Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults (Review)

Petsky HL, Cates CJ, Li A, Kynaston JA, Turner C, Chang AB

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[Intervention Review]

Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults

Helen L Petsky[1], Christopher J Cates[2], Albert Li[3], Jennifer A Kynaston[4], Cathy Turner[5], Anne B Chang[6]

[1]Department of Respiratory Medicine, Royal Children's Hospital, Brisbane, Australia. [2]Community Health Sciences, St George's, University of London, London, UK. [3]Department of Paediatrics, Prince of Wales Hospital, Shatin, Hong Kong. [4]Royal Children's Hospital, Brisbane, Australia. [5]School of Nursing, University of Queensland, Herston, Australia. [6]Queensland Children's Respiratory Centre and Queensland Children's Medical Research Institute, Royal Children's Hospital, Brisbane and Menzies School of Health Research, CDU, Darwin, Brisbane, Australia

Contact address: Helen L Petsky, Department of Respiratory Medicine, Royal Children's Hospital, Herston Road, Brisbane, Queensland, 4029, Australia. helen_petsky@health.qld.gov.au.

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ABSTRACT

Background

The measurement of severity and control of asthma in both children and adults can be based on subjective or objective measures. It has been advocated that fractional exhaled nitric oxide (FeNO) can be used to monitor airway inflammation as it correlates with some markers of asthma. Interventions for asthma therapies have been traditionally based on symptoms and/or spirometry.

Objectives

To evaluate the efficacy of tailoring asthma interventions based on exhaled nitric oxide in comparison to clinical symptoms (with or without spirometry/peak flow) for asthma related outcomes in children and adults.

Search methods

We searched the Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and reference lists of articles. The last search was completed in February 2009.

Selection criteria

All randomised controlled comparisons of adjustment of asthma therapy based on exhaled nitric oxide compared to traditional methods (primarily clinical symptoms and spirometry/peak flow).

Data collection and analysis

Results of searches were reviewed against pre-determined criteria for inclusion. Relevant studies were independently selected in duplicate. Two authors independently assessed trial quality and extracted data. Authors were contacted for further information with response from one.

Main results

Two studies have been added for this update, which now includes six (2 adults and 4 children/adolescent) studies; these studies differed in a variety of ways including definition of asthma exacerbations, FeNO cut off levels, the way in which FeNO was used to adjust therapy and duration of study. Of 1053 participants randomised, 1010 completed the trials. In the meta-analysis, there was no significant difference between groups for the primary outcome of asthma exacerbations or for other outcomes (clinical symptoms, FeNO level and spirometry). In post-hoc analysis, a significant reduction in mean final daily dose inhaled corticosteroid per adult was found in the group where treatment was based on FeNO in comparison to clinical symptoms, (mean difference -450 mcg; 95% CI -677 to -223 mcg budesonide equivalent/day). However, the total amount of inhaled corticosteroid used in one of the adult studies was 11% greater in the FeNO arm. In contrast, in the paediatric studies, there was a significant increase in inhaled corticosteroid dose in the FeNO strategy arm (mean difference of 140 mcg; 95% CI 29 to 251, mcg budesonide equivalent/day).

Authors' conclusions

Tailoring the dose of inhaled corticosteroids based on exhaled nitric oxide in comparison to clinical symptoms was carried out in different ways in the six studies and found only modest benefit at best and potentially higher doses of inhaled corticosteroids in children. The role of utilising exhaled nitric oxide to tailor the dose of inhaled corticosteroids cannot be routinely recommended for clinical practice at this stage and remains uncertain.

PLAIN LANGUAGE SUMMARY

Tailoring asthma interventions based on exhaled nitric oxide

In this review involving 1010 adults and children with asthma, we found that tailoring the dose of inhaled corticosteroids based on exhaled nitric oxide (compared to clinical symptoms with or without spirometry/peak flow) was beneficial in reducing the final (but not the overall) daily inhaled corticosteroid doses in adults. However in children inhaled corticosteroid dose was increased when exhaled nitric oxide guided strategy was used. There was no difference between groups in other asthma outcomes (exacerbations, spirometry, FeNO or symptom control). Thus tailoring the dose of inhaled corticosteroids based on exhaled nitric oxide cannot be routinely advocated.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults

Patient or population: Adults and children with asthma
Settings:
Intervention: Tailored intervention based on FeNO
Comparison: Intervention based on clinical symptoms

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Intervention based on clinical symptoms	Tailored intervention based on FeNO				
Number of subjects who had one or more exacerbations over the study period in adults (follow-up: 52 weeks)	**30 per 100**	**27 per 100** (12 to 51)	**OR 0.85** (0.3 to 2.43)	197 (2)	⊕⊕⊕◯ **moderate**[1]	
Number of subjects who had one or more exacerbations over the study period in children and adolescents (follow-up: 26-52 weeks)	**36 per 100**	**30 per 100** (24 to 36)	**OR 0.75** (0.55 to 1.01)	782 (3)	⊕⊕⊕◯ **moderate**[2,3,4]	
Number of exacerbations per 52 weeks in adults (follow-up: mean 52 weeks)	The mean number of exacerbations per 52 weeks in adults in the control groups was **0.66**	The mean Number of exacerbations per 52 weeks in adults in the intervention groups was **0.14 lower** (0.41 lower to 0.12 higher)		197 (2)	⊕⊕⊕◯ **moderate**[1]	

Number of exacerbations per 52 weeks in children and adolescents (follow-up: mean 52 weeks)	The mean number of exacerbations per 52 weeks in children and adolescents in the control groups was **0.84**	The mean Number of exacerbations per 52 weeks in children and adolescents in the intervention groups was **0.18 lower** (0.42 lower to 0.06 higher)		546 (1)	⊕⊕⊕◯ **moderate**[3,4]
ICS dose at final visit in adults (follow-up: 52 weeks)	The mean ics dose at final visit in adults in the control groups was **1088 mcg/day (budesonide equivalent)**	The mean ICS dose at final visit in adults in the intervention groups was **450 lower** (677 to 223 lower)		197 (2)	⊕⊕⊕◯ **moderate**[5]
ICS dose at final visit in children and adolescents (follow-up: 26-52 weeks)	The mean ics dose at final visit in children and adolescents in the control groups was **804 mcg/day (budesonide equivalent)**	The mean ICS dose at final visit in children and adolescents in the intervention groups was **140 higher** (29 to 251 higher)		777 (3)	⊕⊕◯◯ **low**[3,6,7]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio;

GRADE Working Group grades of evidance
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Confidence intervals are wide and include clinically important benefit and harm
[2] One study (deJongste 2008) design was open-label which may have introduced bias.
[3] Studies reported technical difficulties with FeNO analysers as reported in risk of bias table.
[4] Medication increased prior to commencement of study.

[5] In one study the overall dose of ICS was higher with FeNO based interventions even though the final ICS dose was lower
[6] One study presented in these results was single blinded with intervention arm analysing FeNO only.
[7] Final inhaled corticosteroid doses were quite varied. With one study having particularly high doses.

BACKGROUND

The severity and control of asthma in both children and adults can be based on subjective or objective measures. Subjective measures usually involve a series of questions used for clinical assessment, diary cards and quality of life questionnaires. Traditional objective measures include peak flow monitoring, spirometry and degree of airway hyper-responsiveness (AHR) (Zacharasiewicz 2005). Based on current data on airway inflammation and asthma, exhaled nitric oxide (FeNO) is advocated as a monitoring marker for asthma control in adults and children. Some have suggested use of an algorithm that is based on FeNO to tailor asthma medications (Szefler 2005) instead of the traditional use of clinical symptoms and simple spirometry.

In asthma, inflammation can be eosinophilic or non-eosinophilic (Douwes 2002). Corticosteroids which targets eosinophilic inflammation is a key medication in the management of asthma. Assessing airway inflammation by quantitative measurements of eosinophilic inflammation, instead of subjective data, potentially allows the physician to tailor personal asthma interventions. In patients with eosinophilic inflammation the use of inhaled corticosteroids (ICS), reduces exacerbations and improves symptoms and asthma control. Eosinophilic inflammation can be measured by cell count in sputum or FeNO level. FeNO correlates with other markers of asthma e.g.. eosinophilia in induced sputum (Jatakanon 1998) and bronchial reactivity in non-steroid treated subjects (Dupont 1998). However, induced sputum and sputum analysis is labour intensive and not widely available in non-research laboratories. Hypertonic saline, used to induce sputum may also temporarily increase asthma symptoms. Measures of FeNO thus confer some advantage over measurements of sputum eosinophils. However it does not provide any data on non-eosinophilic inflammation and the equipment required to measure FeNO is relatively expensive.

A systematic review evaluating the efficacy of tailoring asthma interventions based on exhaled nitric oxide in comparison with the traditional reliance upon clinical symptoms of asthma (with or without spirometry/peak flow) will be useful to guide clinical practice.

OBJECTIVES

To evaluate the efficacy of tailoring asthma interventions based on exhaled nitric oxide in comparison to clinical symptoms (with or without spirometry/peak flow) for asthma related outcomes in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing adjustment of asthma medications based on exhaled nitric oxide levels in comparison to clinical symptoms (with or without spirometry/peak flow).

Types of participants

Children and adults with 'classical asthma'.
Exclusion criteria: eosinophilic bronchitis, asthma related to an underlying lung disease such as bronchiectasis and chronic obstructive airway disease, or diagnostic categories such as 'cough variant asthma' and 'wheezy bronchitis' where controversies exist.

Types of interventions

All randomised controlled comparisons of adjustment of asthma therapy based on exhaled nitric oxide compared to clinical symptoms (with or without spirometry/peak flow). Trials that included the use of other interventions were included if all participants had equal access to such interventions.

Types of outcome measures

Attempts were made to obtain data on at least one of the following outcome measures:

Primary outcomes

Asthma exacerbations during follow-up, or exacerbation rates.

Secondary outcomes

1. Objective data,
2. Symptom based data,
3. Medications.

The proportions of participants and the mean clinical improvement were determined using the following hierarchy of assessment measures (i.e. where two or more assessment measures are reported in the same study, the outcome measure that is listed first in the hierarchy was used);
i) Hospitalisation, acute presentations to an emergency facility for asthma;
ii) Rescue courses of oral corticosteroids;
iii) Symptomatic (Quality of life, Likert scale, asthma diary, visual analogue scale) - assessed by the patient (adult or child);
iv) Symptomatic (Quality of life, Likert scale, asthma diary, visual analogue scale) - assessed by the parents/carers;
v) Symptomatic (Likert scale, visual analogue scale) - assessed by clinicians;
vi) Indices of spirometry, peak flow, airway hyperresponsiveness; and
vii) Beta-agonist used.
Dose of inhaled corticosteroid used was also described as a post-hoc analysis

Search methods for identification of studies

Trials were identified from the following sources:
1. The Cochrane Airways Group Specialised Register of Trials
2. The Cochrane Central Register of Controlled Trials (CENTRAL) Issue 4, 2008
3. MEDLINE (1966 to February 2009). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.
4. OLDMEDLINE (1950 to 65). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.
5. EMBASE (1980 to February 2009). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.
6. The list of references in relevant publications.
7. Written communication with the authors of trials included in the review.
Searches for the electronic databases were based on the following terms:
"asthma" AND ("exhaled nitric oxide" OR "FeNO" OR "FeNO" OR "airway inflammation") all as (textword) or (MeSH)
For the full search strategies see Appendix 1.

Data collection and analysis

Selection of studies

From the title, abstract, or descriptors, the literature search was reviewed independently in triplet (HP reviewed all and two sets of reviewers: AL; AK paired with CT) to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. From the full text using specific criteria, the same sets of reviewers independently selected trials for inclusion. There was no disagreement although it was planned that disagreement would have been resolved by third party adjudication.

