treatment regimen for each eligible patient, from six that were defined in our protocol, based on their previous treatment, adherence and asthma control (panel). Every patient had a 10-min session with a trained asthma counsellor to reinforce the importance of adherence to medication and environmental control of asthma. We measured adherence during the run-in period with a built-in dose counter (Diskus, Glaxo Smith Kline, Zebulon, NC, USA) and structured questionnaire. Participants were excluded if their adherence to the control regimen was less than 25%. We also identified participants who were active smokers, as those who had more than 100 mg/mL cotinine in their urine, and excluded them. All prescribed medications were provided without charge, and study participants were given a 24 h telephone number to call for medical advice.

Procedures

After the run-in period, we used centralised block randomisation, with a block size of ten, to assign patients to receive either guideline-based care or guideline-based care supplemented by NO monitoring. The randomisation sequence was generated from a random number table and was stratified by site by use of SAS statistical software (version 9.1.3). A computer program generated a treatment option for each patient according to the study allocation, so that investigators and patients were not aware of individual treatment assignments.

After randomisation, every patient had a scheduled visit every 6 to 8 weeks for 46 weeks. At each visit, the study physician assessed fraction of exhaled NO, days of asthma symptoms, use of rescue drugs, pulmonary function, use of health care, adherence to treatment regimen, and missed days of school because of asthma. We measured the fraction of exhaled NO for all participants with a rapid-response chemiluminescent analyser (flow rate 50 mL/s; NIOX System, Aerocrine, Sweden) according to the guidelines of the American Thoracic Society.[32] Skin tests used the prick-puncture method on the volar surface of the forearm, with a Multi-Test II device (Lincoln Diagnostics, Decatur, IL, USA). Allergen extracts were obtained from Greer Laboratories (Lenoir, NC, USA). The webappendix lists the 14 extracts, concentrations, and positive and negative controls, and describes the test methods and assessment of results.

For each patient, all data for control level and fraction of exhaled NO were entered into a computer program.

The program selected a treatment option for that patient based on their random allocation and the treatment steps defined in the panel.

If a patient had good control of their symptoms (level 1), and their adherence to treatment was at least 50%, their treatment would either not change, or—after two consecutive visits with good control—would be decreased by one step. If the patient's control level was 2, treatment was increased by a step, and if it was 3, by two steps. If control of symptoms was poor (level 4), physicians had the option to increase treatment by three steps or by two steps plus a course of prednisone (panel). When adherence to treatment was 50% or greater, and fraction of exhaled NO was high relative to control levels for symptoms or lung function, patients in the NO monitoring group had an additional one-step increase in treatment compared with what would be given to controls.

When adherence was less than 50%, treatment was only increased if the current treatment step was inadequate for the current control level. At control levels 2 and 3, treatment step 2 was prescribed, if the participant was currently on a lower treatment step. At control level 4, a prednisone course was prescribed, if needed. Treatment was also increased to step 3 if the participant was on a lower step.

For safety reasons, patients at control level 1 with elevated eNO in the NO monitoring group did not have their doses of treatment increased on the third consecutive visit unless their symptoms had worsened. Neither were drug doses reduced solely on the basis of low fraction of exhaled NO, without a corresponding reduction in symptoms. Because of the common increase in asthma symptoms expected in September in the USA, treatments were not reduced during the August visit.

A coordinator who was aware of treatment allocation dispensed the appropriate treatment regimen to the physician for each patient, based on the recommendation generated by the computer algorithm, the participant's group assignment, and their fraction of exhaled NO. After each visit, the patient's asthma counsellor reviewed the treatment plan, and met the patient to reinforce the importance of adherence to the regimen and environmental control of asthma.

The primary outcome was the mean of maximum days with symptoms for each 2-week recall at each visit during the 46-week treatment period. We defined maximum number of days with symptoms, as in previous inner-city asthma studies[33,34] as the largest of the following variables reported over the previous 2 weeks: (1) number of days with wheezing, chest tightness, or cough; (2) number of nights of sleep disturbance; (3) number of days when activities were affected. This measure allows asthma symptoms to be correctly gauged whether the study participant expresses their asthma as reduction in play, sleep disturbance, or wheeze. We then calculated the mean of maximum days with symptoms for all visits.

Statistical methods

For power calculations, we assumed that the average maximum number of days with symptoms for each participant in the control group would be 4·2 days (SD 2·4) over each 2-week period.[34] We decided that the smallest difference between the groups that would be clinically meaningful was 0·70 days of symptoms per person in 2 weeks.[34] We calculated that, to detect such a difference with 90% power (α=0·05, two-sided), we would need 165 patients in each group. On the assumption that 30–35% of people would not complete the study, we aimed to enrol 500 participants (250 per group). We analysed the difference in asthma-related outcomes between groups with a linear mixed model. We used fixed effects for treatment group and visit, with adjustment for control level at randomisation and study site.

Secondary outcomes were admissions to hospital, unscheduled visits to emergency departments or clinics, prednisone courses for asthma, asthma exacerbations, days of wheeze, days of interference with activities, nights of sleep disruption, days of school or work missed, and days of interruption of guardian's activities. Asthma

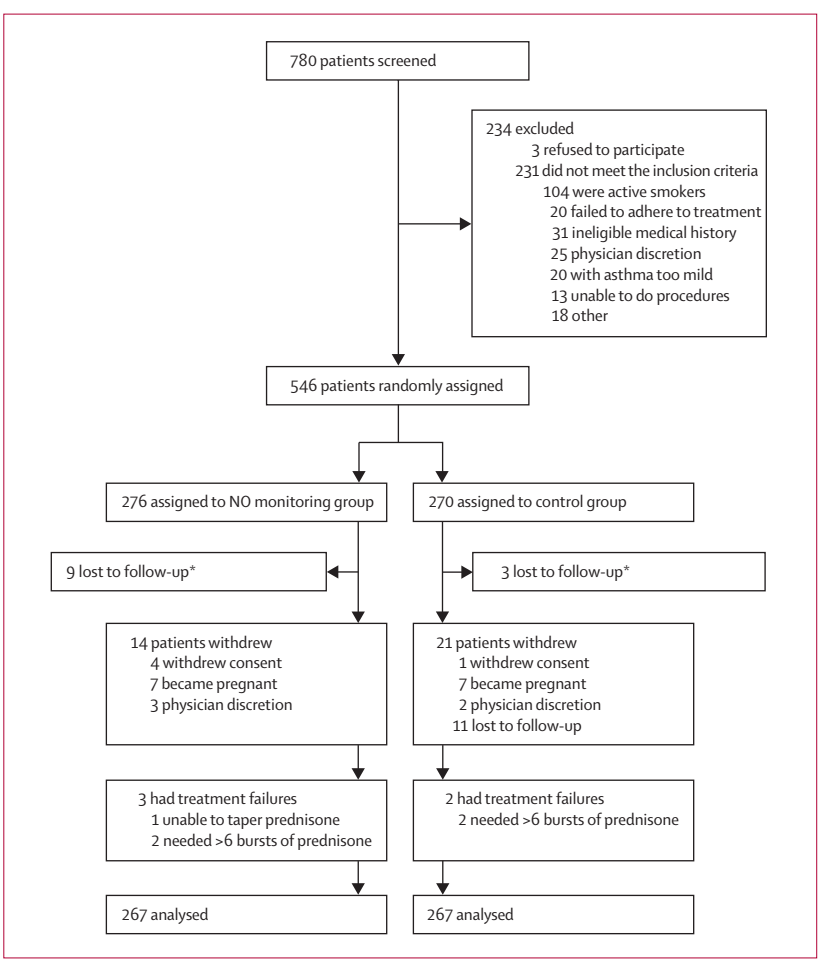

Figure 1: **Trial profile**
*These participants withdrew after random assignment, but before the first outcome data were collected at week 9.