Data extraction and management

Trials that satisfied the inclusion criteria were reviewed and the following information recorded: study setting, year of study, source of funding, patient recruitment details (including number of eligible subjects), inclusion and exclusion criteria, other symptoms, randomisation and allocation concealment method, numbers of participants randomised, blinding (masking) of participants, care providers and outcome assessors, dose and type of intervention, duration of therapy, co-interventions, numbers of patients not followed up, reasons for withdrawals from study protocol (clinical, side-effects, refusal and other), details on side-effects of therapy, and whether intention-to-treat analyses were possible. Data was extracted on the outcomes described previously and data from included studies was double entered into RevMan 5.0 for meta-analysis. Initial attempts to contact the corresponding authors were not successful, but further information was made available by one author from a new paper de Jongste 2009 for this update.

Assessment of risk of bias in included studies

Studies included in the review underwent quality assessment and entered into Risk of Bias table.Four components were assessed:
1. Adequate sequence generation.
2. Allocation concealment.
3. Blinding. Classified
4. Free of other bias.

Measures of treatment effect

For the dichotomous outcome variables of each individual study, relative and absolute risk reductions were calculated using a modified intention-to-treat analysis when the outcome event is a beneficial event. When the event is non-beneficial event (such as exacerbation), "treatment received" analysis was utilised. A modified intention-to-treat analysis assumes that participants not available for outcome assessment have not improved (and probably represents a conservative estimate of effect). An initial qualitative comparison of all the individually analysed studies examined whether pooling of results (meta-analysis) was reasonable. This took into account differences in study populations, inclusion/exclusion criteria, interventions, outcome assessment, and estimated effect size.

Data synthesis

The results from studies that met the inclusion criteria and reported any of the outcomes of interest were included in the subsequent meta-analyses. The summary weighted risk ratio and 95% confidence interval (fixed effects model) were calculated (Cochrane statistical package, RevMan 5.0). For Rate Ratios of common events whereby one subject may have more than one event, GIV was utilised. The Rate Ratios were taken from the published papers and the standard errors were calculated from confidence intervals or P values published in the papers. It was planned for cross-over studies, mean treatment differences would be calculated from raw data, extracted or imputed and entered as fixed effects generic inverse variance (GIV) outcome, to provide summary weighted differences and 95% confidence intervals. Numbers needed to treat (NNT) were calculated from the pooled OR and its 95% CI applied to a specified baseline risk using an online calculator (Cates 2003). The outcome indices were assumed to be normally distributed continuous variables so the mean difference in outcomes could be estimated (weighted mean difference). If studies reported outcomes using different measurement scales, the standardised mean difference was estimated. Any heterogeneity between the study results was described and tested to see if it

reached statistical significance using a chi-squared test. The 95% confidence interval estimated using a random effects model was included whenever there are concerns about statistical heterogeneity. Heterogeneity is considered significant when the P value is <0.10 (Higgins 2005).

Subgroup analysis and investigation of heterogeneity

An a priori sub-group analysis was planned for
a) adults vs children
It was planned that sensitivity analyses be done to assess the impact of the potentially important factors on the overall outcomes:

a) variation in the inclusion criteria;
b) differences in the medications used in the intervention and comparison groups;
c) analysis using random effects model;
d) analysis by "strategy received";
e) analysis by "intention-to-treat".

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

From the 2006 searches, the Airways Group specialised register/ search identified 1278 potentially relevant titles. After assessing the abstracts, 20 papers were obtained for consideration to be included into review, 4 papers were included. From 2009 searches, 52 additional abstracts were identified, 2 fulfilled the inclusion criteria..

Included studies

Six studies were included (see table "Characteristics of included studies"), four were uni-centre studies (Fritsch 2006; Pijnenburg 2005; Shaw 2007; Smith 2005) and two were multi-centred (de Jongste 2009, Szefler 2008). Four studies were in children or adolescents (de Jongste 2009, Fritsch 2006; Pijnenburg 2005, Szefler 2008), one with adult patients (Shaw 2007) and one combining adolescents and adults (Smith 2005). Two studies were double blind, parallel groups (Pijnenburg 2005, Szefler 2008) whereas four were single blind, parallel groups (de Jongste 2009, Fritsch 2006; Shaw 2007; Smith 2005). All were published in English.
In all studies (de Jongste 2009; Fritsch 2006; Pijnenburg 2005; Shaw 2007; Smith 2005; Szefler 2008) asthma management were based on either clinical strategy/symptoms (control arm) or exhaled nitric oxide, with or without taking the symptoms into account (intervention arm). The management of the control arm in the studies differed. In de Jongste 2009 treatment was based on symptom score which was sent by electronic diary every 3 weeks. One study, Fritsch 2006 based their treatment decision on symptoms, use of short acting beta-2-agonists and lung function. Pijnenburg 2005 used symptom scores from diary cards to guide their decision on treatment; it was a cumulative score for the 2 weeks prior to each visit. Shaw 2007, used the British Thoracic Society asthma guidelines to base their treatment decisions which included traditional assessment of symptoms (using validated Juniper asthma control questionnaire). Smith 2005 used asthma symptoms, nighttime waking, bronchodilator use, variation in peak expiratory flow rate in previous 7 days and FEV_1. Subjects had their asthma management based on standard treatment as per the guidelines of National Asthma Education and Prevention Program (NAEPP) in Szefler 2008.
The intervention arm in all 6 studies, although primarily based on FeNO level, differed in the cut off for FeNO for change in therapy. In de Jongste et al's study and Fritsch et al's study, anti-inflammatory treatment was based on keeping FeNO below 20 ppb. In Pijnenburg et al's study, medication was adjusted to keep FeNO less than 30 ppb. Shaw et al's study aimed at keeping FeNO below 26 ppb with a minimum dose of anti-inflammatory treatment. In Smith et al's study, medications were based on maintaining FeNO less than 15 ppb at a flow rate of 250 ml per second, which the authors found to be equivalent to 35 ppb at a flow rate of 50 ml per second. Szefler et al used a combination of different levels of FeNO and symptoms with control level of no anti-inflammatory treatment changes if FeNo was less than 20 ppb. All other studies utilised a single cut off for FeNO and none of the studies took into account the presence of atopy.
The measurement of FeNO was different among studies. All but one study (de Jongste 2009) was a hospital based FeNO measurement. De Jongste used a portable at home exhaled nitric oxide analyser. Four studies (Fritsch 2006, Pijnenburg 2005, Shaw 2007, Szefler 2008) were performed in accordance to ATS/ERS guidelines for measuring FeNO (flow rate 50mL/s). Smith et al used a flow rate of 250mL/s.
The follow up of the six studies also differed: one of the studies de Jongste 2009 had a duration of 30 weeks with treatment potentially being altered every 3 weeks; (Fritsch 2006) ran for 6 months with the participants being assessed in 6 week intervals; Pijnenburg 2005 ran for twelve month duration with three monthly visits; Shaw 2007 had a study duration of twelve months with participants being assessed 10 times;Smith 2005 had a study duration for a maximum of 2 years, with phase 1 running between 3 and 12 months and phase 2 having 6 visits in 12 months; and Szefler 2008 ran for 46 weeks with scheduled visits every 6 to 8 weeks
Exacerbations were defined differently in each included study. An exacerbation was defined as: emergency visit, hospitalization or

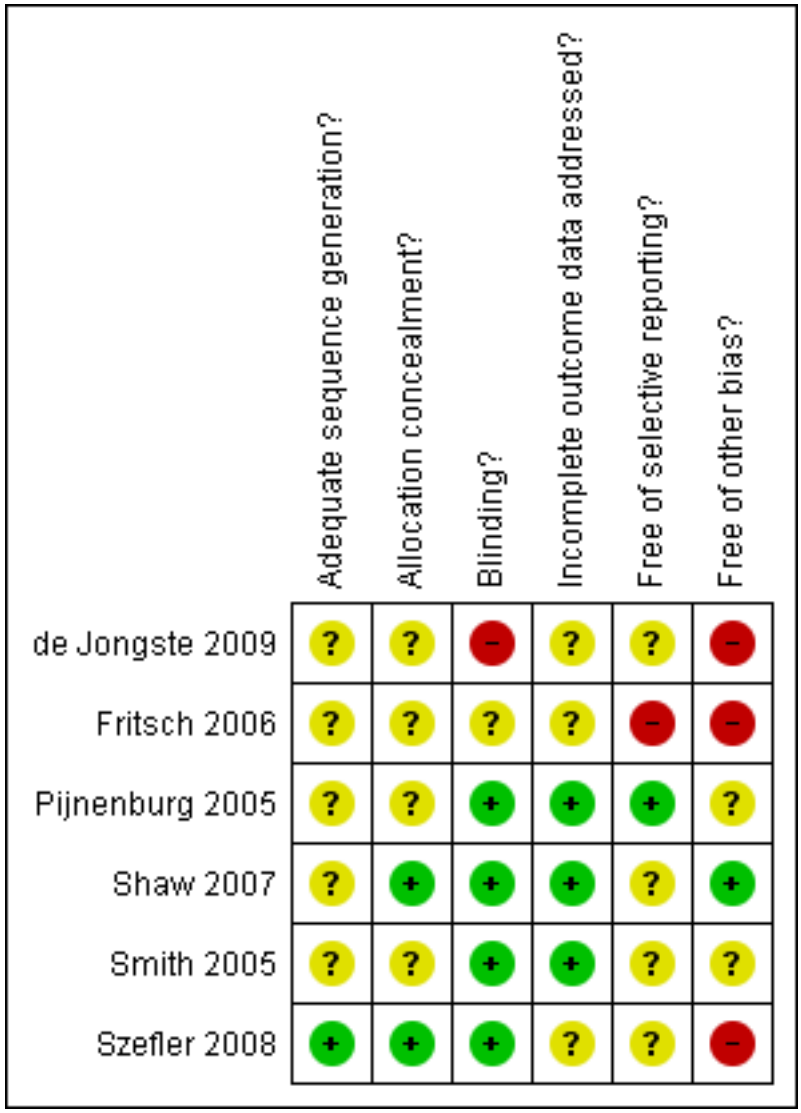
prednisolone course in de Jongste 2009. In Fritsch 2006 study asthma exacerbations were defined by 4 parameters: oral steroid courses, and/or off-scheduled visit because of asthma symptoms over the past 4 weeks, and/or increase of asthma symptoms from a symptom score 0 or 1 to a symptom score 2 and/or decline of FEV_1 (L) more than 10% compared to the previous visit. Pijnenburg 2005 defined an exacerbation as a deterioration in symptoms requiring oral prednisone course. Shaw 2007 also used a definition of an increase in symptoms requiring oral steroids or antibiotics. Smith 2005 defined exacerbations as minor or major; a minor exacerbation was defined as a daily asthma score of 2 or more on 2 or more consecutive days, whereas a major exacerbation was a daily asthma score of 3 or more on 2 or more consecutive days. Szefler 2008 combined admissions to hospital, unscheduled visits and oral prednisone use to define an exacerbation in their study.

Two studies were in adults (Smith 2005, Shaw 2007) and four children/adult studies (Fritsch 2006, Pijnenburg 2005, Szefler 2008, de Jongste 2009). We classified studies into children/adolescent studies based on the mean age reported as opposed to the entry criteria. Thus although Szefler 2008 study's entry criteria included young adults (up to 20 years), the mean age of the participants were 14·4 years (IQR 13-16) and hence included in the children/adolescent analysis.

Risk of bias in included studies

Figure 1

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation concealment was unclear in 5 studies (de Jongste 2009; Fritsch 2006; Pijnenburg 2005; Shaw 2007; Smith 2005). Only two studies (Pijnenburg 2005; Szefler 2008) was double blinded. In 3 studies (Shaw 2007; Smith 2005; Szefler 2008) the outcome assessor was blinded. In de Jongste 2009 there was no blinding, the FeNO group only had FeNO levels assessed. The final study (Fritsch 2006) was unclear in their blinding. All 6 studies (de Jongste 2009; Fritsch 2006; Pijnenburg 2005; Shaw 2007; Smith 2005; Szefler 2008) reported on the progress of all randomised subjects. Five studies (de Jongste 2009; Fritsch 2006; Pijnenburg 2005; Smith 2005; Szefler 2008) were able to measure outcomes in >90% of randomised participants. Shaw 2007 was able to measure outcomes in 80-90% of the participants who were randomised. .

Effects of interventions

See: **Summary of findings for the main comparison**

The six studies (de Jongste 2009; Fritsch 2006; Pijnenburg 2005; Shaw 2007; Smith 2005; Szefler 2008) included 1053 randomised participants with 1010 completing the trials.

Adults

Of the 215 adult participants who were randomised in Smith 2005

and Shaw 2007, 197 completed the trials.

ASTHMA EXACERBATIONS (Outcome 1)

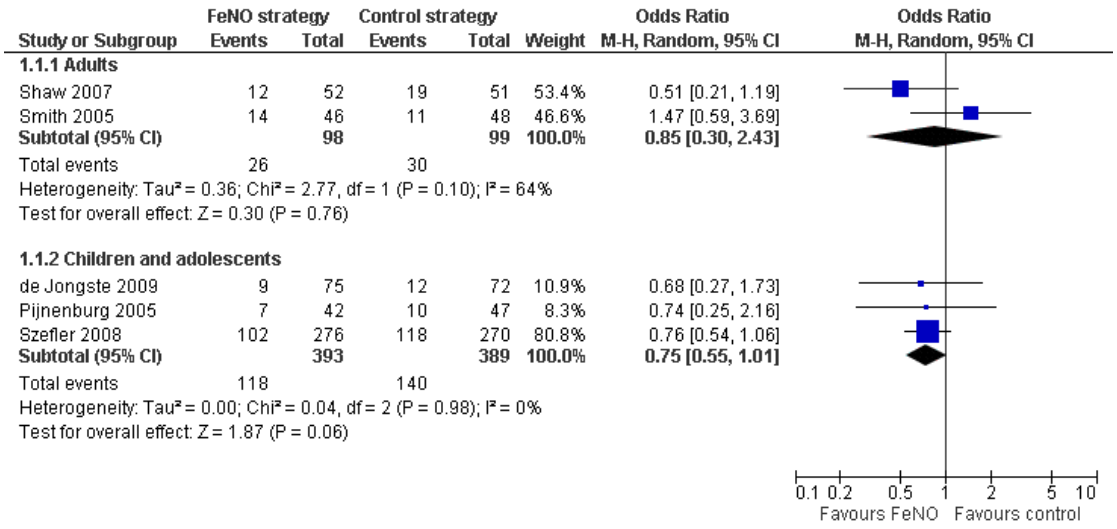
Both adult papers (Shaw 2007; Smith 2005) used asthma exacerbations as the primary outcome and both described a reduction in various aspects of asthma exacerbations in the arm that utilised treatment based on exhaled nitric oxide (FeNO) when compared to the clinical symptom arm (control arm whereby treatment was based primarily on clinical symptoms). Both adult studies reported their FeNO group experienced fewer exacerbations than the clinical symptom group but the difference between groups was not significant.

Outcomes are described below

1.1.1 Number of subjects who had one or more exacerbations (as defined by the author) over the study period

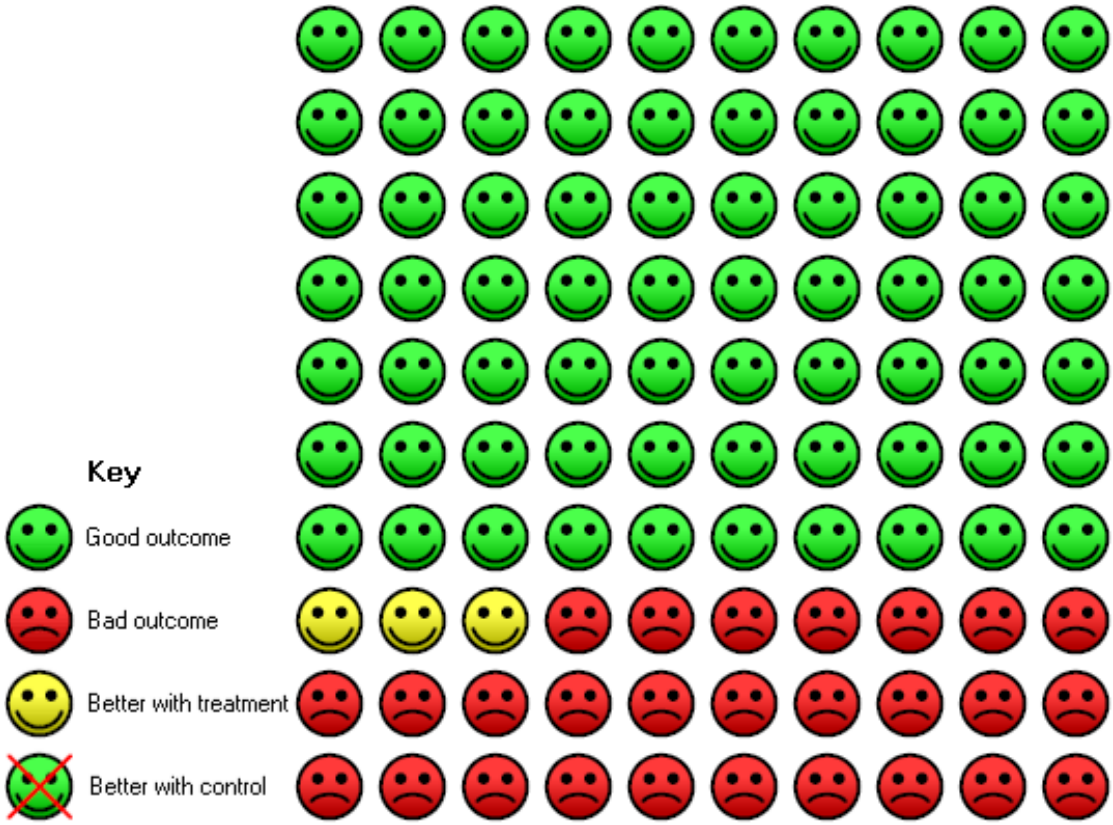
Figure 2

Figure 2. Forest plot of comparison:1 Exacerbations, outcome: 1.1 Number of subjects who had one or more exacerbations over the study period.



Combined data from the two studies showed that the number of participants experiencing any exacerbations was not significantly different (P=0.76) between the FeNO group and clinical symptom group. Pooled OR estimate effect (random model) was 0.85 (95% CI 0.30 to 2.43). There was heterogeneity between the studies, I^2 = 63.9%. In the symptom control group 30 people out of 100 had one of more exacerbations over the study period over 52 weeks, compared to 27 (95% CI 12 to 51) out of 100 for the FeNO group, Figure 3.

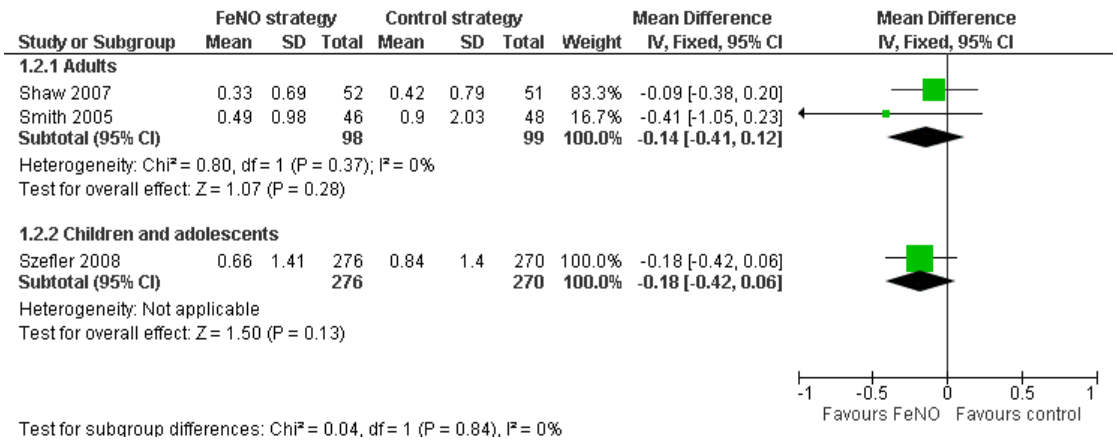
Figure 3. In the symptom control group 30 people out of 100 had one of more exacerbations over the study period (Adults) over 52 weeks, compared to 27 (95% CI 12 to 51) out of 100 for the FeNO group.



1.2.1 Exacerbation rates

Figure 4

Figure 4. Forest plot of comparison: 1 Exacerbations, outcome: 1.2 Exacerbation rates.



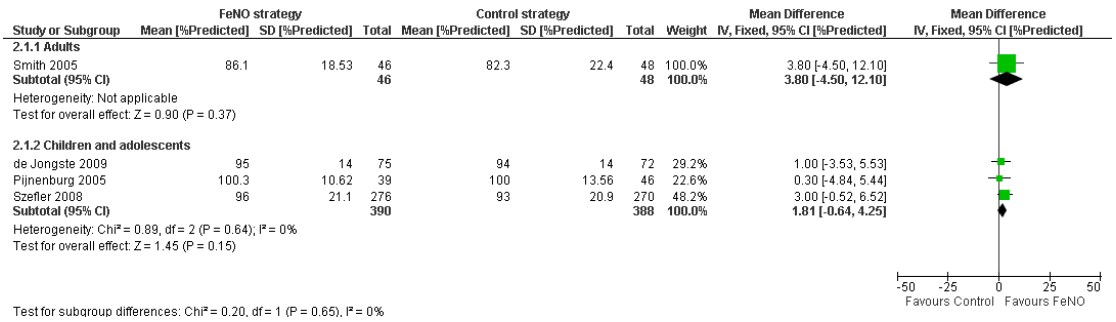
There was also no significant difference between the groups for the outcome of occurrence of any exacerbation in adults (MD -0.14; 95% CI -0.41 to 0.12), and there was no significant heterogeneity between studies.

OBJECTIVE DATA (Outcome 2)

2.1.1 FEV_1 % predicted at final visit

Figure 5

Figure 5. Forest plot of comparison: 2 Objective data, outcome: 2.1 FEV_1 % predicted at final visit [%Predicted].