	All participants at enrolment (n=546)	NO monitoring group at random assignment (n=276)	Control group at random assignment (n=270)
Demographic characteristics			
Age at recruitment (years)	14·4 (2·1)	14·4 (2·1)	14·4 (2·1)
Sex (male)	288/546 (53%)	146/276 (53%)	142/270 (53%)
Ethnic origin			
Black	347/546 (64%)	183/276 (66%)	164/270 (61%)
Hispanic	125/546 (22%)	62/276 (22%)	63/270 (23%)
Other or mixed	74/546 (14%)	31/276 (11%)	43/270 (16%)
Guardian completed secondary school	358/468 (76%)	182/232 (78%)	176/236 (75%)
≥1 household member employed	450/546 (82%)	237/276 (86%)	213/270 (79%)
Household income <US$15 000	262/502 (52%)	121/251 (48%)	141/251 (56%)
Asthma-related characteristics			
Duration of asthma (years)	10·6 (4·3)†	10·7 (4·3)‡	10·5 (4·3)§
Asthma control test score in the last month (possible range 5–25)	18·2 (4·2)	21·1 (3·6)	21·3 (3·2)
Days with asthma-related symptoms			
Maximum days with symptoms*	5·6 (4·6)	2·1 (2·7)	2·4 (3·0)
Days of wheeze, chest tightness, or cough*	4·5 (4·1)	1·8 (2·7)	2·2 (3·0)
Days of interference with activities*	3·3 (4·1)	1·2 (1·9)	1·0 (1·7)
Nights of sleep disruption*	2·7 (3·7)	0·6 (1·5)	0·6 (1·4)
Days of school missed	0·7 (1·4)¶	0·2 (0·6)‖	0·3 (1·0)**
Lung function and exhaled nitric oxide (NO)			
FEV_1 (proportion of best FEV_1)	92·1% (16·6)††	95·9% (15·5)‡‡	95·7% (15·9)§§
FEV_1/FVC	77·8 (9·4)††	79·8 (9·0)‡‡	80·4 (8·3)§§
Fraction of exhaled NO (ppb)	31·7 (14·1–65·4)	20·5 (11·5–45·3)	19·7 (10·9–38·0)
Use of asthma-related health care in the year before enrolment			
≥1 admission to hospital	80/546 (14%)	40/276 (14%)	40/270 (15%)
≥1 unscheduled visit	375/546 (69%)	187/276 (68%)	188/270 (69%)
≥1 prednisone course	284/546 (52%)	144/276 (52%)	140/270 (52%)
≥1 exacerbation	431/546 (79%)	219/276 (79%)	212/270 (79%)

FEV_1=forced expiratory volume in 1 second. FVC=forced vital capacity. Data are mean (SD), number (%), or median (IQR). *Participant recall of the 2 weeks before random assignment. †n=471. ‡n=232. §n=239. ¶n=398. ‖n=196. **n=185. ††n=529. ‡‡n=269. §§n=263.

Table 2: **Demographic and clinical characteristics at random assignment by study group**

See Online for webtable

exacerbations were assessed as a composite outcome, consisting of admissions to hospital, unscheduled visits, and prednisone use. Because these were rare events, we summed the events over the course of the study and analysed them with a logistic regression of 'any' versus 'none', instead of analysing the data longitudinally.

We analysed patients on an intention-to-treat basis. We planned subanalyses to assess heterogeneity of treatment effects across nine characteristics, with a statistical test for interaction.[35] We analysed all data with SAS statistical software (version 9.1.3). This trial is registered with clinicaltrials.gov, number NCT00114413.