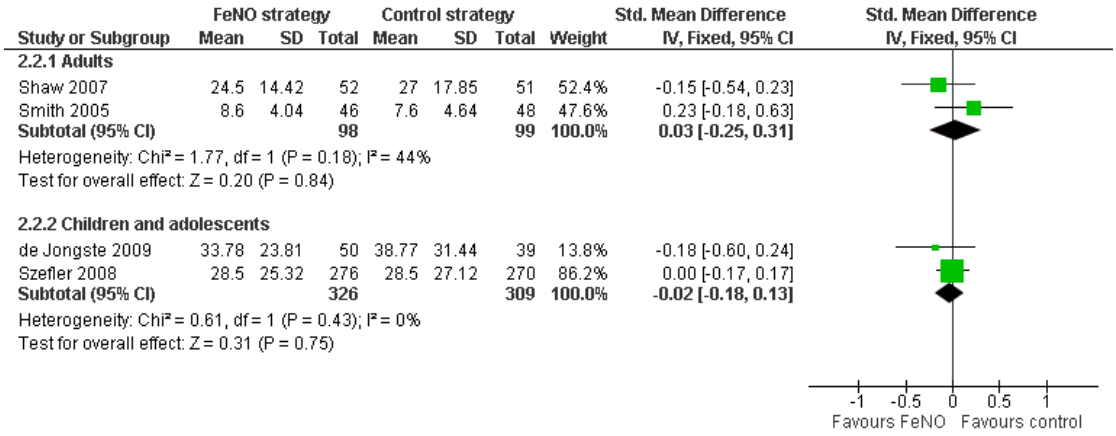


Data was only available from Smith et al which showed no significant difference between groups (MD 3.80 %Predicted; 95% CI -4.50 to 12.10). Shaw and colleagues reported that "there was no difference in FEV_1 between the groups over the duration of the study", but no details were provided.

2.2.1 FeNO at final visit

Figure 6

Figure 6. Forest plot of comparison: 2 Objective data, outcome: 2.2 FeNO at final visit.



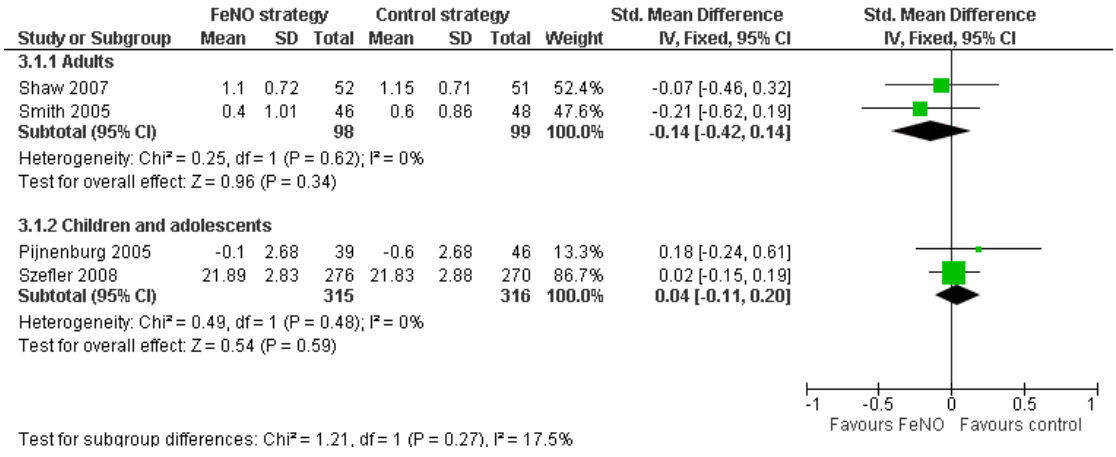
At final visit there was no significant difference between the group's FeNO level, (SMD 0.03; 95% CI -0.25 to 0.31). The statistical heterogeneity for this outcome was I^2 = 44% (P=0.18), and a random effects analysis yielded a wider confidence interval (SMD 0.03; 95% CI -0.34 to 0.41).

SYMPTOM BASED DATA (Outcome 3)

3.1.1 Symptom score

Figure 7

Figure 7. Forest plot of comparison: 3 Symptom based data, outcome: 3.1 Symptom score.

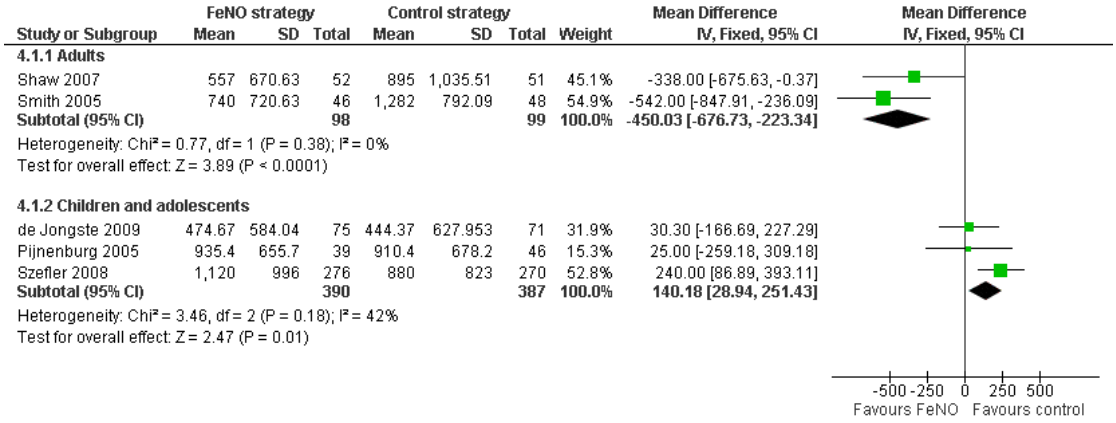


There was no significant difference between groups for symptom scores (SMD -0.14; 95% CI -0.42 to 0.14).

MEDICATIONS (Outcome 4)

4.1.1 *Inhaled corticosteroids dose at final visit*
Figure 8

Figure 8. Forest plot of comparison: 4 Medications, outcome: 4.4 ICS dose at final visit.



At final visit there was a significant difference between the group's inhaled corticosteroid dose (budesonide equivalent in mcg/day) with lower doses in the group whose treatment was based on FeNO, (MD -450.03; 95% CI -676.73 to -223.34). However Shaw 2007 also reported an 11% increase in the total amount of inhaled corticosteroids used during the study (95% CI; -15% to 37%).

Children and Adolescents

Of the 838 children and adolescents recruited in these studies Szefler 2008, Pijnenburg 2005, Fritsch 2006 and de Jongste 2009, 813 completed.

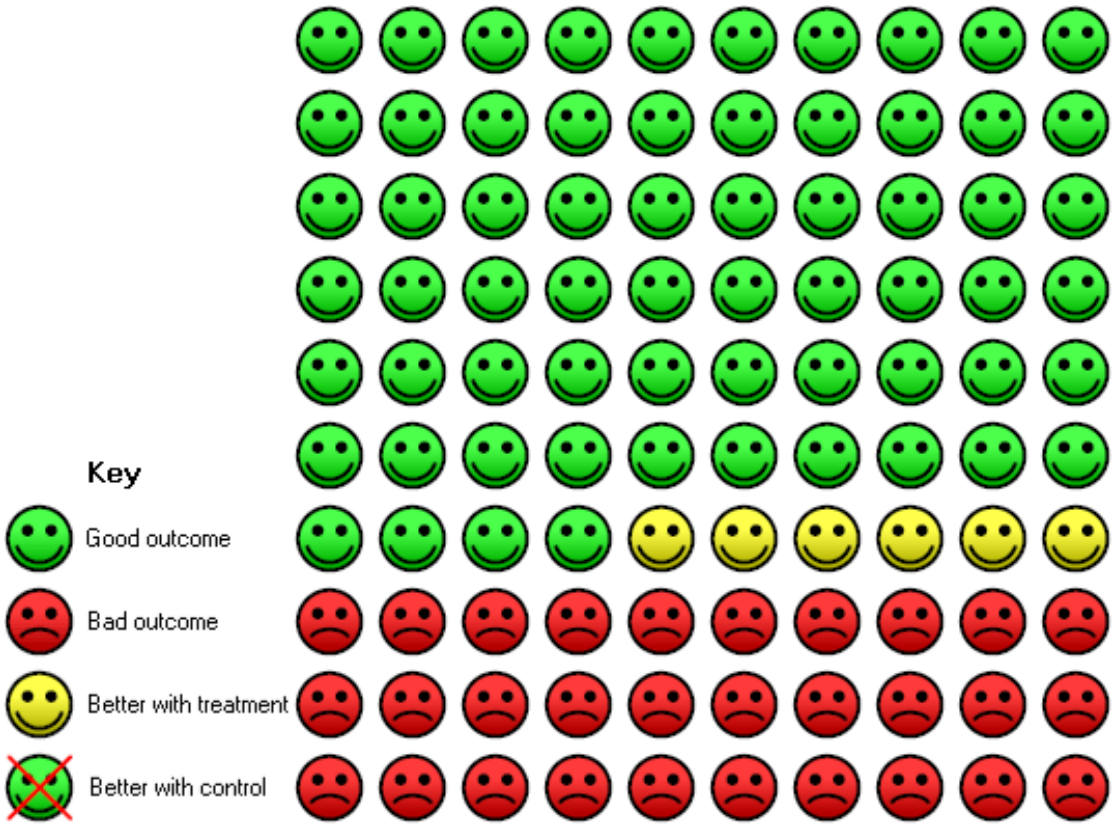
EXACERBATIONS (Outcome 1)

None of the papers (de Jongste 2009; Fritsch 2006; Pijnenburg 2005; Szefler 2008) used asthma exacerbations as the primary outcome, however they all used exacerbations as a secondary outcome. As described above the definition of exacerbations differed between the studies. Outcomes are described below.

1.1.2 Number of subjects who had one or more exacerbations (as defined by the author) over the study period

Figure 2
Combination of data from the 4 studies found no significant difference between the groups (P=0.06), with 118 exacerbations in the FeNO group versus 140 in the control group, (OR 0.75; 95% CI 0.55 to 1.01). There was no significant heterogeneity between the studies. In the symptom control group 36 people out of 100 had one of more exacerbations over the study period (children) over 26-52 weeks, compared to 30 (95% CI 24 to 36) out of 100 for the FeNO treatment group, Figure 9.

Figure 9. In the symptom control group 36 people out of 100 had one of more exacerbations over the study period (children) over 26-52 weeks, compared to 30 (95% CI 24 to 36) out of 100 for the FeNO treatment group.



1.2.2 Exacerbation rate

Figure 4

For this outcome, data was only available from Szefler 2008 with no difference between the groups (MD -0.18; 95% CI -0.42 to 0.06).

OBJECTIVE DATA (Outcome 2)

2.1.2 FEV_1% predicted at final visit

Figure 5

At final visit, there was no significant difference between the groups for FEV_1% predicted (MD 1.81 %Predicted; 95% CI -0.64 to 4.25) in the meta-analysis of data from 3 studies, and there was no significant heterogeneity. In Fritsch 2006's study, FEV_1 was the primary outcome, but data could not be extracted. Howeverbut they reported no significant differences between the groups.

2.2.2 FeNO at final visit

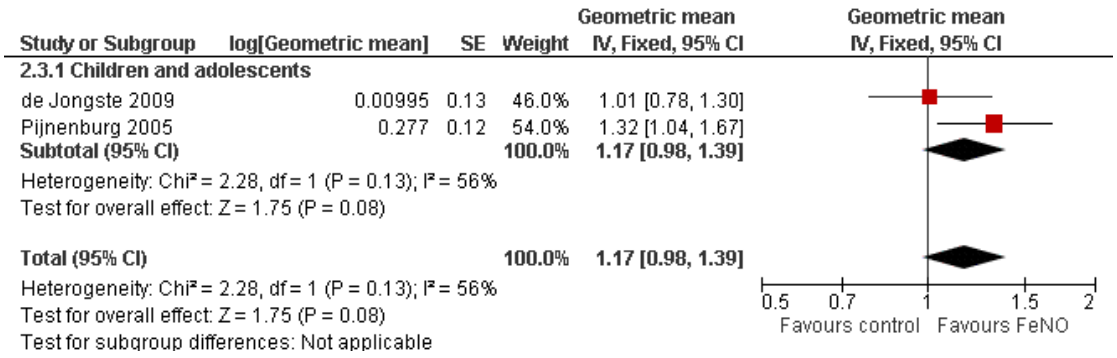
Figure 6

Combining Szefler 2008 and de Jongste 2009 data there was no difference between the two groups final FeNO (SMD -0.02; 95% CI -0.18 to 0.13). Data from Fritsch 2006 and Pijnenburg 2005 could not be included in meta-analysis; Fritsch 2006 described no significant difference between groups, but Pijnenburg 2005 described that a significant change in FeNO between the groups (ratio of geometric means, adjusted for baseline was 1.32 (95% CI, 1.04 to 1.68), with the control arm having a higher FeNO at the end of study.