Role of the funding source

The sponsor of the study participated in protocol development, study oversight, regulatory reporting, monitoring, data analysis, data interpretation, and writing of this report. A Principal Investigator at each research centre was responsible for ensuring completeness and quality of data collection, with support from a central statistical and clinical coordinating centre. The corresponding author and all co-investigators had full access to all study data after the trial was closed, and had final responsibility for the decision to submit for publication.

Results

Between September, 2004, and December, 2005, we screened 780 patients and excluded 234 who refused consent, did not adhere to treatment during the run-in period, or were active smokers (figure 1). The mean age of the 546 patients who were enrolled and randomly assigned was 14·4 years (IQR 13–16). At enrolment, 422 (77%) of the 546 participants did not have good control of their asthma symptoms (control level >1). 313 (57%) of the 546 participants were assessed to have control levels of 3 or 4, consistent with moderate to severe asthma. Table 2 shows that, at random assignment, lung function was low in these patients. 119 (22·5%) of 529 participants had a forced expiratory volume in 1 second (FEV_1) that was less than 80% of the predicted value.[36] 467 (88%) of 531 participants tested positive for allergy in at least one of the 14 skin tests (webtable); the median number of positive tests was 5 (IQR 2–7). 347 (64%) of 546 participants had a fraction of exhaled NO of 20 ppb or greater.

Table 2 shows that demographic characteristics of participants in the two treatment groups did not differ. 494 (90%) of the 546 participants completed the study; rates of withdrawal and treatment failure rates were low, and did not differ between groups (figure 1). After random assignment, the 276 patients in the NO monitoring group had their treatment adjusted at 1558 visits, with an average of 5·6 visits per patient. The 270 controls had 1525 visits, with an average of 5·6 visits each.

Compared with pre-study levels, doses of inhaled corticosteroids were increased at enrolment by an average of 219 μg (95% CI 199–238; p<0·0001) and long-acting β_2 agonists by an average of 6·04 μg (0·78–11·30; p=0·0243). These drugs improved asthma control over the run-in period: the maximum number of days with symptoms was reduced to 2·3 days in 2 weeks, with a mean reduction for each participant of 3·4 days (3·0–3·8, p<0·0001, figure 2). The mean score on the asthma control test also improved by 3·0 points (2·7–3·4; p<0·0001). At random assignment, only 161 (29·5%) of 546 participants did not have good control of their asthma symptoms (level >1). However, 68 (12·4%) of 546 participants had poorly controlled asthma (levels 3 and 4). Lung function also improved over the run-in period. The mean change in proportion of predicted FEV_1 was 3·3% (2·4–4·2, p<0·0001, figure 2), and mean change in ratios of FEV_1 to FVC was 2·2 (1·6–2·8, p<0·0001). Fraction of exhaled NO decreased to a median of 20·1 ppb (IQR 11·2–40·6), with a mean reduction of 12·9 ppb (95% CI 10·1–15·6, p<0·0001).

Table 3 shows that maximum days with symptoms, which was our primary endpoint, did not differ between treatment groups over the study period (p=0·78). Other asthma symptoms and asthma control scores did not differ between groups over the study period (table 3). After the run-in period, asthma symptoms remained low in both groups throughout the study period (figure 2). The distribution of control level was very consistent after random assignment. The proportion of participants who had good control of their asthma (control level=1) stayed between 71% and 78% throughout the follow-up period. Control levels did not differ between groups: 306 (57·3%) of 534 patients had their asthma under good control (control level=1) for at least 80% of visits. In 122 (22·8%) of 534 patients, asthma control was at level 3 or 4 for at least 20% of visits (59 [22·1%] of 267 in NO monitoring group; 63 [23·6%] of 267 in control group; χ^2=0·17, p=0·6801).

Figure 2 also shows that lung function, fraction of exhaled NO, and adherence did not differ between groups during the study; however, despite the level of control achieved, fraction of exhaled NO was less than 20 ppb in only 190 (35·6%) of 534 participants on at least 80% of visits during the treatment period. Adherence to treatment averaged 86·6% (SD 27·7) during the study. Fraction of exhaled NO was 23·9 ppb in the group with adherence of 50% or more, compared with a geometric mean of 30·8 ppb in the group with less than 50% adherence (ratio of means: 1·28, 95% CI 1·24–1·34; p<0·0001).

Table 3 shows that 115 (43%) of 270 controls (covariate adjusted value 42·0%, 95% CI 35·1–47·4) had at least one course of prednisone, compared with only 91 (33%) of 276 in the NO group (covariate adjusted value 32·1%, 95% CI 25·3–36·7). However, the mean number of courses per year did not differ between groups (NO monitoring group 0·66 [SE 0·085] *vs* control group 0·84 [0·085], mean difference 0·17, 95% CI –0·08 to 0·41, p=0·14). Overall use of health care was low (mean 0·04 admissions to hospital per participant year [SD 0·25]). Admissions to hospital, unscheduled use of health care, or asthma exacerbations did not differ between groups (table 3), but were much lower overall than they had been in the year before the study (table 2).

To assess whether the intervention could prove effective for patients with certain characteristics, we tested for heterogeneity of treatment effects across nine baseline characteristics. We did post-hoc subanalyses in groups defined by body-mass index (with a threshold of 30 kg/m^2), body-mass index percentile (with a threshold of 97%), allergenic skin tests (10 positive tests), blood eosinophils (100 per µL), serum immunoglobulin E (460 kU/L), asthma severity and lung function (treatment step of 4 or greater at week 0), fraction of exhaled NO (30 ppb), age (15 years), and sex.

NO monitoring differed from standard treatment in patients with body-mass index (BMI) of 30 kg/m² or greater (p=0·0117) and those with a BMI above the 97th percentile (p=0·0291). For example, among participants with body-mass index of 30 kg/m² or greater, those in the NO monitoring group had 0·60 fewer maximum days with symptoms in 2 weeks than did the control group (95% CI 0·08–1·13, p=0·0245). The intervention was also effective in those with 10 or more positive skin tests out of 14 allergens tested (p=0·0170). In patients with a high number of positive skin tests, the NO monitoring group had 0·84 fewer maximum days with symptoms in 2 weeks than did the control group (95% CI 0·11–1·58, p=0·0243). The intervention was also effective in patients with serum immunoglobulin E of greater than 460 kU/L (p=0·0072). Among patients with high serum immunoglobulin E, the NO monitoring group had 0·51 fewer maximum days with symptoms in 2 weeks than did the control group (95% CI 0·05–0·96, p=0·0296). The other five characteristics tested—asthma severity, lung function and