2.3.1 Geometric mean change in FeNO from baseline (control/FeNO level)

Figure 10

Figure 10. Forest plot of comparison: 2 Objective data, outcome: 2.3 Geometric mean change in FeNO from baseline (control/FeNO level).



Data from Pijnenburg et al's and de Jongste et al's studies using GIV analysis, showing no significant difference between groups (Geometric mean 1.17; 95% CI 0.98 to 1.39). Fritsch 2006 described "the repeated measurement analysis demonstrated no significant differences between groups with regards to FeNO".

3.1.2 Symptom scores

Figure 7

Date combined from two studies (Pijnenburg 2005, Szefler 2008) resulted in no significant difference between the groups for respiratory symptoms (SMD 0.04; 95% CI -0.11 to 0.20). Data from de Jongste 2009 study could not be added to the meta-analysis but they described no significant difference in percentage of symptom-free days during the whole study period between both groups. Likewise, Fritsch 2006 described no significant differences between the control and FeNO groups, and data could not be included in the meta-analysis.

4.1.2 Inhaled corticosteroids dose at final visit

Figure 8

Two studies (Fritsch 2006, Pijnenburg 2005) reported the children in the control strategy as having lower mean daily dose of inhaled corticosteroids. Fritsch 2006 et al's data presented doses as medians (and IQR) and thus data was not combined. In Fritsch study, the daily ICS dose was 200 mcg higher in the FeNO group compared to the control group and authors reported that this difference was significant (P<0.01). The forest plot shows data from Pijnenburg's, Szefler's and deJongste's papers depicting a significant difference between the groups, with higher doses of inhaled corticosteroids in the FeNO group (MD 140.18; 95% CI 28.94 to 251.43 mcg/day budesonide equivalent). There was, however heterogeneity in this outcome, $Chi^2 = 3.46$, df = 2 (P = 0.18); $I^2 = 42\%$. A random effects model gave a wider confidence interval that included no difference between the groups (MD 121.89; 95% CI -32.24 to 276.03).

Sensitivity Analyses

Sensitivity analyses could not be performed for most specified criteria. Analysis using random effects is reported for individual outcomes above. Using intention to treat analysis did not alter direction or significance of events.

DISCUSSION

This meta-analysis based on six studies in 1053 adults and children (with 1010 completed), has showed that tailoring the dose of inhaled corticosteroids based on exhaled nitric oxide (FeNO) in comparison with usual traditional methods (based primarily on clinical symptoms) did not significantly reduce exacerbations or improve FEV_1 or asthma symptoms. In children/adolescents there was a trend favouring the FeNO strategy in number of participants with one or more exacerbation, but this was at the expense of higher levels of inhaled corticosteroids. In adults, the FeNO based strategy enabled a reduction in the final (but not the overall) daily dose of inhaled corticosteroids .

Tailoring medications based on FeNO has been advocated in editorials (Szefler 2005). This Cochrane review has shown that the benefits of utilising this strategy (as opposed to standard strategy based on clinical symptoms and simple tests like FEV_1) is at best modest and could potentially be harmful with increased ICS use in children. There was no significant difference between the two strategies in both adult and paediatric studies in the primary outcome of exacerbation, FEV_1, FeNO levels or symptom control scores. The only significant beneficial difference found between groups was the final daily dose of ICS in adults. However this finding is limited as this was a post-hoc analysis. Even though the final ICS dose was lower at final visit, Shaw 2007 reported overall higher doses of ICS in the FeNO based strategy through the duration of study and was only lower on final visit. They related this

to a proportion of patients who showed an elevated FeNO that was associated with a normal eosinophil count (identified by sputum eosinophil testing as a safety measure when the dose of ICS reached 2000 mcg/day). Furthermore in children where high ICS doses are of more concern due to potential adverse events, there was a significant increase in ICS dose in the FeNO strategy arm (mean difference of 140 ug (95% CI 29 to 251) of budesonide equivalent/day). In a previous systematic review we found that there was no significant difference in doses of ICS when asthma treatment was based on sputum eosinophils, as opposed to clinical symptoms (Petsky 2007).

The results of this review need to be considered in light of several issues. Firstly, all the studies except Szefler 2008 used a single but different cut-off level of FeNO to adjust ICS in the entire cohort, yet studies have demonstrated that FeNO is significantly influenced by atopic status (with a dose response) (Franklin 1999; Franklin 2003). In some studies, use of FeNO levels do not differentiate between children with and without asthma once atopy is taken into account (Malmberg 2004; Prasad 2006) as atopic subjects have elevated exhaled nitric oxide levels (Franklin 1999; Franklin 2003; Prasad 2006). Other studies have shown that FeNO is independently influenced by allergic rhinitis (Nordvall 2005) and a 40% coefficient of variation between morning and evening FeNO with no change in symptoms has been reported (Pijnenburg 2006). None of the six included studies considered presence or severity of atopy in their algorithm of management although some but not all subjects were atopic. Shaw and colleagues reported that some of their participants were atopic (62% in FeNO group, 70% in control group). Smith et al did not describe whether their subjects were atopic or not. 'Atopic asthma' was an inclusion criteria for Pijnenburg et al as defined as RAST class 2 or higher for at least 1 airborne allergan ever. Similarly all children in Fritsch et al had an inclusion criteria of positive skin prick test or radioallergosorbent test.

Secondly FeNO levels are also influenced by age and height (Malmberg 2006) and are elevated even in well non-asthmatic adults with a acute respiratory viral infection (Sanders 2004). Thus arguably one single cut-off for the entire cohort irrespective of significant biological influences of FeNO (such as atopy (Prasad 2006) and age (Strunk 2003) would not be appropriate. However, how FeNO levels should be adjusted for these factors is currently unknown.

Thirdly, the cut offs of FeNO utilised for stepping up or down therapy was different between studies (ranging from 15 to 30 ppb). Pijnenburg et al (paediatric study) subjects had the highest mean daily dose of ICS and subjects in this study also had quite high FeNO at the final visit. Disconcertingly, use of FeNO strategy did not result in a lower FeNO level at the end of trial. Smith et al mentioned that their 15 ppb threshold is equivalent to 35 ppb at a slower 50 ml/second flow rate.

Fourthly, tailoring interventions based on exhaled nitric oxide requires a nitric oxide analyzer that needs calibration and maintenance. Nitric oxide analysers are relatively expensive and adding FeNO as a monitoring tool adds not only cost but also another layer of complexity in asthma care. Analysers have only been approved by United States Food and Drug Administration for clinical monitoring of anti-inflammatory treatment in 2003 (ATS 2005). As reported in Risk of Bias table (Figure 1) obtaining accurate FeNO measurements each visit could not be obtained, either due to a faulty analyzer (de Jongste 2009) or technical issues (Fritsch 2006). Also, many aspects need to be considered when analysing exhaled nitric oxide; this includes the timing of spirometry (transiently reduces FeNO), food and beverage, circadian rhythm, smoking history, ambient NO and exercise (ATS 2005).

Although tests for FeNO are non-invasive and relatively easy to obtain measurements in children (when compared with obtaining and analysing sputum), it is not clear how to tailor the dose of inhaled corticosteroids based on exhaled nitric oxide in comparison to clinical symptoms. This is in contrast to tailoring asthma interventions based on sputum eosinophils where it is beneficial in reducing the frequency of asthma exacerbations in adults with asthma (Petsky 2007).

Limitations of review

This systematic review is limited to six studies with only 1010 subjects completing the trials. While the studies share some common issues, there are also significant differences, notably, the definition of asthma exacerbation, the cut off levels for FeNO were different, the control strategy and the steps for tailoring medications.

AUTHORS' CONCLUSIONS

Implications for practice

The studies included in this review highlight the difficulties involved in tailoring the dose of inhaled corticosteroids based on exhaled nitric oxide, instead of primarily on clinical symptoms. At present this approach cannot be advocated as routine clinical practice.

Implications for research

Further RCT's in both adults and children with groups with other significant influences of FeNO taken into account (such as atopy) are required. A-priori pragmatic issues of clinical practice such as high vs low doses of ICS and to a lesser extent eosinophilic vs non-eosinophilic asthma should be considered with costs analysis for each sub-group. The design of future RCT's should preferably be parallel multi-centre studies and include outcomes of exacerbations, subjective measures (such as scores for asthma control and

quality of life) as well as objective measures (FEV_1 etc). Analysis of costs and possible adverse events of inhaled and oral corticosteroids would also provide additional important information.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

de Jongste 2009

Methods	Prospective, open label, randomised, multicentre, parallel group study where ICS was adjusted every 3 weeks on the basis of FeNO and symptom scores, or symptom scores alone 4 randomised subjects (2 in FeNO group, 2 in symptom group) were excluded from final results due to severe non-compliance (n=2), inappropriate inclusion (no allergy = 1) and 1 moving abroad Study duration was 30 weeks.
Participants	151 children were randomised. FeNO group = 75: mean age 11.6 (SD 2.6), 46 males, 29 females. Symptom group = 72: mean age 11.8 (SD 4.3), 54 males, 18 females Inclusion criteria: aged 6-18 years, stable mild-moderate asthma, diagnosed according to Global Initiative for Asthma (GINA) guidelines, treatment with 200 - 1000ug of inhaled budesonide or equivalent daily for 2 months before randomisation, and RAST class 2 or higher or a positive skin prick test to at least one airborne allergen Exclusion criteria: active smoking, previous admission to an intensive care unit for asthma, and concomitant disease that might affect FeNO
Interventions	All participants scored asthma symptoms in an electronic diary over 30 weeks. 77 received a portable nitric oxide (NO) analyser. Data was transmitted daily to the coordinating centres. Patients were phoned every 3 weeks and their steroid dose was adapted according to FeNO and symptoms (FeNO group), or according to symptoms (Symptom group) . Children were seen at 3, 12, 21 and 30 weeks for examination, assessment of FeNO, spirometry before and after salbutamol and recording of adverse events
Outcomes	Primary outcome: Proportion of symptom-free days over the last 12 study weeks Secondary outcomes: cumulative symptom scores, ICS dose as budesonide equivalent, FEV_1 and reversibility, $FeNO_{0.05}$, prednisone courses, emergency visits, hospitalisations for asthma, and PACQLQ scores
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Insufficient information in published article
Allocation concealment?	Unclear	Insufficient information of randomisation in published article
Blinding? All outcomes	No	Open label study

de Jongste 2009 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	"Intention-to-treat analysis was performed for all subjects who were enrolled" however data not shown (stated same in published article)
Free of selective reporting?	Unclear	Outcomes of interest were reported incompletely and were unable to be entered into the meta-analysis
Free of other bias?	No	The calibration of the NIOX Minos after the study showed drift outside the manufacturer's specifications in 11 of 77 instruments. The article has also reported that "a number" of the NIOX Mino's had to be replaced as a risk of malfunctioning was detected Study was supported by the company (Aerocrine AB, Sweden) who manufactured the FeNO analyser