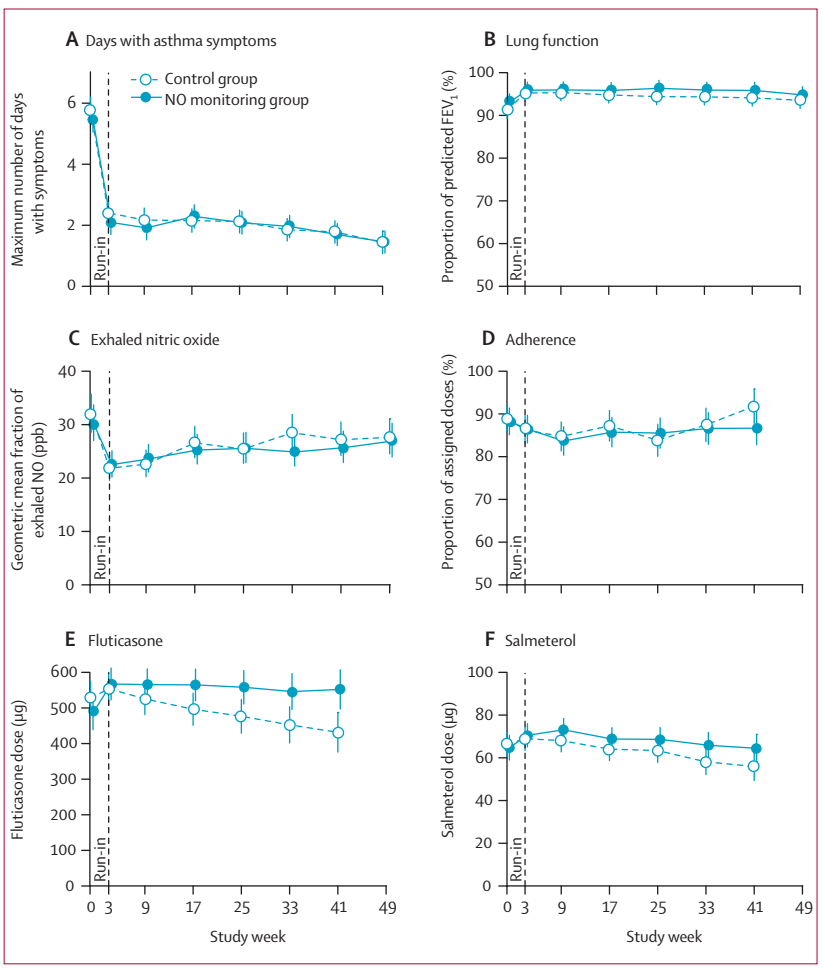

Figure 2: **Mean asthma outcomes and drugs over course of study ***
Vertical bars show 95% CIs. Primary outcome, or maximum number of days with symptoms (A), proportion of predicted FEV_1 (B), fraction of exhaled NO (C), adherence to medication (D), dose of inhaled corticosteroids (E), and dose of long-acting ß$_2$ agonist (F). *Treatment-related variables (D, E, and F) were assessed until the final treatment visit at week 41, whereas follow-up data (A, B, and C) were assessed until the end of the study period, at week 49.

	NO monitoring group (n=276)	Control group (n=270)	Difference (95% CI)	p value
Asthma-related symptoms				
Maximum days with symptoms*	1·93 (2·60)	1·89 (2·69)	0·04 (−0·22 to 0·29)	0·78
Days of wheeze*	1·71 (2·52)	1·69 (2·64)	0·03 (−0·21 to 0·26)	0·83
Days of interference with activities*	0·87 (1·79)	0·95 (1·98)	−0·08 (−0·26 to 0·10)	0·38
Nights of sleep disruption*	0·52 (1·30)	0·50 (1·25)	0·03 (−0·11 to 0·16)	0·71
Days of school missed*	0·19 (0·79)	0·23 (0·84)	−0·04 (−0·12 to 0·05)	0·38
Asthma control test score in the last month	21·89 (2·83)	21·83 (2·88)	0·06 (−0·28 to 0·40)	0·72
Lung function				
FEV_1 (proportion of predicted value)	96·3% (7·00)	95·5% (6·70)	0·8% (−0·51 to 2·07)	0·23
FEV_1/FVC	80·3 (3·90)	79·7 (3·97)	0·6 (−0·13 to 1·34)	0·11
Asthma-related use of health care				
≥1 admission to hospital	3·3% (1·78)	4·1% (1·98)	−0·8 (−4·0 to 2·3)	0·61
≥1 unscheduled use of health care	21·3% (4·09)	22·7% (4·19)	−1·4 (−9·3 to 6·7)	0·74
≥1 prednisone course	32·1% (4·67)	42·0% (4·94)	−10·3 (−18·5 to -2·2)	0·01
≥1 exacerbation	37·0% (4·83)	43·6% (4·96)	−6·5 (−14·4 to 1·4)	0·11

Data are mean (SD), unless otherwise specified. Values are adjusted for study site and values at random assignment, except for asthma-related use of healthcare, for which data were insufficient. *Participant recall of the 2 weeks before the study visit.

Table 3: **Asthma symptoms and use of health care during 46 weeks of treatment and follow-up**

	NO monitoring group	Control group	p value
Eyes, ears, nose, and throat	28 (8·3%)	26 (8·1%)	0·8674
Gastrointestinal disorders	57 (13·4%)	52 (14·1%)	0·7793
Haematology disorders	112 (27·2%)	124 (28·9%)	0·4414
Infections	305 (55·8%)	276 (52·2%)	0·4609
Musculoskeletal symptoms	59 (15·9%)	69 (18·5%)	0·4386
Nervous-system disorders	182 (34·4%)	146 (33·7%)	0·1999
Respiratory signs and symptoms	177 (33·7%)	176 (34·1%)	0·9168
Skin symptoms	52 (15·6%)	68 (17·8%)	0·1764
Other adverse events	105 (24·6%)	94 (21·5%)	0·6460

Data are numbers of adverse events (percentage of patients who had at least one adverse event).

Table 4: **Adverse events during study participation**

fraction of exhaled NO at baseline, age and sex—were not associated with differences between study groups.

The NO monitoring group received supplementary treatment because the fraction of exhaled NO was high at 405 (26%) of the 1558 visits in this group. Figure 2 shows that use of inhaled corticosteroids was reduced faster in controls than in the NO monitoring group (p=0·0054 for difference in slope), resulting in a difference of 118·9 µg of inhaled fluticasone per day by the final visit (95% CI 48·5–189·3, p=0·0010). By the end of the study, 139 (52·1%) of 267 controls had at least a one-step reduction in treatment, compared with 105 (39·3%) of 267 in the NO monitoring group (χ^2=8·723, p=0·0031). Although doses of long-acting β_2 agonists did not decrease at different rates in the two groups, 56·3% (SD 26·18) of the control group were on long-acting β_2 agonists at the end of the study as compared with 64·8% (24·48) in the NO monitoring group (mean difference: 8·5, 95% CI 0·04–16·93, p=0·0490, figure 2).

Major adverse event categories are presented in table 4. None of these events differed by treatment group.

Discussion

We sought to determine whether measurement of fraction of exhaled NO added value to commonly used control measures for asthma treatment based on national guidelines.[1,2] Whereas other studies on fraction of exhaled NO have typically replaced usual measures of symptoms and pulmonary function with NO as the basis for determining asthma treatment, we aimed to assess its use in combination with standard symptom-based approaches to treatment. We showed that use of current guidelines for asthma treatment provided good asthma control in most inner-city adolescents and young adults. Asthma management that incorporated measurement of fraction of exhaled NO resulted in higher doses of inhaled corticosteroids and long-acting β_2 agonists than did standard guideline-based treatment. This treatment option was associated with a small reduction in the need for prednisone courses, but did not produce an overall improvement in asthma symptoms, lung function, or need for health care.

The theoretical basis of our algorithm was that patients with continuing airway inflammation who needed increased doses of drugs to control their asthma would be identified because of a higher fraction of exhaled NO than other patients. Therefore, the NO monitoring group would be expected to receive higher amounts of medication over the course of the study. However, this increase in treatment did not result in any clinical important outcomes. Four other small clinical trials—two in adults[24,25] and two in children[22,23]—have used fraction of exhaled NO for asthma management. These studies either used fraction of exhaled NO as a guide for steroid reduction, or used it in conjunction with other symptoms to guide treatment. Management was modified on the basis of pulmonary function in some but not all the studies.

Petsky and colleagues[37] published a meta-analysis of these four studies that concluded that the groups did not differ in asthma exacerbations, symptoms, or spirometry. The decreased steroid use reported in adults whose treatment was guided by fraction of exhaled NO was discounted, because the finding was based on a post-hoc study analysis and was not replicated in other studies. All the studies included in the meta-analysis shared limitations of small size, single location, and varying outcomes. We avoided many of these concerns by designing a multi-site study, with a large sample size and standardised measures. However, our findings also show that monitoring of fraction of exhaled NO did not improve asthma management.