Fritsch 2006

Methods	A prospective, randomised, single-blind parallel trial examining the inclusion of repeated FeNO measurements into asthma monitoring over a period of 6 months. In the FeNO group therapy was based on symptoms, beta-agonists use, lung function and FeNO, in comparison to the control group where therapy was based on symptoms, beta-agonists use and lung function only There were 5 patients who dropped out, unsure of when these occurred Over the 6 months, there were 5 visits in 6 weeks intervals.
Participants	52 patients entered the study. FeNO group n=22: mean age 11.3 (SD +/- 3.4), 14 males, 8 females. Control group n=25: mean age 12.1 (+/- 2.8), 14 males, 11 females. Attended paediatric pulmonology outpatient clinic from University Children's Hospital, Vienna Inclusion: Children aged between 6 -18 years with asthma diagnosis as based on American Thoracic Society's criteria. Positive skin prick test (SPT) or radioallergosorbent test (RAST>1). Exclusion: Received oral or IV steroid treatment 4 weeks prior to their first visit
Interventions	Subjects were run-in for 4 weeks. Randomised at visit 1 then outpatient visits at 6, 12, 18 and 24 weeks. Control group: treatment based on symptoms, beta-agonists and lung function. FeNO group: treatment based on symptoms, beta-agonists, lung function and FeNO
Outcomes	Primary outcome: FEV1 Secondary outcomes: Number of exacerbations, MEF 50% predicted, better symptom control, less short acting beta-agonists and inhaled corticosteroid dose

Fritsch 2006 (*Continued*)

Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Insufficient information of randomisation in published article
Allocation concealment?	Unclear	Insufficient information of randomisation in published article
Blinding? All outcomes	Unclear	Single blind
Incomplete outcome data addressed? All outcomes	Unclear	Insufficient information published.
Free of selective reporting?	No	Primary outcome was not reported completely to allow data to be entered into meta-analysis
Free of other bias?	No	FeNO measurements could not be performed in 23 observations due to technical problems

Pijnenburg 2005

Methods	Randomised, double blind study evaluating whether titrating steroids on FeNO improved asthma management in children. Stratified by baseline FeNO (>30 or <30ppb) and dose of ICS (>400 or <400ug budesonide or equivalent daily dose) Neither subjects nor physicians were aware of which group they were randomised to There were 7 drop outs: 3 during run-in, 3 from FeNO group (1 admitted to ICU) and 1 from symptom group The study duration was 12 months, with 5 visits at 3 monthly intervals
Participants	89 children randomised from 108 invited. FeNO group N= 39 : mean age 11.9 (SD 2. 9), 25 males, 14 females. Symptom group N= 46: mean age 12.6 (SD 2.8), 30 males, 16 females. Visiting outpatient clinic Inclusion: use of ICS at constant dose for at least 3 months preceding study, atopy defined as RAST class 2 or higher for at least 1 airborne allergan
Interventions	Children were run-in for 2 weeks, then 3 monthly visits. FeNO group: FeNO guided ICS dosing according to predetermined algorithm. Symptom group: symptom scores influenced ICS dosing.

Pijnenburg 2005 (*Continued*)

Outcomes	Primary outcome: cumulative steroid dose (sum of mean daily steroid doses of visits 1 to 5) Secondary outcomes: mean daily symptom score, mean daily number of bronchodilator doses taken, percentage of symptom free days during the last 4 weeks of the study, number of oral prednisone courses during the study, and provocative dose of methacholine causing a 20% fall in FEV1, FVC, FEV1 and MEF25 during final visit
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Insufficient information of randomisation in published article
Allocation concealment?	Unclear	Insufficient information of randomisation in published article
Blinding? All outcomes	Yes	Parents and physician were blinded to allocated group. The investigators provided the physician with an ICS dose recommendation according to pre-determined algorithm
Incomplete outcome data addressed? All outcomes	Yes	All outcomes are reported.
Free of selective reporting?	Yes	Pre-specified outcomes are reported and entered into meta-analysis
Free of other bias?	Unclear	No information provided on the success in obtaining FeNO measurements at each visit

Shaw 2007

Methods	Randomised, single blind controlled trial comparing exacerbation frequency and corticosteroid dosage in patients whose asthma management was based on measurements of FeNO to a control group where management was based on the British Thoracic Society and Scottish Intercollegiate Guidelines Network treatment guidelines. Stratified by baseline sputum eosinophil count, baseline rescue steroid course in last year The subjects were blinded to which group they were randomised to, at completion the participants were asked to record which record they thought they had been assigned There were 15 drop outs, 6 in FeNO group and 9 in control group The study ran for 12 months and the subjects were assessed 10 times
Participants	900 adults were contacted from general practice registers of which 118 were randomised. FeNo group N=58 : median age 50 (range 20-75), 27 males, 31 females. Control group N=60 : median age 52 (range 24-81), 27 males, 33 females. Attending a general practice in Leicester, UK. Inclusion: >18 years old, diagnosis of asthma and at least one prescription for anti-asthma medication in the past 12 months. Exclusion: Current smokers, past smoking history of >10 pack - year or physician determines that they are poorly compliant
Interventions	Subjects were seen at baseline, 2 weeks, month: 1, 2, 3, 4, 6, 8, 10 and 12. FEV1, FeNO and Juniper asthma control score (JACS) was undertaken at each visit. Methacholine and sputum induction was undertaken at initial visit, 6 months and at completion of 12 months In control group: treatment was doubled if JACS >1.57 and treatment halved if JACS <1.57 for 2 consecutive months. In FeNO group: FeNO>26ppb, ICS was increased. If <16ppb or <26ppb on 2 separate occasions, treatment was decreased
Outcomes	Primary outcome: Number of exacerbations. Secondary outcomes: Total inhaled corticosteroid dose.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Insufficient information provided in published article.
Allocation concealment?	Yes	Randomisation was done by an independent individual using minimisation method, stratified by baseline sputum eosinophil count, FeNO and rescue steroid courses in the last year
Blinding? All outcomes	Yes	Single blind. Participants were assessed at completion of study regarding the group they thought they were assigned to, 49%

Shaw 2007 (*Continued*)

		were unsure of which group they were assigned, 33% correctly identified their group, and 18% incorrectly identified their group
Incomplete outcome data addressed? All outcomes	Yes	No missing outcome data.
Free of selective reporting?	Unclear	Insufficient information.
Free of other bias?	Yes	Measurement of FeNO was successful on every occasion.

Smith 2005

Methods	Randomised, placebo controlled, single blind study. It was a 2 phase study, with phase 1 varying in duration (3-12 months) where the dose of inhaled fluticasone was titrated down in a stepwise manner until the optimal dose was deemed to have been achieved. During phase 2 (12 months) optimal dose from phase 1 was continued and therapy was stepped up if asthma control was lost Subjects were blinded to which group they were assigned. In phase 1 there was 16 drop outs, 13 during run in and 3 during follow up. Phase 2 had 5 drop outs during the 12 months
Participants	97 patients randomised from 110 patients recruited. 46 in FeNO group achieved optimal dose in phase 1 and 48 achieved optimal dose in control group Inclusion criteria: Inhaled corticosteroids for 6 months with no dose change in previous 6 weeks. Exclusion criteria: >4 courses of oral prednisolone in previous 12 months, admission to hospital in the last 6 months, any intensive care admissions, or cigarette smoking (current or past history of >10 pack-years)
Interventions	Phase 1 Run-in period was for 6 weeks, after 2 weeks fluticasone 750ug/day was commenced. Visits were every 4 weeks until optimal dose was achieved. FeNO group: adjustment of dose of ICS was based solely to keep FeNO <15ppb at 250mL/sec. Control group: dose adjustment based on asthma symptoms, nighttime waking, bronchodilator use, variation in PEFR and FEV1. Phase 2 Visits every 2 months. Upward adjustments made as per phase 1 but no downward adjustments would be made from optimal dose
Outcomes	Primary outcome: Frequency of exacerbation. Secondary outcome: Mean daily dose of inhaled corticosteroids
Notes	

Smith 2005 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Insufficient information of randomisation and sequence generation in published article
Allocation concealment?	Unclear	Insufficient information of randomisation in published article
Blinding? All outcomes	Yes	Single blind. All treatment orders were verified independently by an investigator who was blinded to treatment group
Incomplete outcome data addressed? All outcomes	Yes	Missing data has been imputed using appropriate methods.
Free of selective reporting?	Unclear	Insufficient information provided in published article.
Free of other bias?	Unclear	Nil information provided in published article regarding success of measuring FeNO

Szefler 2008

Methods	Randomised, double-blind, parallel-group trial. Subjects had their asthma management based on standard treatment as per the guidelines of National Asthma Education and Prevention Program (NAEPP) or standard treatment modified on the basis of measurements of fraction of exhaled nitric oxide The subjects and physicians were not aware of their treatment assignment The study duration was 46 weeks, with visits every 6 - 8 weeks Twelve randomised participants were lost to follow-up before the first outcome data was collected. During the 46-week follow-up, 17 participants in NO monitoring group dropped out and 23 in control group
Participants	546 participants randomised from 780 patients screened. 276 assigned to NO monitoring group (Mean age 14.4, 146 males, 130 females), 270 assigned to control group (Mean age 14.4, 142 males, 128 females) Inclusion criteria: Aged between 12-20 years, diagnosed with asthma by their physician, symptoms of persistent asthma or evidence of uncontrolled disease as defined by NAEPP guidelines, and residents of urban census tracts in which at least 20% of households had incomes below the federal poverty threshold
Interventions	Run-in period of 3 weeks then scheduled visits every 6 to 8 weeks for 46 weeks At each visit FeNO was measured, days of asthma symptoms assessed, use of rescue drugs, pulmonary function, use of health care, adherence to treatment regime and missed days of school because of asthma

	Control group: Standard treatment based on the guidelines of National Asthma Education and Prevention Program (NAEPP) FeNO group: Standard treatment modified on the basis of measurements of fraction of exhaled NO
Outcomes	Primary outcome: Number of days with asthma symptoms. Secondary outcomes: Admission 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
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Centralised block randomisation with a block size of 10. The randomisation sequence was generated from a random number table and was stratified by site by the use of statistical software
Allocation concealment?	Yes	Centralised block randomisation, with a block size of 10. The randomisation sequence was generated from a random number table and was stratified by site by the use of statistical software
Blinding? All outcomes	Yes	Double blind.
Incomplete outcome data addressed? All outcomes	Unclear	No reason for missing data provided.
Free of selective reporting?	Unclear	Insufficient information provided in published article.
Free of other bias?	No	No information published on the success of obtaining FeNO measurements. On enrolment doses of inhaled corticosteroids were increased by average of 219ug (95%CI 199-238) which is a large increase and could influence the reporting of participants

FeNO: fractional exhaled nitric oxide; n: number; SD: standard deviation; IV: intravenous; FEV1: forced expiratory volume in 1 second; MEF50%: mean expiratory flow at 50%.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Gelb 2006	Non RCT nor treatment based on eNO. Prospective study to assess eNO and spirometry to predict asthma exacerbations
Griese 2000	Non RCT nor treatment based on eNO. Prospective study to assess eNO in comparison to symptoms, treatment adjusted using clinical symptoms
Jatakanon 1999	Excluded as treatment not based on eNO. Randomised into two double blind, placebo controlled studies (1 was parallel study involving 3 groups receiving either budesonide 100ug/day, budesonide 400ug/day or placebo, the second was a crossover randomised to receive budesonide 1600ug or placebo)
Jones 2001	Non RCT. Observational study to determine if FeNO is useful in diagnosing and predicting loss of asthma control. Subjects had ICS withdrawn until loss of control or for a maximum of 6 weeks
Jones 2002	Excluded as treatment not based on eNO. Double blind, parallel group, placebo controlled trial of 50, 100, 200 or 500ug budesonide per day
Kharitonov 1996	Non RCT. Observational study of the effect of increasing and then reducing the dose of ICS on eNO, lung function and symptoms in patients with asthma
Kharitonov 2002	Excluded as treatment not adjusted according to eNO. Double blind, placebo controlled, parallel group study of 100 or 400ug budesonide or placebo in subjects with mild asthma
Lim 1998	Excluded as treatment not adjusted according to eNO. Randomised, longitudinal study monitoring the effect of increasing anti-inflammatory medication or to continue unchanged using conventional measures of lung function, symptoms scores, medication usage and peak expiratory flow rate variability
Zacharasiewicz 2005	Non RCT. Prospective and observational study in children using non-invasive measures (eNO, induced sputum and exhaled breath condensate) to monitor airway inflammation to result in optimal treatment