Symptoms were used both as a measure for determining treatment and as the primary outcome, which might seem unusual. However, for management purposes, the asthma control levels that determined treatment were based on both a range of days with symptoms and measures of

pulmonary function. For example, control level 1 was assessed from a range of 0 to 3 days of symptoms over the 2 weeks before each study visit. Therefore, for asthma management purposes, a person with 0 days with symptoms would be treated the same as a person with 3 days with symptoms. By contrast, for assessment of our outcome, we used days with symptoms as a continuous variable; the study was powered to detect a change of 0·70 days between groups. Although symptoms were used to determine treatment, the analytic approach examined symptoms 2 months after the treatment adjustment to assess the effect of management based on monitoring of fraction of exhaled NO. Therefore, the use of symptoms as both the main outcome of the study and one of several criteria used to adjust treatment did not bias the study against finding a difference between groups.

One limitation of our study was that thresholds for fraction of exhaled NO cut-points could have been too high. However, if we had used lower thresholds, for example, of less than 20 ppb to identify good control, doses of inhaled corticosteroids would have been even higher, with no guarantee of clinical benefit. Further, although the four studies included in the review by Petsky and colleagues[37] used a single threshold of 15–35 ppb NO, our study used three thresholds, ranging from 20 to 40 ppb. The use of multiple thresholds over this extended range increased the likelihood that treatment would be modified on the basis of fraction of exhaled NO, irrespective of the severity of asthma at baseline. Treatment was modified on the basis of fraction of exhaled NO in about 26% of the study visits in the NO monitoring group. The risk of at least one prednisone course for asthma exacerbations was lower in the NO monitoring group than in controls. Because the risk of asthma exacerbation is not tightly correlated with ongoing asthma symptoms and pulmonary function, modification of treatment according to fraction of exhaled NO might have greater potential to reduce exacerbations than to improve day-to-day control. However, measures of asthma exacerbations, such as unscheduled visits and admissions to hospital, did not differ between groups (table 2).

The post-hoc analyses of intervention effects within various sample strata suggested that treatment based on fraction of exhaled NO could offer benefits to subsets of inner-city asthmatics. In participants with obesity, high blood eosinophil count, and atopy, the NO monitoring group showed a larger decrease in days with asthma symptoms. Measurements of the fraction of exhaled NO might be particularly helpful for management of obese patients because symptoms related to dyspnea might be difficult to interpret for assessment of asthma control.[38] In addition, obesity, elevated blood eosinophils, and a high degree of atopy might be associated with airway inflammation that makes the measurement of fraction of exhaled NO more germane to the assessment of asthma control. However, these findings should be interpreted with caution because they are based upon post-hoc analyses of our primary outcome data, and we had insufficient numbers on which to make conclusions.

In summary, in inner-city adolescents and young adults with asthma, modifications of treatment based on measurements of the fraction of exhaled NO did not improve management of asthma based on other symptoms and spirometry alone. Monitoring of the fraction of exhaled NO slowed the rate at which clinicians could lower doses of inhaled steroids. The observed decrease in the proportion of participants who needed one or more bursts of prednisone is of questionable clinical significance because other indicators of exacerbation did not change. Therefore, in the context of our study, measurements of fraction of exhaled NO add little benefit to a carefully applied guidelines approach to asthma management.

Contributors

All authors contributed to the design of the study and its execution. JJW and HM did all data analyses. SJS, PG, MK, HM, WJM, GTO'C, JAP, CAS, and SJT helped to write the draft of this manuscript. All authors have seen and approved the final version.

Conflict of interest statement

CAS receives research support from GlaxoSmithKline, Schering, and Pharmaxis and is a consultant for GSK. WJM is a consultant to Genentech and was an invited speaker at the European Respiratory Society for Aerocrine. Other authors declare no other conflicts of interest.

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