Characteristics of ongoing studies *[ordered by study ID]*

Petsky

Trial name or title	Asthma management in children based on exhaled nitric oxide: A randomised controlled study
Methods	
Participants	100 children aged <4 years randomised into FeNO group or control group. All children attend outpatient clinics at Royal Children's Hospital, Brisbane Inclusion: Children aged >4 years with asthma attending a paediatric specialist clinic. Exclusion: Presence of other cardiorespiratory illness such as cystic fibrosis, tracheomalacia, etc. Poorly complaint to treatment. Inability to take inhaled corticosteroids or long acting beta-2-antagonists (LABA)

Petsky (*Continued*)

Interventions	Subjects will be run-in for 2 weeks. Randomised at visit 1 and then outpatient visits at month 1, 2, 3, 4, 6, 8, 10, and 12 FeNO group: Treatment based on FeNO. Control group: Treatment based on symptoms, beta-agonists and lung functions
Outcomes	Primary outcome: Exacerbation of asthma requiring oral corticosteroids and/or hospitalisation for asthma. Secondary outcomes: FEV1, daily dose of inhaled corticosteroids
Starting date	17.01.06
Contact information	Helen Petsky Queensland Children's Respiratory Centre Royal Children's Hospital Helen_Petsky@health.qld.gov.au Ph: 61-7-36361684
Notes	

Roberts

Trial name or title	No details available
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

DATA AND ANALYSES

Comparison 1. Exacerbations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of subjects who had one or more exacerbations over the study period	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Adults	2	197	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.30, 2.43]
1.2 Children and adolescents	3	782	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.55, 1.01]
2 Mean number of exacerbations per 52 weeks	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Adults	2	197	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.41, 0.12]
2.2 Children and adolescents	1	546	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.42, 0.06]

Comparison 2. Objective data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV_1 % predicted at final visit	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Adults	1	94	Mean Difference (IV, Fixed, 95% CI)	3.80 [-4.50, 12.10]
1.2 Children and adolescents	3	778	Mean Difference (IV, Fixed, 95% CI)	1.81 [-0.64, 4.25]
2 FeNO at final visit	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Adults	2	197	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.25, 0.31]
2.2 Children and adolescents	2	635	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.18, 0.13]
3 Geometric mean change in FeNO from baseline (control/FeNO level)	2		Geometric mean (Fixed, 95% CI)	1.17 [0.98, 1.39]
3.1 Children and adolescents	2		Geometric mean (Fixed, 95% CI)	1.17 [0.98, 1.39]

Comparison 3. Symptom based data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Symptom score	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Adults	2	197	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.42, 0.14]
1.2 Children and adolescents	2	631	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.11, 0.20]

Comparison 4. Medications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ICS dose at final visit	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Adults	2	197	Mean Difference (IV, Fixed, 95% CI)	-450.03 [-676.73, -223.34]
1.2 Children and adolescents	3	777	Mean Difference (IV, Fixed, 95% CI)	140.18 [28.94, 251.43]

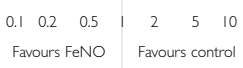
Analysis 1.1. Comparison 1 Exacerbations, Outcome 1 Number of subjects who had one or more exacerbations over the study period.

Review: Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults

Comparison: 1 Exacerbations

Outcome: 1 Number of subjects who had one or more exacerbations over the study period

Study or subgroup	FeNO strategy n/N	Control strategy n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Adults					
Shaw 2007	12/52	19/51		53.4 %	0.51 [0.21, 1.19]
Smith 2005	14/46	11/48		46.6 %	1.47 [0.59, 3.69]
Subtotal (95% CI)	**98**	**99**		**100.0 %**	**0.85 [0.30, 2.43]**
Total events: 26 (FeNO strategy), 30 (Control strategy)					
Heterogeneity: $Tau^2 = 0.36$; $Chi^2 = 2.77$, df = 1 (P = 0.10); $I^2 = 64\%$					
Test for overall effect: Z = 0.30 (P = 0.76)					
2 Children and adolescents					
de Jongste 2009	9/75	12/72		10.9 %	0.68 [0.27, 1.73]
Pijnenburg 2005	7/42	10/47		8.3 %	0.74 [0.25, 2.16]
Szefler 2008	102/276	118/270		80.8 %	0.76 [0.54, 1.06]
Subtotal (95% CI)	**393**	**389**		**100.0 %**	**0.75 [0.55, 1.01]**
Total events: 118 (FeNO strategy), 140 (Control strategy)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.04$, df = 2 (P = 0.98); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.87 (P = 0.062)					

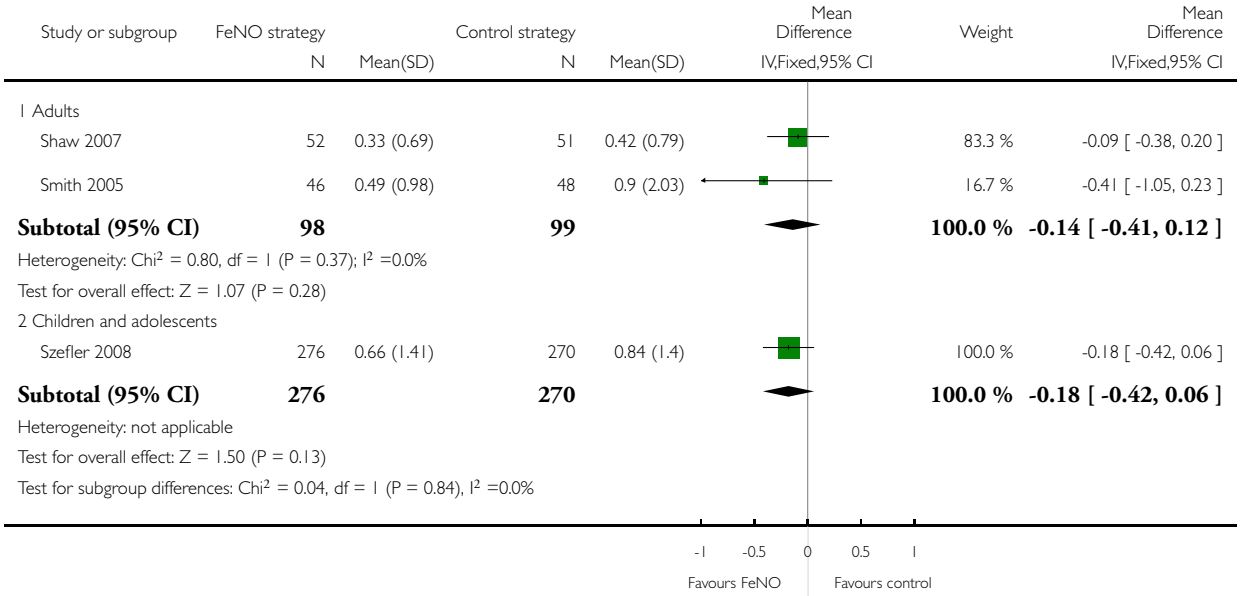


Analysis 1.2. Comparison 1 Exacerbations, Outcome 2 Mean number of exacerbations per 52 weeks.

Review: Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults

Comparison: 1 Exacerbations

Outcome: 2 Mean number of exacerbations per 52 weeks

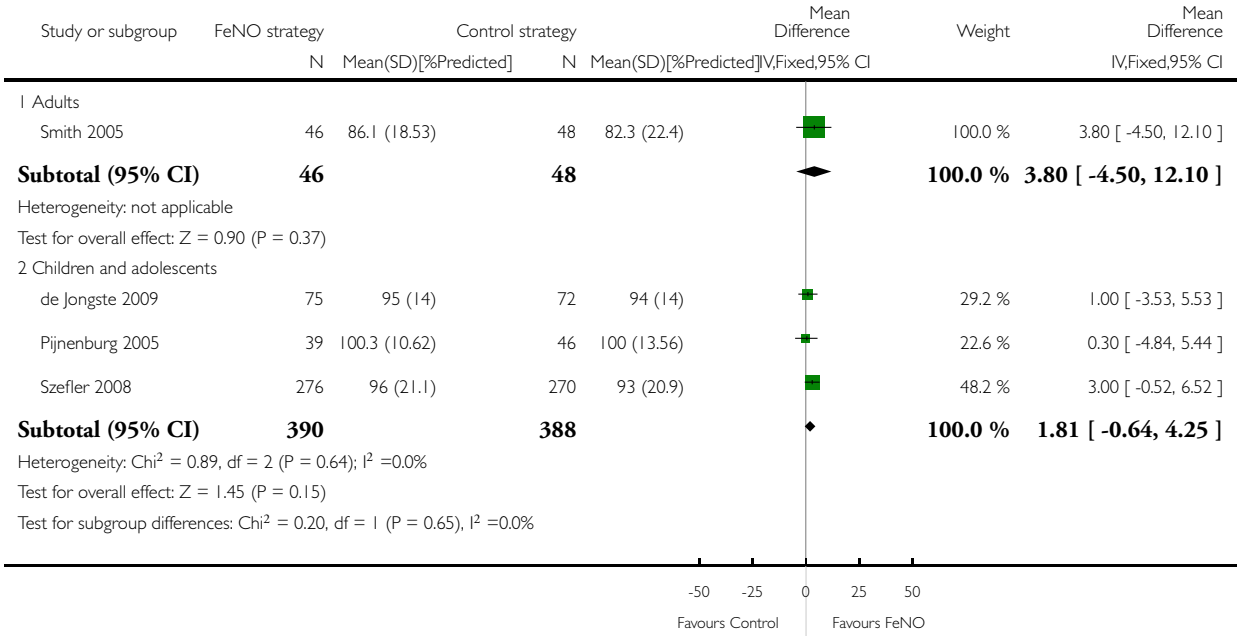


Analysis 2.1. Comparison 2 Objective data, Outcome 1 FEV_1 % predicted at final visit.

Review: Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults

Comparison: 2 Objective data

Outcome: 1 FEV_1 % predicted at final visit

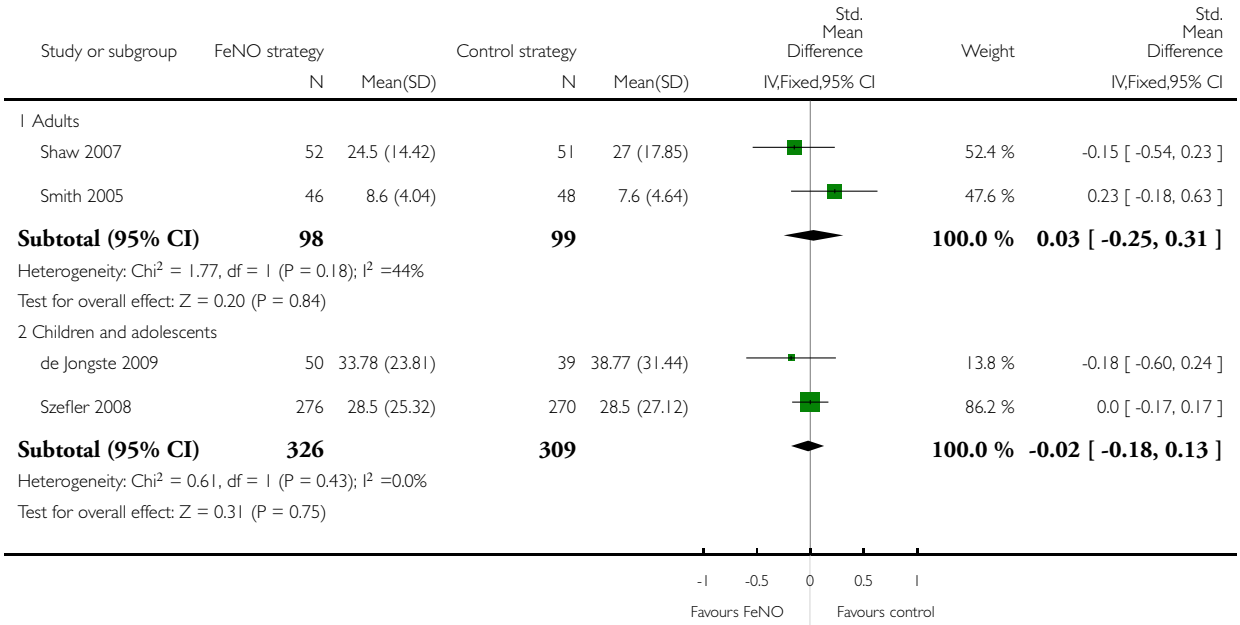


Analysis 2.2. Comparison 2 Objective data, Outcome 2 FeNO at final visit.

Review: Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults

Comparison: 2 Objective data

Outcome: 2 FeNO at final visit

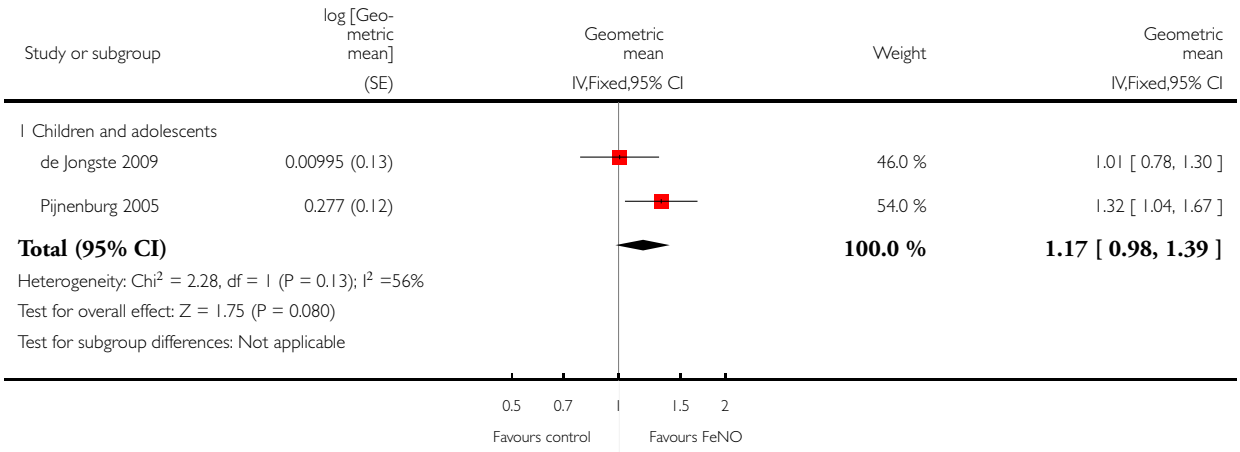


Analysis 2.3. Comparison 2 Objective data, Outcome 3 Geometric mean change in FeNO from baseline (control/FeNO level).

Review: Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults

Comparison: 2 Objective data

Outcome: 3 Geometric mean change in FeNO from baseline (control/FeNO level)



Analysis 3.1. Comparison 3 Symptom based data, Outcome 1 Symptom score.

Review: Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults

Comparison: 3 Symptom based data

Outcome: 1 Symptom score

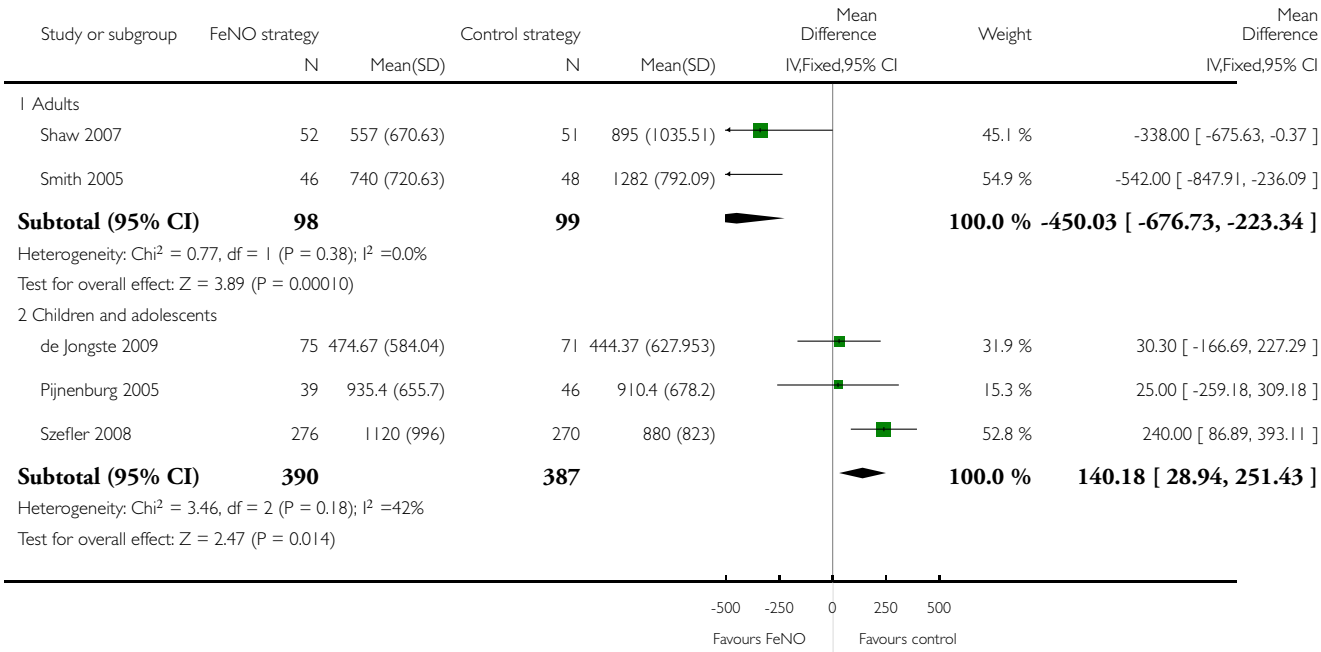
Study or subgroup	FeNO strategy N	Mean(SD)	Control strategy N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Adults							
Shaw 2007	52	1.1 (0.72)	51	1.15 (0.71)		52.4 %	-0.07 [-0.46, 0.32]
Smith 2005	46	0.4 (1.01)	48	0.6 (0.86)		47.6 %	-0.21 [-0.62, 0.19]
Subtotal (95% CI)	**98**		**99**			**100.0 %**	**-0.14 [-0.42, 0.14]**
Heterogeneity: Chi^2 = 0.25, df = 1 (P = 0.62); I^2 =0.0%							
Test for overall effect: Z = 0.96 (P = 0.34)							
2 Children and adolescents							
Pijnenburg 2005	39	-0.1 (2.68)	46	-0.6 (2.68)		13.3 %	0.18 [-0.24, 0.61]
Szefler 2008	276	21.89 (2.83)	270	21.83 (2.88)		86.7 %	0.02 [-0.15, 0.19]
Subtotal (95% CI)	**315**		**316**			**100.0 %**	**0.04 [-0.11, 0.20]**
Heterogeneity: Chi^2 = 0.49, df = 1 (P = 0.48); I^2 =0.0%							
Test for overall effect: Z = 0.54 (P = 0.59)							
Test for subgroup differences: Chi^2 = 1.21, df = 1 (P = 0.27), I^2 =18%							

Analysis 4.1. Comparison 4 Medications, Outcome 1 ICS dose at final visit.

Review: Tailored interventions based on exhaled nitric oxide versus clinical symptoms for asthma in children and adults

Comparison: 4 Medications

Outcome: 1 ICS dose at final visit



APPENDICES

Appendix 1. Database Search Strategies

Database	Search string
MEDLINE	1 exp asthma/ 2 exp Bronchial Spasm/ 3 asthma$.mp. 4 wheez$.mp. 5 bronchospas$.mp. 6 (bronch$ adj3 spas$).mp. 7 bronchoconstrict$.mp. 8 (bronch$ adj3 constrict$).mp.

(*Continued*)

	9 airway$ inflammation$.mp. 10 or/1-9 11 Nitric Oxide/ 12 exhaled nitric oxide.mp. 13 nitric$.mp. 14 eno.mp. 15 feno.mp. 16 or/11-15 17 10 and 16 (Combined with RCT filter)
EMBASE	1 exp asthma/ 2 Bronchospasm/ 3 asthma$.mp. 4 wheez$.mp. 5 bronchospas$.mp. 6 (bronch$ adj3 spas$).mp. 7 bronchoconstrict$.mp. 8 (bronch$ adj3 constrict$).mp. 9 airway$ inflammation$.mp. 10 or/1-9 11 Nitric Oxide/ 12 exhaled nitric oxide.mp. 13 nitric$.mp. 14 eno.mp. 15 feno.mp. 16 or/11-15 17 16 and 10 (combined with RCT filter)
CENTRAL	#1. MeSH descriptor Asthma explode all trees #2. MeSH descriptor Bronchial Spasm explode all trees #3. asthma* #4. wheez* #5. bronchospas* #6. bronch* near spas* #7. bronchoconstrict* #8. bronch* near constrict* #9. airway* inflammation* #10.(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9) #11.MeSH descriptor Nitric Oxide, this term only #12. exhaled nitric oxide #13.nitric* #14.eno #15. feno #16. (#11 OR #12 OR #13 OR #14 OR #15) #17. (#10 AND #16)

WHAT'S NEW

Last assessed as up-to-date: 27 February 2009.

Date	Event	Description
31 March 2009	New citation required and conclusions have changed	2 studies added with data and conclusions amended, following new search in February 2009. Risk of bias and summary of findings tables added

HISTORY

Protocol first published: Issue 1, 2007

Review first published: Issue 2, 2008

Date	Event	Description
30 January 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Protocol: Written by HP and AC. AL, JAK and CT reviewed protocol

Review: All reviewed manuscript. HP and AC extracted data and performed the analysis. CJC triple checked data analysis and data extraction.

DECLARATIONS OF INTEREST

Some of the authors are currently running a RCT on this subject.

SOURCES OF SUPPORT

Internal sources

- Royal Children's Hospital Foundation, Brisbane, Australia.

External sources

- National Health and Medical Research Council, Australia.
- Queensland Smart State Clinical Fellowship, Australia.

Support for AC

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The outcome dose of inhaled corticosteroids was added post-hoc to the review. Risk of Bias tables have been added for the 2009 update.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*administration & dosage]; Anti-Asthmatic Agents [*administration & dosage]; Asthma [*drug therapy; metabolism]; Biological Markers [analysis]; Breath Tests [methods]; Nitric Oxide [*analysis]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans