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Exhaled nitric oxide levels to guide treatment for adults with asthma (Review)

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Exhaled nitric oxide levels to guide treatment for adults with asthma

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ABSTRACT

Background

Asthma guidelines aim to guide health practitioners to optimise treatment for patients so as to minimise symptoms, improve or maintain good lung function, and prevent acute exacerbations or flare-ups. The principle of asthma guidelines is based on a step-up or step-down regimen of asthma medications to maximise good health outcomes using minimum medications. Asthma maintenance therapies reduce airway inflammation that is usually eosinophilic. Tailoring asthma medications in accordance with airway eosinophilic levels may improve asthma outcomes such as indices of control or reduce exacerbations or both. Fractional exhaled nitric oxide (FeNO) is a marker of eosinophilic inflammation, and as it is easy to measure, has an advantage over other measurements of eosinophilic inflammation (for example sputum eosinophils).

Objectives

To evaluate the efficacy of tailoring asthma interventions based on exhaled nitric oxide (FeNO), in comparison to not using FeNO, that is management based on clinical symptoms (with or without spirometry/peak flow) or asthma guidelines or both, for asthma-related outcomes in adults.

Search methods

We searched the Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CEN-TRAL), MEDLINE, EMBASE, and reference lists of articles. The last searches were undertaken in June 2016.

Selection criteria

All randomised controlled trials (RCTs) comparing adjustment of asthma medications based on exhaled nitric oxide levels compared to not using FeNO, that is management based on clinical symptoms (with or without spirometry/peak flow) or asthma guidelines or both.

Data collection and analysis

We reviewed results of searches against predetermined criteria for inclusion. We independently selected relevant studies in duplicate. Two review authors independently assessed trial quality and extracted data. We contacted study authors for further information, receiving responses from four.

Main results

We included seven adult studies; these studies differed in a variety of ways including definition of asthma exacerbations, FeNO cutoff levels used (15 to 35 ppb), the way in which FeNO was used to adjust therapy, and duration of study (4 to 12 months). Of 1700 randomised participants, 1546 completed the trials. The mean ages of the participants ranged from 28 to 54 years old. The inclusion criteria for the participants in each study varied, but all had a diagnosis of asthma and required asthma medications. In the meta-analysis, there was a significant difference in the primary outcome of asthma exacerbations between the groups, favouring the FeNO group. The number of people having one or more asthma exacerbations was significantly lower in the FeNO group compared to the control group (odds ratio (OR) 0.60, 95% confidence interval (CI) 0.43 to 0.84). The number needed to treat to benefit (NNTB) over 52 weeks was 12 (95% CI 8 to 32). Those in the FeNO group were also significantly more likely to have a lower exacerbation rate than the controls (rate ratio 0.59, 95% CI 0.45 to 0.77). However, we did not find a difference between the groups for exacerbations requiring hospitalisation (OR 0.14, 95% CI 0.01 to 2.67) or rescue oral corticosteroids (OR 0.86, 95% CI 0.50 to 1.48). There was also no significant difference between groups for any of the secondary outcomes (FEV_1, FeNO levels, symptoms scores, or inhaled corticosteroid doses at final visit).

We considered three included studies that had inadequate blinding to have a high risk of bias. However, when these studies were excluded from the meta-analysis, the difference between the groups for the primary outcomes (exacerbations) remained statistically significant. The GRADE quality of the evidence ranged from moderate (for the outcome 'exacerbations') to very low (for the outcome 'inhaled corticosteroid dose at final visit') based on the lack of blinding and statistical heterogeneity. Six of the seven studies were industry supported, but the company had no role in the study design or data analyses.

Authors' conclusions

With new studies included since the last version of this review, which included adults and children, this updated meta-analysis in adults with asthma showed that tailoring asthma medications based on FeNO levels (compared with primarily on clinical symptoms) decreased the frequency of asthma exacerbations but did not impact on day-to-day clinical symptoms, end-of-study FeNO levels, or inhaled corticosteroid dose. Thus, the universal use of FeNO to help guide therapy in adults with asthma cannot be advocated. As the main benefit shown in the studies in this review was a reduction in asthma exacerbations, the intervention may be most useful in adults who have frequent exacerbations. Further RCTs encompassing different asthma severity, ethnic groups in less affluent settings, and taking into account different FeNO cutoffs are required.

PLAIN LANGUAGE SUMMARY

Exhaled nitric oxide to guide asthma treatment for adults

Background

We examined whether exhaled nitric oxide (a marker in the breath which can show a type of lung inflammation) is useful in adjusting asthma medications in adults in comparison to the usual ways that asthma medications are adjusted. Exhaled nitric oxide levels are easily obtained by getting the person to breathe into a commercially available analyser.

Study characteristics

We included all randomised controlled trials that compared adjustment of asthma medications by usual clinical care (control group) versus using exhaled nitric oxide. The participants included in the trials had asthma diagnosed as per relevant asthma guidelines.

The evidence is current to June 2016, when the searches were last completed.

We found seven studies in the searches. Of 1700 randomised participants, 1546 completed the trials. The studies varied in a few aspects including duration, cutoff levels used for altering medications based on fractional exhaled nitric oxide (FeNO), and the way each study defined exacerbations. The included studies ranged from 4 months to 12 months in duration. The FeNO cutoff values the studies

used also varied. The levels used for decreasing medications ranged from 10 ppb to 25 ppb. Likewise, the levels used for increasing medications ranged from 15 ppb to 35 ppb in the included studies. The majority of the studies were industry supported.

The mean ages of the participants ranged from 28 to 54 years old.

Key results

In this review involving 1700 adults with asthma, we found that guiding the dose of asthma medications based on exhaled nitric oxide (compared to a control group) was beneficial in reducing the number of exacerbations (flare-ups) during the study period. However, we did not find a difference between groups for other asthma outcomes that impact on day-to-day clinical symptoms, hospitalisations, or inhaled steroid dose. Thus, using exhaled nitric oxide levels to adjust asthma therapy may reduce the risk of adults having an asthma flare-up but did not impact on day-to-day symptoms.

Quality of the evidence

The quality of evidence ranged from moderate when comparing the two groups for the exacerbation outcomes, to very low when comparing the groups for inhaled corticosteroid dose at final visit.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Tailoring asthma treatment using FeNO versus clinical symptoms

Patient or population: adults with asthma
Setting: outpatient
Intervention: asthma treatment tailored on FeNO
Comparison: asthma treatment tailored on clinical symptoms

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with asthma treatment tailored on clinical symptoms**	**Risk with asthma treatment tailored on FeNO**				
Number of participants who had ≥ 1 exacerbations over study period Follow-up: range 18 weeks to 52 weeks	25 per 100	**17 per 100** (13 to 22)	**OR 0.60** (0.43 to 0.84)	1005 (5 RCTs)	⊕⊕⊕◯ MODERATE[1]	-
Number of exacerbations per 52 weeks (exacerbation rates) Follow-up: mean 52 weeks	The control group ranged from 0.23 to 0.9 exacerbations per 52 weeks	**Rate ratio 0.59** (0.45 to 0.77)	-	842 (5 RCTs)	⊕⊕⊕◯ MODERATE[1]	-
ICS dose at final visit Follow-up: range 18 weeks to 52 weeks	The mean ICS dose taken by the control group at final visit was **659 mcg**	The mean ICS dose taken in the FeNO groups was 17.01 lower (101.75 lower to 67.72 more) **577 mcg**	-	582 (4 RCTs)	⊕⊕◯◯ VERY LOW[2,3]	A random-effects sensitivity analysis gave a very imprecise result: MD -147.15 (95% CI -380.85 to 86.56)

*****The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

******The control group risks were calculated as a mean of the scores or events in the control groups of the studies contributing to each analysis. We could not calculate a control risk for the number of exacerbations per 52 weeks because we did not have information for each arm of the studies, just ratios between them.

CI: confidence interval; **FeNO:** fractional exhaled nitric oxide; **ICS:** inhaled corticosteroids; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Two studies, Honkoop 2014 and Syk 2013, carrying 36% of the analysis weight, were at high risk of performance and detection
bias due to lack of blinding. There were several uncertainties across studies, particularly with regard to the control of
selection bias (one downgrade for risk of bias).
[2]Final inhaled corticosteroid doses were quite varied, with one study having particularly high doses (360 to 1282 in the control
groups and 423 to 740 in the FeNO groups). There was substantial statistical heterogeneity in the analysis (I^2 = 82%; P =
0.0007). A random-effects sensitivity analysis changed the result substantially to MD -147.15 (95% CI -380.85 to 86.56) (one
downgrade for heterogeneity, one downgrade for imprecision).
[3]One study carrying 51% of the analysis weight, Syk 2013, was open labelled, which may have introduced bias (one downgrade
for risk of bias).

BACKGROUND

Description of the condition

Asthma guidelines aim to guide health practitioners to optimise treatment for patients so as to minimise symptoms, optimise lung function, and prevent acute exacerbations (BTS/SIGN 2014; GINA 2014; National Asthma Council 2014). Exacerbations cause anxiety to patients and their families and are costly to healthcare systems (Weiss 2001), which puts stress on healthcare providers. Preventing exacerbations is thus an important component for maintaining ideal asthma control. The second component in asthma management is monitoring of asthma control (by subjective and objective measures) (BTS/SIGN 2014; GINA 2014; National Asthma Council 2014). Subjective measures usually involve a series of questions used for clinical assessment, diary cards, and quality of life questionnaires. Traditional objective methods include peak flow, spirometry, and degree of airway hyper-responsiveness (Zacharasiewicz 2005). Newer, and arguably more sensitive, methods include measurement of airway inflammation such as airway cellularity in induced sputum or fractional exhaled nitric oxide (FeNO).

In asthma, inflammation can be eosinophilic or neutrophilic (Douwes 2002). Asthma management is arguably best tailored in accordance with the type of airway inflammation, as corticosteroids are more beneficial in eosinophilic inflammation (Wardlaw 2000), and inhaled corticosteroids (ICS) reduce exacerbations and improve symptoms and asthma control (Wardlaw 2000). There are several ways to quantify airway eosinophilic inflammation, such as determining the percentage of eosinophils in the sputum and FeNO. FeNO correlates with other markers of asthma, for example eosinophilia in induced sputum (Jatakanon 1998), and bronchial reactivity in steroid-naive patients (Dupont 1998). Induced sputum and sputum analysis is labour intensive and not widely available in non-research laboratories. Hypertonic saline, which is used to induce sputum, may also temporarily increase asthma symptoms. Measures of FeNO thus confer some advantage over measurements of sputum eosinophils. However, FeNO does not provide any data on non-eosinophilic inflammation, and the equipment required to measure FeNO is relatively expensive.

Description of the intervention

The principle of asthma management is based on a step-up or step-down regimen of asthma medications to reduce airway inflammation, control symptoms, and reduce exacerbations. Tailoring of asthma medications in accordance to airway eosinophilic levels may improve asthma control or reduce exacerbations or both. FeNO levels can be measured using commercially available analysers. These analysers vary in several ways, including methods of measurements (online or offline), complexity, their set-up, calibration procedures, sampling tube design, measuring chamber, and the way expiratory flow is controlled (Muller 2005). Stationary analysers measure FeNO by chemiluminescence, whilst portable FeNO analysers measure FeNO using electrochemistry.

How the intervention might work

As FeNO is reflective of airway eosinophilia in some circumstances, FeNO can be considered as a biomarker. For asthma, FeNO levels can potentially be used in adults with asthma to:

- monitor airway eosinophilia;
- verify the adherence to ICS; and
- predict upcoming asthma exacerbations.

Reduction of airway inflammation improves symptoms and asthma control (Wardlaw 2000). Hence, the use of FeNO levels to tailor asthma medications in adults with asthma may improve asthma control or reduce exacerbations or both.

Why it is important to do this review

A Cochrane review has previously been published combining adults and children in one review (Petsky 2009). Given the clinical heterogeneity between children and adults with asthma, we undertook separate reviews for children and adults for the updates. Hence this is a new review, but is based on our previously published review (Petsky 2009). This review focuses on adults, and there will be a similar systematic review that includes only children as participants (Petsky 2015b).

A systematic review evaluating the efficacy of tailoring asthma interventions based on FeNO levels in comparison with not using FeNO (that is the traditional reliance upon clinical symptoms or following asthma guidelines with or without spirometry/peak flow) will be useful to guide clinical practice in adults with asthma. Using FeNO routinely in clinical practice adds to the burden of asthma care and resource utilisation. On the other hand, routine use of FeNO may improve asthma control and reduce exacerbations and hospitalisations related to asthma.

OBJECTIVES

To evaluate the efficacy of tailoring asthma interventions based on exhaled nitric oxide (FeNO) in comparison to not using FeNO, that is management based on clinical symptoms (with or without spirometry/peak flow) or asthma guidelines or both for asthma-related outcomes in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) comparing adjustment of asthma medications based on exhaled nitric oxide levels compared to those not using FeNO, that is management based on clinical symptoms (with or without spirometry/peak flow) or asthma guidelines or both. We included studies reported as full text, those published as abstract only, and unpublished data.

Types of participants

We included adults with a diagnosis of asthma according to a guideline-defined criteria.

We excluded participants with the following comorbidities/characteristics: eosinophilic bronchitis, asthma related to an underlying lung disease such as bronchiectasis and chronic obstructive pulmonary disease (COPD), or diagnostic categories such as 'cough variant asthma' and 'wheezy bronchitis' where controversies exist.

Types of interventions

We included RCTs comparing adjustment of asthma medications based on FeNO levels versus control groups where FeNO was not used to adjust asthma medications. Control group interventions may include use of clinical symptoms (with or without spirometry/peak flow) or asthma guidelines or both to guide adjustment of asthma medications. We included studies in which other interventions were used if all participants had equal access to such interventions. We included studies of at least 12 weeks' duration.

Types of outcome measures

Primary outcomes

Asthma exacerbations during follow-up, with the following definitions.

1. Number of participants who had one or more exacerbations over the study period.
2. Number of exacerbations per 52 weeks (exacerbation rate).
3. Severe exacerbations requiring oral corticosteroids.
4. Severe exacerbation requiring hospitalisation.

Secondary outcomes

1. Objective measurements of asthma control (FEV_1, peak flow, airway hyper-responsiveness).
2. FeNO level.
3. Symptoms of asthma as reported in Asthma Control Test.
4. Symptoms of asthma as reported in asthma-related quality of life questionnaire score (AQLQ).

5. Inhaled corticosteroid dose at final visit.
Reporting one or more of the outcomes listed here in the study was not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group's Specialised Register (CAGR), which is maintained by the Information Specialist for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We searched all records in the CAGR using the search strategy in Appendix 2. We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO trials portal (www.who.int/ictrp/en/), using the search strategy in Appendix 3. We searched all databases from their inception to June 2016, and we imposed no restriction on language of publication.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for trial information.

We searched for errata or retractions from included studies published in full text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and reported the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (HP, KK) independently screened the titles and abstracts of all the studies we identified as a result of the search for inclusion and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We then retrieved the full-text study reports/publication, and two review authors (HP, KK) independently screened the full text and identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. We planned to resolve any disagreements through discussion or, if required, by consulting a third review author (AC). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1) and Characteristics of excluded studies table.

Figure 1. Study flow diagram.
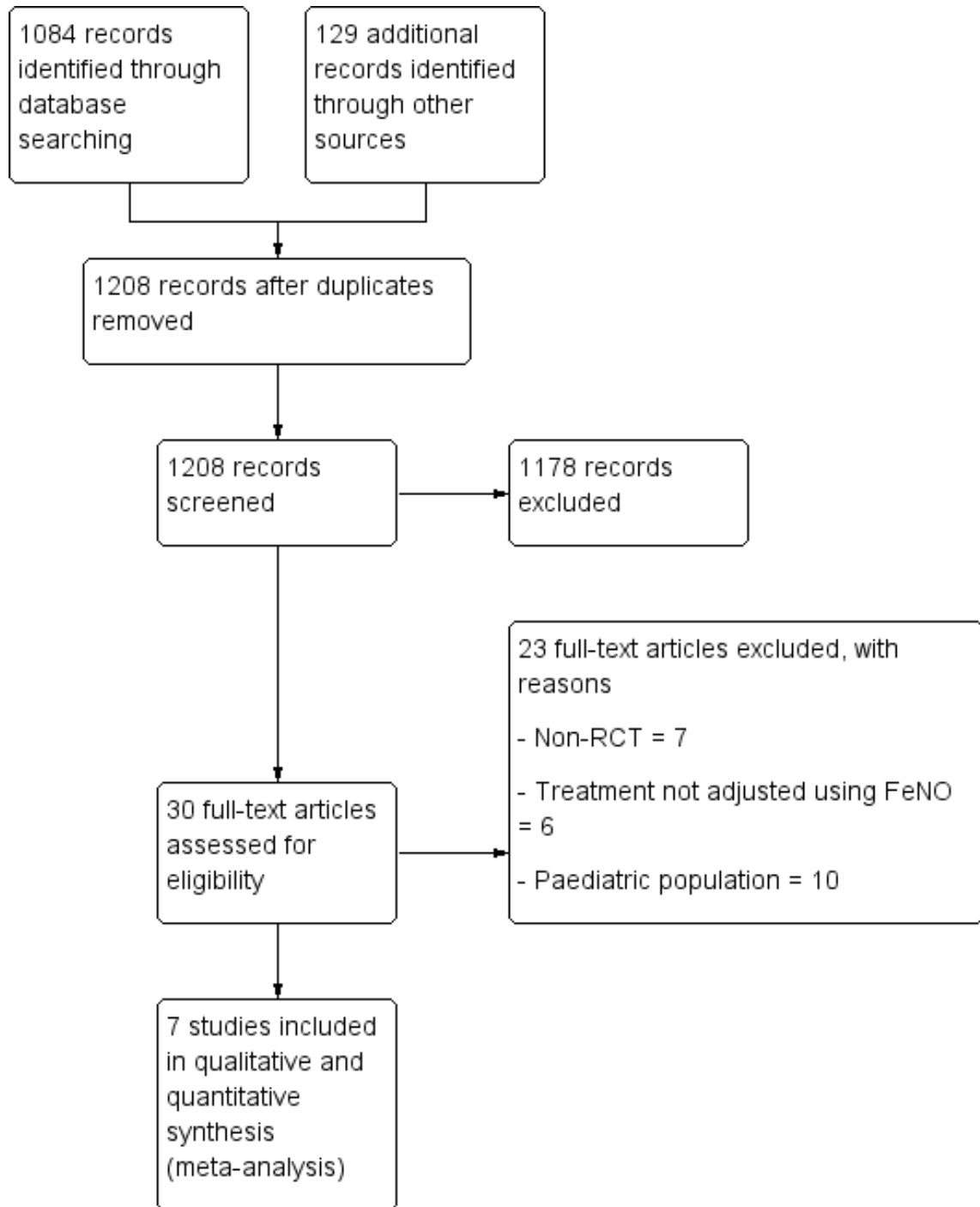
Data extraction and management

We used a data collection form for study characteristics and outcome data that had been piloted on at least one study in the review. One review author (HP) extracted study characteristics from included studies. We then extracted the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.

2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.

3. Interventions: intervention, comparison, concomitant medications, and excluded medications.

4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.

5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (HP, KK) independently extracted outcome data from included studies from the 2015 and 2016 searches. We then noted in the Characteristics of included studies table if outcome data were not reported in a useable way. We planned to resolve disagreements by consensus or by involving a third review author (AC). One review author (HP) transferred data into the RevMan 2014 file. We double-checked that data had been entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (KK) checked the study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (HP, KK) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to resolve any disagreements by discussion or by involving another review author (AC). We assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low, or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We then summarised the 'Risk of bias' judgements across different studies for each of the domains listed. We planned to judge blinding separately for different key outcomes where necessary (for example for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to this published protocol and reported any deviations from it in the Differences between protocol and review section of the systematic review.

Measures of treatment effect

We analysed dichotomous data as odds ratios and continuous data as mean difference or standardised mean difference. We then entered data presented as a scale with a consistent direction of effect. We undertook meta-analyses only where it was meaningful, that is if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

We narratively described skewed data that was reported as medians and interquartile ranges.

Where multiple trial arms were reported in a single trial, we included only the relevant arms. If two comparisons (for example drug A versus placebo and drug B versus placebo) were combined in the same meta-analysis, we halved the control group to avoid double-counting.

Unit of analysis issues

For dichotomous data, we reported the proportion of participants contributing to each outcome in comparison with the total number randomised. For rate ratios of common events whereby one participant may have more than one event, we used generic inverse variance (GIV). We took the rate ratios from the published papers and calculated the standard errors from confidence intervals (CI) or P values published in the papers. It was planned that for cross-over studies, mean treatment differences were to be calculated from raw data, and variances extracted or imputed and entered as fixed-effect GIV outcome, to provide summary weighted differences and 95% CIs.

Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data where possible (for example when a study was identified as abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results with a sensitivity analysis.

Assessment of heterogeneity

We described and tested any heterogeneity between study results to see if it reached statistical significance using a Chi^2 test. We planned to include the 95% CI estimated using a random-effects model whenever there was concerns about statistical heterogeneity. Heterogeneity is considered significant when the P value is less than 0.10 (Higgins 2011). We then used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity, we reported it and explored possible causes by prespecified subgroup analysis.

Assessment of reporting biases

As we were unable to pool more than 10 trials, we did not create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

We included the results from studies that met the inclusion criteria and reported any of the outcomes of interest in the subsequent meta-analyses. We calculated the summary weighted risk ratio and 95% CI (fixed-effect model) (RevMan 2014). For rate ratios of common events whereby one participant had more than one event, we utilised GIV. We took the rate ratios from the published papers and calculated the standard errors from CI or P values published in the papers. For cross-over studies, we planned to calculate mean treatment differences from raw data, and extract or impute variances and enter them as fixed-effect GIV, to provide summary weighted differences and 95% CI. We calculated number needed to treat to benefit (NNTB) from the pooled odds ratio and its 95% CI applied to a specified baseline risk using an online calculator (Cates 2008). The outcome indices were assumed to be normally distributed continuous variables so the mean difference in outcomes could be estimated. If studies reported outcomes using different measurement scales, we estimated the standardised mean difference.

'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes.

1. Number of participants who had one or more exacerbation over the study period.
2. Number of exacerbations per 52 weeks.
3. Inhaled corticosteroid (ICS) dose at final visit.

The 'Summary of findings' table in the previous combined review, Petsky 2009, was amended to reflect the new data and restricted to the inclusion criteria of this review. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contributed data to the meta-analyses for the prespecified outcomes. We then used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions,* Higgins 2011, using GRADEpro software. We justified all decisions to down- or up-grade the quality of studies using footnotes, and we made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analysis for the following.

1. Basis for adjustment of ICS in the control group (guideline-driven monitoring versus non-guideline driven).
2. Use of spirometry or peak flow as an adjunctive monitoring tool for adjustment of medications (versus non-use of spirometry or peak flow).
3. Baseline ICS dose at commencement of intervention (low-medium (< 800 mcg/day budesonide equivalent) versus high dose (800 mcg/day or more budesonide equivalent)).
4. FeNO cutoffs for adjustment of medications ($\leq$ 20 ppb versus > 20 ppb).
5. FeNO cutoffs, based on presence of atopy.

Sensitivity analysis

We carried out the following sensitivity analyses.

1. Sensitivity analysis excluding studies with a high risk of bias based on the 'Risk of bias' assessment. Studies that did not have adequate allocation concealment and sequence generation were removed.
2. Variation in the inclusion criteria. Studies that included adults not receiving ICS at recruitment were removed.
3. Differences in the medications used in the intervention and comparison group. Studies that adjusted medications only for one arm were removed.
4. Analysis that used the random-effects model.
5. Analysis that used 'strategy received'. Studies with hierarchy management protocols that only considered use of steroids for each step (i.e. without consideration for using montelukast or long-acting beta-agonist or both at any point) were removed.

R E S U L T S

Description of studies

Please see: Characteristics of included studies; Characteristics of excluded studies; and Characteristics of ongoing studies.

Results of the search

The Cochrane Airways Group's Specialised Register identified 1084 potentially relevant titles from the 2015 and 2016 searches (Figure 1). We identified an additional 129 titles through searches of ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO trials portal (www.who.int/ictrp/en/). After assessing the abstracts, we obtained 30 papers for consideration after removal of duplicates. We excluded 14 papers due to non-randomisation or treatment not adjusted based on FeNO. Of the remaining 16 papers, seven papers included adult participants, and nine were based on children or adolescents, which will be presented in a separate Cochrane Review (Petsky 2015b).

Included studies

See Characteristics of included studies table.
We included seven studies involving a total of 1700 randomised participants, of which 1546 completed the trial (Calhoun 2012; Hashimoto 2011; Honkoop 2014; Powell 2011; Shaw 2007; Smith 2005; Syk 2013). .

Study design

Six of the seven studies were parallel-group studies, and one used cluster randomisation (Honkoop 2014). Five were multicentre studies (Calhoun 2012; Hashimoto 2011; Honkoop 2014; Shaw 2007; Syk 2013); the remaining two were a dual-centre study, in Powell 2011, and a single-centre study, in Smith 2005.
Two studies used a three-arm strategy to adjust inhaled corticosteroids (Calhoun 2012; Honkoop 2014). Calhoun et al's strategy arms were based on (i) National Heart, Lung, and Blood Institute guidelines (physician assessment-based adjustment (PABA) group), (ii) measurement of exhaled nitric oxide (biomarker-based adjustment (BBA)), or (iii) occurrence of symptoms prompting rescue use of albuterol (symptom-based adjustment (SBA)). As the PABA strategy utilised a national guideline, we used this group as the control group and the BBA strategy as the intervention group. Honkoop et al's study also had three arms, which targeted (i) partially controlled asthma (PCa), (ii) controlled asthma (Ca), or (iii) FeNO-driven controlled asthma (FCa) (Honkoop 2014). The controlled asthma strategy was used as the control group.
Despite Hashimoto et al's study fitting the inclusion criteria (Hashimoto 2011), we could not include some of their data in the meta-analysis as the adjustments were based on the dose of oral corticosteroids. Hashimoto 2011 used an internet-based management tool comprised of (i) an electronic diary that included FeNO measurement, (ii) treatment decision support for the participants, and (iii) monitoring support by the study nurse.
Of the seven studies, two were double blind (Calhoun 2012; Powell 2011), two were single blind (Shaw 2007; Smith 2005), and three had no blinding (Hashimoto 2011; Honkoop 2014; Syk 2013).
The study duration varied, ranging from 4 months to 12 months (Table 1). Each study defined exacerbations differently (Table 1).

Control group

Four of the seven studies utilised existing asthma guidelines to adjust treatment in the control group (Calhoun 2012; Hashimoto 2011; Shaw 2007; Smith 2005). Two studies used the Asthma Control Test (Honkoop 2014; Powell 2011). One study utilised a combination of patient-reported symptoms, bronchodilator use, physical examination, and spirometry results (Syk 2013) (Table 1).

FeNO strategy

The intervention arm in all seven studies, although primarily based on FeNO level, differed in the cutoff for FeNO for change in therapy. Syk 2013 was the only study utilising different cutoffs for men and women. No studies took into account the presence of atopy.
The FeNO cutoffs used for the studies are presented in Table 1.

Participants

The seven included studies used different inclusion criteria to recruit participants. While all participants had to have asthma, how the diagnosis was defined varied across the studies. Two studies defined asthma as per current guidelines (Hashimoto 2011; Honkoop 2014). Six studies defined asthma as the current use of asthma medications (Hashimoto 2011; Honkoop 2014; Powell 2011; Shaw 2007; Smith 2005; Syk 2013). Calhoun 2012 and Syk 2013 based their definition of asthma on physician diagnosis and positive airway hyper-responsiveness.

Outcomes

Four studies used asthma exacerbations or time-to-treatment failure as their primary outcome (Calhoun 2012; Powell 2011; Shaw 2007; Smith 2005). Each study defined exacerbations differently; see Table 1. Hashimoto 2011 used Asthma Control Questionnaire and quality of life as their primary outcome. Honkoop 2014 used quality-adjusted life years as their primary outcome. One study used the change in Juniper Mini Asthma Quality of Life Questionnaire as their primary outcome (Syk 2013).

Secondary outcomes also varied among the studies. Four studies used spirometry (Calhoun 2012; Hashimoto 2011; Honkoop 2014; Syk 2013). Two studies included asthma exacerbations (Hashimoto 2011; Honkoop 2014). In four studies asthma-related quality of life was a secondary outcome (Calhoun 2012; Honkoop 2014; Powell 2011; Syk 2013), and three studies used dose of inhaled corticosteroids (Shaw 2007; Smith 2005; Syk 2013).

Excluded studies

We excluded 24 studies; the reasons for the exclusion are presented in the Characteristics of excluded studies table. The most common reasons for exclusion were: not a randomised controlled trial (n = 7), treatment not adjusted to FeNO (n = 6), and participants were not adults (n = 9). We found a further study in abstract form only (Duong-Quy 2015). We contacted the study author of Duong-Quy 2015 in June 2016 and confirmed that the paper was in preparation, therefore we judged this study as ongoing, to be included in the next update.

Risk of bias in included studies

Full details of 'Risk of bias' judgements can be found in the 'Risk of bias' section at the end of each Characteristics of included studies table; a 'Risk of bias' summary can be found in Figure 2. Overall, the methodological quality of the included studies was high.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Generation of the randomisation sequence was described in three studies (Hashimoto 2011; Powell 2011; Syk 2013), and unclear in four studies (Calhoun 2012; Honkoop 2014; Shaw 2007; Smith 2005). We determined the method of allocation concealment to be adequate in three studies (Powell 2011; Shaw 2007; Syk 2013), and unclear in three (Calhoun 2012; Honkoop 2014; Smith 2005). However, we assessed one study as at high risk of bias for allocation concealment (Hashimoto 2011).

Blinding

We deemed the risk associated with participant blinding to be low when the study authors reported blinding of the assessors. These were: "a third party provided advice on treatment decisions" and "both arms of the study received the same follow-up including measurements and tests".

We considered risk of detection bias due to inadequate blinding of outcome assessors to be high in three studies (Hashimoto 2011; Honkoop 2014; Syk 2013), and unclear in one (Calhoun 2012), as there was not enough information in the published protocol and article. We judged three studies as having a low risk of bias (Powell 2011; Shaw 2007; Smith 2005).

Incomplete outcome data

We assessed all studies as having a low risk of attrition bias.

Selective reporting

We considered three studies to have a low risk of reporting bias (Hashimoto 2011; Honkoop 2014; Powell 2011), with all outcome measures being reported. We judged three studies as unclear as there was not enough information provided in the published article (Shaw 2007; Smith 2005; Syk 2013). We judged Calhoun 2012 as high risk as some of the secondary outcomes reported were not correctly labelled or an incorrect analysis method was utilised.

Other potential sources of bias

Another source of bias was the success of obtaining FeNO levels at each visit according to current guidelines. Six studies did not report the success of obtaining FeNO at each time point (Calhoun 2012; Hashimoto 2011; Honkoop 2014; Powell 2011; Smith 2005; Syk 2013). One study reported that they successfully obtained FeNO at each visit (Shaw 2007).

Effects of interventions

See: **Summary of findings for the main comparison** Tailoring asthma treatment using FeNO versus clinical symptoms
See Summary of findings for the main comparison for the main comparisons.

Primary outcome: Asthma exacerbations

Four of the included studies used asthma exacerbations as their primary outcome (Calhoun 2012; Powell 2011; Shaw 2007; Smith 2005). See Table 1 for the definitions of exacerbations used. Five studies reported a reduction in asthma exacerbations in the intervention arm compared to the controls (treatment was based primarily on clinical symptoms) (Honkoop 2014; Powell 2011; Shaw 2007; Smith 2005; Syk 2013). For the various types of exacerbations, data from the studies were combined into the meta-analysis, as described below.

1.1 Number of participants who had one or more exacerbations over the study period

Analysis 1.1
Hashimoto 2011 did not report on this outcome in the paper and provided their data through correspondence (31 in FeNO group and 24 in control group had one or more exacerbation). Combined data from five studies showed that the number of participants experiencing an exacerbation was significantly lower (P = 0.003) in the FeNO group compared to the control (clinical symptom) group over the study period; pooled odds ratio (OR) (fixed-effect model) was OR 0.60 (95% confidence interval (CI) 0.43 to 0.84; participants = 1005; studies = 5). There was no heterogeneity among the studies; I^2 = 13%. In the control group 149 out of 529 participants had at least one exacerbation over the study period, compared to 116 out of 539 for the FeNO group. The number needed to treat to benefit (NNTB) over 52 weeks was 12 (95% CI 8 to 32).

1.2 Number of exacerbations per 52 weeks (exacerbation rate)

Analysis 1.2
Combined data from five studies for this outcome also showed a significant (P = 0.0001) reduction favouring the FeNO group; rate ratio (RR) 0.59 (95% CI 0.45 to 0.77; participants = 842; studies = 5). There was no statistical no heterogeneity among the studies. The rate of exacerbation over the 52 weeks in the control group ranged from 0.23 to 0.9.

1.3 Severe exacerbations requiring oral corticosteroids

Analysis 1.3

Three studies reporting the use of oral corticosteroids could be combined in a meta-analysis, showing no significant difference between the groups (OR 0.86, 95% CI 0.50 to 1.48; participants = 495; studies = 3; I^2 = 0%).

1.4 Severe exacerbations requiring hospitalisation

Analysis 1.4

Five studies reported hospitalisations due to worsening of asthma symptoms, but no participants were hospitalised in two studies (Shaw 2007; Syk 2013). We did not include Hashimoto 2011 and Honkoop 2014 in the meta-analysis because they were cluster randomised trials or due to the complexity of the intervention used. In the Hashimoto 2011 study a total of nine people were hospitalised (four in FeNO group and five in the control strategy). The meta-analysis showed no significant difference between the groups (OR 0.14, 95% CI 0.01 to 2.67; participants = 488; studies = 3; I^2 = 0%).

Secondary outcomes

1.5 FEV$_1$% predicted at final visit

Analysis 1.5

None of the included studies reported lung function, but we obtained further data from the authors of four studies. There was no significant difference between groups (mean difference (MD) 0.11, 95% CI -1.15 to 1.37; participants = 802; studies = 4). Shaw et al reported that "there was no difference in FEV1 between the groups over the duration of the study", but no details were provided (Shaw 2007).

1.6 FeNO level (ppb) at final visit

Analysis 1.6

Five studies reported FeNO at final visit. The forest plot showed no significant difference between the groups (standardised mean difference (SMD) -0.00, 95% CI -0.16 to 0.15; participants = 668; studies = 5; I^2 = 0%). A random-effects analysis did not change the results (SMD -0.00, 95% CI -0.16 to 0.15; participants = 668; studies = 5).

1.7 Symptom score: Asthma Control Test

Analysis 1.7

Four studies reported Asthma Control Test results. Meta-analysis showed no significant difference between groups (MD -0.08, 95% CI -0.18 to 0.01; participants = 707; studies = 4; I^2 = 0%).

1.8 Symptom score: Asthma-related quality of life

Analysis 1.8

Combined data from only two studies found no significant difference between groups for the Asthma Quality of Life Questionnaire (AQLQ) (MD 0.00, 95% CI -0.10 to 0.10; participants = 621; studies = 2). Data from Hashimoto et al could not be included in the meta-analysis, but reported that asthma-related quality of life did not differ between the study groups (Hashimoto 2011).

1.9 Inhaled corticosteroids dose at final visit (budesonide equivalent in mcg/day)

Analysis 1.9

There was no significant difference between the groups' inhaled corticosteroid (ICS) dose at final visit in the meta-analysis of four studies (MD -17.01, 95% CI -101.75 to 67.72; participants = 582; studies = 4; I^2 = 82%). There was significant statistical heterogeneity for this outcome, likely due to the large doses of steroids used in one study (Smith 2005). Using random-effects, the difference between groups remained non-significant (MD -147.15 mcg/day, 95% CI -380.85 to 86.56).

Subgroup analysis and investigation of heterogeneity

1. Basis for adjustment of ICS in the control group (guideline-driven monitoring versus non-guideline driven)

Analysis 1.10 and Analysis 1.11

Four of the included studies utilised guideline-driven monitoring for the control group (Calhoun 2012; Hashimoto 2011; Shaw 2007; Smith 2005). In this subgroup, for the primary outcome of exacerbation, the significant difference between groups was no longer present. There were no differences between groups for the number of participants who had one or more exacerbations (OR 0.87, 95% CI 0.47 to 1.61). The exacerbation rate was also not significantly different between groups (RR 0.76, 95% CI 0.48 to 1.19; P = 0.23).

In the other three studies (Honkoop 2014; Powell 2011; Syk 2013), the adjustments were not guideline based. The meta-analysis of this subgroup significantly favoured the FeNO arm compared to the control arm; the number of participants who had one or more exacerbation (OR 0.51, 95% CI 0.34 to 0.76) and exacerbation rate between groups (RR 0.51, 95% CI 0.37 to 0.71).

When testing the subgroup differences, there was no difference between the two subgroups for either outcome; Analysis 1.10 reports no subgroup difference (P = 0.16). Likewise, Analysis 1.11 reports no difference (P = 0.17).

2. Use of spirometry or peak flow as an adjunctive monitoring tool for adjustment of medications (versus non-use of spirometry or peak flow)

Two studies utilised spirometry when adjusting medications in the control group (Honkoop 2014; Syk 2013), however as spirometry was not the sole measurement for adjusting the medications, this subgroup analysis could not be done. As per Table 1, Honkoop 2014 utilised the Asthma Control Test, 7-item version, which includes spirometry, and Syk 2013 used patient-reported symptoms, short-acting beta-agonist use, physical review in addition to spirometry.

3. Baseline ICS dose at commencement of intervention (low-medium (< 800 mcg/day budesonide equivalent) versus high dose (800 mcg/day or more budesonide equivalent))

In four studies (Calhoun 2012; Hashimoto 2011; Shaw 2007; Syk 2013), the median ICS dose at baseline was less than 800 mcg/day budesonide equivalent. However, none of the studies analysed their data based on baseline ICS dose, hence this subgroup analysis could not be done.

4. FeNO cutoffs for adjustment of medications ($\leq$ 20 ppb versus > 20 ppb)

Five studies adjusted medications if FeNO levels were less than or equal to 20 ppb, as described in Table 1 (Hashimoto 2011; Powell 2011; Shaw 2007; Smith 2005; Syk 2013). When considering this in the subgroup analysis, the results were similar to the main analyses.

For the primary outcomes of exacerbation, the FeNO group continued to have fewer exacerbations. By removing Honkoop 2014, who adjusted medications when FeNO was greater than 20 ppb, from the first outcome, the number of participants who had more than one exacerbation over the study period, the difference remained statistically different (OR 0.59, 95% CI 0.41 to 0.85; P = 0.004). Likewise, for the second primary outcome of exacerbation rate, by removing Calhoun 2012 the FeNO group was favoured (RR 0.57, 95% CI 0.43 to 0.75).

5. FeNO cutoffs, based on presence of atopy

None of the included studies considered atopy in their algorithm for FeNO levels, therefore it was not possible to explore atopy through subgroup analysis.

Sensitivity analyses

1. Excluding studies with a high risk of bias based on the 'Risk of bias' assessment

Three of the included studies did not use blinding (Hashimoto 2011; Honkoop 2014; Syk 2013). However, removing the data from these studies did not alter the results of the primary outcome (exacerbations) found in the main analyses; the number of participants who had one or more exacerbations over the study period (OR 0.63, 95% CI 0.41 to 0.96; participants = 432; studies = 3) and exacerbation rate (RR 0.61, 95% CI 0.45 to 0.82; participants = 661; studies = 4).

2. Variation in the inclusion criteria

One study involving pregnant women only reported that not all included adults were receiving ICS at recruitment (Powell 2011); only 43.1% of control group and 41.1% of FeNO group were receiving ICS at baseline. Removing this study had little impact on the effect estimate, but resulted in reduced precision for number of participants with one or more exacerbations (OR 0.67, 95% CI 0.44 to 1.01; P = 0.06; participants = 785; studies = 4). The group differences for exacerbation rate remained significantly different between groups, favouring the FeNO group, but again with reduced precision (RR 0.66, 95% CI 0.47 to 0.93; P = 0.02; participants = 622; studies = 4).

3. Differences in the medications used in the intervention and comparison group

No studies adjusted medications for only one arm, therefore we did not undertake this planned sensitivity analysis.

4. Analysis used random-effects model

Using random-effects did not change the significant group differences for the primary outcomes, that is results favoured the FeNO arm; the number of participants who had one or more exacerbations over the study period (OR 0.61, 95% CI 0.42 to 0.87; participants = 1005; studies = 5) and exacerbation rate (RR 0.59, 95% CI 0.45 to 0.77; participants = 842; studies = 5).

5. Analysis by 'strategy received'

Four studies used hierarchy management protocols that were based solely on the use of steroids for each step (that is without consideration for using montelukast or long-acting beta-agonist or both at any point) (Calhoun 2012; Hashimoto 2011; Shaw 2007; Smith 2005). Removing these studies from the analyses did not alter the significant group differences found in the main analyses, which favoured the FeNO arm; the number of participants who had one or more exacerbation over the study period (OR 0.51, 95% CI 0.34 to 0.76; participants = 793; studies = 3) and exacerbation rate (RR 0.51, 95% CI 0.37 to 0.71; participants = 401; studies = 2).

DISCUSSION

Summary of main results

We found seven RCTs involving 1700 participants (1546 completed) that could be included in this review. The studies varied in the FeNO levels and algorithms used. The duration of the studies also differed, ranging from 4 to 12 months.

All studies reported our review's primary outcome (exacerbation), but the definition varied among the studies. We could combine data from a maximum of five studies for the meta-analysis of the different exacerbation types. The number of people having one or more asthma exacerbation was significantly lower in the FeNO group compared to the control group (OR 0.60, 95% CI 0.43 to 0.84). The NNTB over 52 weeks was 12 (95% CI 8 to 32). Those in the FeNO group were also significantly more likely to have a lower exacerbation rate than the controls (RR 0.59, 95% CI 0.45 to 0.77). However, we did not find a difference between the groups for exacerbations requiring hospitalisation (OR 0.14, 95% CI 0.01 to 2.67) or rescue oral corticosteroids (OR 0.86, 95% CI 0.50 to 1.48); only three studies contributed to the latter outcome.

There was also no significant difference between groups for any of the secondary outcomes (FEV_1, FeNO levels, symptoms scores, or ICS doses at final visit).

In the subgroup analyses, when the analyses were restricted to the studies that utilised guidelines as the control group, the main analyses for the primary outcome of exacerbations were altered, with no difference seen between the FeNO and control groups for the number of participants who had one or more exacerbation (OR 0.87, 95% CI 0.47 to 1.61) or exacerbation rate (RR 0.76, 95% CI 0.48 to 1.19). There were no subgroup differences for either primary outcome.

In the sensitivity analyses, the only changes from the primary outcome analyses were seen when removing one study that included pregnant participants not receiving ICS at the beginning of the study (Powell 2011). The pooled effect size was similar, but there was a loss of precision for both number of participants with one or more exacerbation (OR 0.67, 95% CI 0.44 to 1.01; P = 0.06) and exacerbation rate (RR 0.66, 95% CI 0.47 to 0.93; P = 0.02).

Overall completeness and applicability of evidence

This review included seven studies, but the meta-analyses could only include data from between two and five studies for the various outcomes, including our review's primary outcome. The total number of participants for the various outcomes ranged from 488 (outcome: severe exacerbations requiring hospitalisation) to 1005 (outcome: number of participants who had one or more exacerbations over the study period). Thus, although we contacted authors of the studies, the completeness of the review was limited by availability of data.

Despite two of the primary outcomes ('number of participants

who had one or more exacerbations over the study period' and 'exacerbation rate') favouring the FeNO arm, there were no significant group differences for severe exacerbations (requiring oral corticosteroids or hospitalisation) or for symptom scores and end-of-study FEV_1, FeNO, or ICS doses. In the subgroup analyses, when considering only the studies that utilised guidelines for the control group (Calhoun 2012; Hashimoto 2011; Shaw 2007; Smith 2005), for the primary outcomes of exacerbations we found no difference between the FeNO and control groups. However, undertaking the sub-analysis resulted in a loss of power. In contrast, when analyses were restricted to the studies that did not utilise guidelines (Honkoop 2014; Powell 2011; Syk 2013), the difference in exacerbation rates between the FeNO and control groups remained significant.

Hashimoto 2011 included participants with severe asthma who had received long courses of oral corticosteroids (daily up to 46 median months) and who were on high doses of ICS. Including this study, which involved the most severe type of patients with asthma, in the meta-analyses would have made some of the outcomes difficult to interpret, as it was designed to taper oral steroids, whereas the other six included studies were adjusting inhaled asthma medications. One study examined pregnant women (Powell 2011); as it is unknown how FeNO levels are affected during pregnancy, extrapolation of this review to pregnancy is limited. Furthermore, less than 50% of women in this study were on ICS at baseline. As the participants in the rest of the studies were on ICS, results of this review should not be extrapolated to adults with asthma who do not require daily ICS to control their symptoms.

One study used cluster randomisation with three treatment strategies (Honkoop 2014), therefore not all data could be included in the meta-analyses, as the raw data did not allow for the clustering and inclusion of this data could have resulted in a unit-of-analysis error.

The study setting also varied among the seven studies, with five studies undertaken in primary care and two hospital-based. All of the studies were undertaken in the last 11 years in affluent countries: two in the Netherlands (Hashimoto 2011; Honkoop 2014), one in Sweden (Syk 2013), one in the US (Calhoun 2012), one in Australia (Powell 2011), one in the UK (Shaw 2007), and one in New Zealand (Smith 2005). Given the absence of data from low- and middle-income countries, the findings of our review have limited applicability in resource-poor settings.

Furthermore, as ethnicity likely influences FeNO levels in otherwise healthy people (ATS FeNO 2005), the FeNO cutoff values used to adjust the medications may be race or ethnicity dependent. Some of the included studies were over 10 years old, and substantial research has been undertaken and published in the past decade. Recently, Harnan et al conducted a systematic review and economic evaluation for the National Institute for Health and Care Excellence (NICE) to assess the diagnostic accuracy, clinical effectiveness, and cost-effectiveness of three hand-held FeNO analysers (Harnan 2015). The review, which included 27 studies,

concluded that FeNO-guided management has the potential to be cost-effective. However, the evidence for using FeNO for diagnosis and management was deemed inconclusive (Harnan 2015). Lastly, asthma is a heterogenous condition, and there is increasing appreciation of non-eosonophilic asthma and overlap syndromes (with COPD) (Karampitsakos 2016). As FeNO levels reflect lower airway eosinophilia in steroid-naive people, the data from this review is unlikely to be applicable to those with non-eosonophilic asthma, smokers, overlap syndromes, and/or exacerbations that are non-eosonophilic asthma.

Quality of the evidence

We summarised the evidence for the three main outcomes related to exacerbations and ICS dose in the 'Summary of findings' table. Overall, we judged the quality of evidence to be very low to moderate. Three studies were non-blinded (Hashimoto 2011; Honkoop 2014; Syk 2013), which reduced our confidence in the accuracy in these reported studies. The sensitivity analysis without these studies indicated that the results from the blinded studies still showed a reduction in the risk of exacerbations, but in view of the different FeNO cutoffs used between the studies for adjustment of maintenance treatment and the shortage of evidence from trials that compared FeNO to guideline-adjusted treatment, we downgraded the evidence in GRADE, as displayed in Summary of findings for the main comparison.

The quality of evidence for the outcome of ICS dose at final visit was very low. This could be due to variation in the ICS doses, with one study having particularly high doses (360 to 1282 mcg in the control groups and 423 to 740 mcg in the FeNO groups). There was substantial statistical heterogeneity in the analysis (I^2 = 82%; P = 0.0007). We therefore downgraded this outcome by one for heterogeneity and one for imprecision.

Potential biases in the review process

We are unaware of any biases in the review process. We used a comprehensive search strategy and adhered to the protocol. Two review authors (HP, KK) independently assessed the risk of bias. We contacted the corresponding authors of all the studies for raw data to include in the meta-analysis. KK and the review editor (Christopher Cates) independently checked the data extraction,

'Risk of bias' assessment, and downgrading decisions for the 'Summary of findings' table in order to minimise the risk of bias in the review process.

The inclusion of Hashimoto 2011 in the meta-analyses would have introduced bias, as the strategy used was a complex intervention of which FeNO was only one part, however this study contributed only to the meta-analysis of the final FeNO level (Analysis 1.6).

Agreements and disagreements with other studies or reviews

This review updated a previous Cochrane review that included paediatric and adult studies (Petsky 2009). We decided to separate the reviews based on population ages and the increased clinical trials on the subject. The original review included two adult studies and four paediatric studies involving a total of 1010 participants who completed the trials (Petsky 2009). This adult-only review includes seven studies involving a total 1546 participants who completed the trials. A separate paediatric review includes nine studies with a total of 1390 children who completed the trials. The paediatric Cochrane review has yet to be completed to compare the results with this Cochrane review involving adults (Petsky 2015b). The results of Petsky 2009 differed from this current review, showing no difference between the groups for the primary outcome of exacerbations. Both adult papers included in the original review, Shaw 2007 and Smith 2005, reported that their FeNO group experienced fewer exacerbations than the clinical-symptoms group, but the differences were not significant. When the data were combined, the number of participants who had one or more exacerbations over the study period did not differ (P = 0.76) between the FeNO group and the clinical-symptoms group (pooled OR 0.85, 95% CI 0.30 to 2.43). However, the combined data from five studies in this review showed that the number of participants experiencing an exacerbation was significantly lower (P = 0.003) in the FeNO group compared to the control (clinical-symptoms) group over the study period; pooled OR (fixed-effect model) was 0.60 (95% CI 0.43 to 0.84) (Honkoop 2014; Powell 2011; Shaw 2007; Smith 2005; Syk 2013). There was no heterogeneity among the studies (I^2 = 13%). In the control group, 149 out of 529 participants had at least one exacerbation over the study period, compared to 116 out of 539 for the FeNO group. The NNTB over 52 weeks was 12 (95% CI 8 to 32) (Figure 3).

Figure 3. In the control group, 25 people out of 100 had exacerbations over 52 weeks, compared to 17 (95% CI 13 to 22) out of 100 for the active treatment group. NNTB 12 (95% CI 8 to 32).
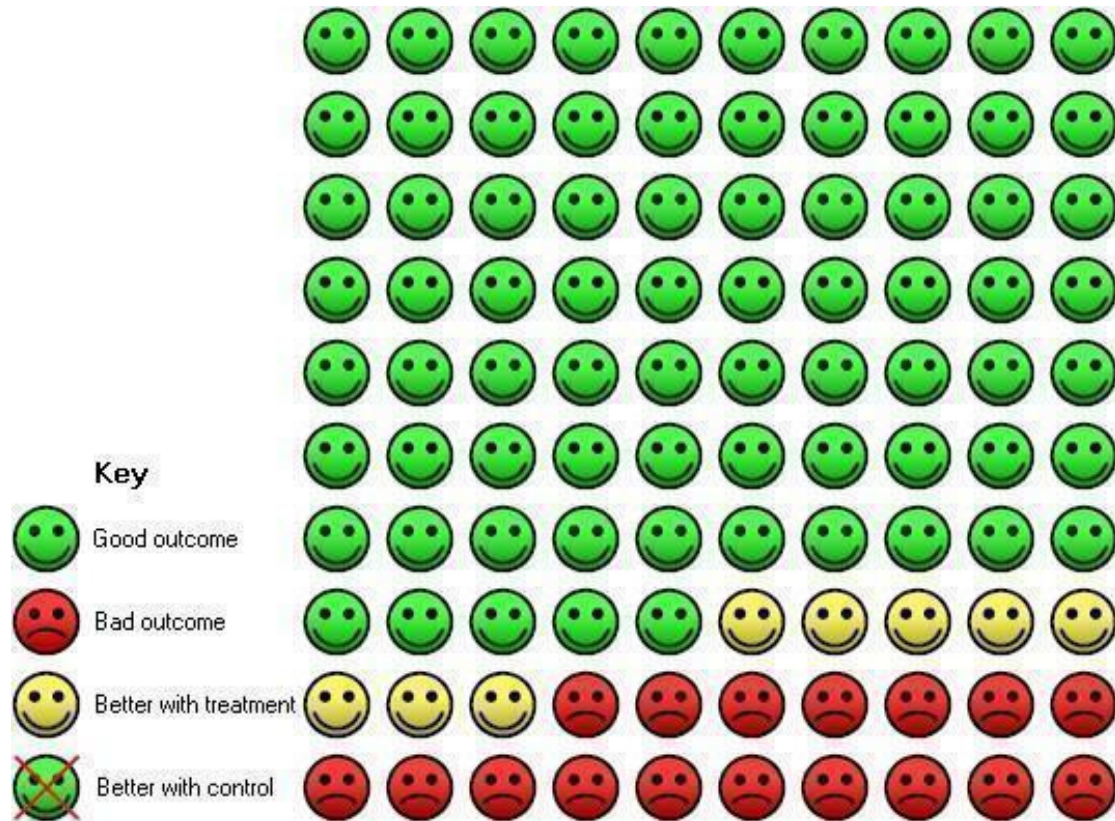
ICS dose at final visit favoured the FeNO group in the original Cochrane review (MD -450.03, 95% CI -676.73 to -222.34; P < 0.0001) (Petsky 2009). The original review combined the data from 98 participants allocated to the FeNO group. In this current review, the combined data for the outcome of ICS dose at final visit included 296 participants and did not favour either group (MD -17.01, 95% CI -101.75 to 67.72; P = 0.69).

Essat et al published a systematic review on the utility of FeNO for adjusting asthma medications. The Essat 2016 review included only six of the seven studies included in our Cochrane review. The Essat 2016 paper also acknowledged the heterogeneity among the studies and called for further research. In contrast to our findings on the lack of difference between groups for ICS dose at final visit, the Essat 2016 paper found a significant difference between groups. In this Cochrane review, we used a standardised dose (that is budesonide equivalent), but this conversion was not undertaken in Essat 2016.

The Essat 2016 paper found a decrease in the FeNO group for the outcome of 'all exacerbation and treatment failure rates' with the inclusion of three studies (RR 0.53, 95% CI 0.46 to 0.61,

P < 0.00001); our Cochrane review found similar results for this outcome involving five studies (Analysis 1.1).

Another published systematic review, Lu 2015, was based on children only and hence not comparable to our review, which evaluated adults only. Likewise, Gomersal et al reported a systematic review in children but did not undertake a meta-analysis comparing FeNO-guided management with any other monitoring strategy for children with asthma (Gomersal 2016). We will consider both these papers, Essat 2016 and Gomersal 2016, in the Cochrane review on children (Petsky 2015b).

No guidelines currently recommend the routine use of FeNO in monitoring asthma. However, NICE guidelines are currently focusing on the impact and feasibility of implementing FeNO in a diagnosis algorithm.

A U T H O R S ' C O N C L U S I O N S

Implications for practice

This review has demonstrated that tailoring asthma medications based on exhaled nitric oxide (FeNO) levels significantly reduce exacerbation numbers and rates, but found no significant difference between groups in hospitalisations or rescue oral corticosteroids courses. There were also no significant differences between groups for any of our secondary outcomes: FEV_1, ICS dosage, FeNO levels, or symptoms scores. Additionally, none of the studies reported a cost analysis. The use of FeNO to help guide therapy in adults with asthma cannot thus be universally advocated, but may be useful in some subpopulations. As the main benefit shown in the studies in this review was a reduction in asthma exacerbations, the intervention may be most useful in adults who have frequent exacerbations.

Implications for research

Further double-blind, parallel-group RCTs are required. Studies should also take into account various cutoffs for FeNO levels and other significant influences on FeNO levels such as atopy, sex, and ethnicity. A one-size-fits-all approach in relation to FeNO levels may not be providing a clear picture. The effects of tailoring asthma medications based on different levels of severity should also be examined. Cost analyses and adverse events of inhaled and oral corticosteroids would also provide additional important information.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Calhoun 2012

Methods	Randomised, parallel, 3-group, placebo-controlled, double-blinded multicentred trial comparing 3 strategies to adjust inhaled corticosteroids in adults with mild to moderate asthma. The 3 strategies were: a strategy based on National Heart, Lung, and Blood Institute guidelines (PABA group), measurement of exhaled nitric oxide (BBA), or occurrence of symptoms prompting rescue use of albuterol (SBA group)
Participants	363 participants were enrolled with 342 randomised. PABA group N = 114; mean age 34 (SD 12), 42 male, 72 female. BBA group N = 115; mean age 35 (SD 11), 33 male, 82 female. SBA group N = 113; mean age 36 (SD 12), 30 male, 83 female. Participants were recruited with a concurrent Asthma Clinical Research Network trial, but it was unclear as to where study visits occurred Inclusion criteria: Physician diagnosis of asthma and either reversible airflow limitation ($\geq$ 12% improvement in FEV_1 after 360 ug albuterol) or airway hyper-responsiveness (provocative concentration of methacholine (< 8 mg/mL) causing a 20% drop in FEV1)
Interventions	The adults with mild to moderate asthma on inhaled corticosteroids had their medications adjusted using 1 of 3 strategies: • PABA group: a strategy based on National Heart, Lung, and Blood Institute guidelines • BBA group: measurement of exhaled nitric oxide • SBA group: occurrence of symptoms prompting rescue use of albuterol
Outcomes	Primary outcome: Time to first treatment failure, a clinically important worsening of asthma Secondary outcomes: Spirometry, albuterol reversibility, methacholine responsiveness, sputum eosinophils, daytime and nighttime symptom and rescue beta-agonist diaries, ACT, Asthma Symptom Utility Index, and AQLQ
Notes	The control group used for the analysis was the PABA group, which utilised guidelines Funding: The study was conducted with the support of the Institute for Translational Sciences at the University of Texas Medical Branch, supported in part by a Clinical and Translational Science Award from the National Center for Advancing Translational Sciences, National Institutes of Health and by National Institutes of Health Grants awarded by the National Heart, Lung, and Blood Institute. Teva Pharmaceuticals provided the study drug and matching placebo. The National Heart, Lung, and Blood Institute had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement

Calhoun 2012 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No description of how sequence was generated. Protocol from Asthma Clinical Research Network also had no details of sequence generation
Allocation concealment (selection bias)	Unclear risk	Concealment not described in the publication. Protocol states that "the module set up by DCC" will be used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study states multiblinded study and puffers labelled A, B, C. However, it is unclear if the puffers could be recognised by participants or physicians or both, i.e. whether they identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	As for blinding of participants, this is also unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary outcome was time to treatment failure (asthma exacerbation) and secondary outcomes reported
Selective reporting (reporting bias)	High risk	Some secondary outcomes are reported incorrectly, with label not correlating with the results published
Other bias	Unclear risk	Days from school lost was reported, but unsure of age used in the inclusion criteria. The mean ages of the groups ranged from 34.2 to 36 years old

Hashimoto 2011

Methods	Randomised, parallel, multicentred trial comparing 2 oral corticosteroid tapering strategies. The 2 strategies were: internet-based monitoring system (internet strategy) or conventional treatment based on GINA guidelines (conventional strategy)
Participants	150 people were assessed for eligibility, 95 participants were randomised. 89 participants were included in the ITT analysis Internet strategy N = 51, mean age 48.5 (SD 12.5), 23 male, 28 female Conventional strategy N = 38, mean age 52.4 (SD 11.7), 18 male, 20 female All participants were outpatients from 2 tertiary academic hospitals or 4 large community hospitals in the Netherlands Inclusion criteria: Aged 18 to 75 years, diagnosis of severe refractory asthma as per ATS minor and major criteria. Their asthma needed to be uncontrolled and being assessed by a respiratory physician for at least 1 year, currently on oral corticosteroids, high doses of ICS and long-acting bronchodilators

Hashimoto 2011 *(Continued)*

	Exclusion criteria: Smokers or non-smokers with history of > 15 pack-years. No internet or mobile telephone
Interventions	Monthly visits for 6 months with usual respiratory physician. Daily, participants registered their dose of oral corticosteroids, lung function, and FeNO before taking their medications. Weekly, they completed the ACT. AQLQ completed at baseline and 3 monthly after this. Participants also registered every asthma event such as hospital visit, deterioration in symptoms, and antibiotic use Internet strategy: Had steroid dose adjusted based on the 3 components: electronic diary, in-built algorithm (which includes FeNO levels), and monitoring support, e.g. coaching by study nurse and monitoring data, which was entered Conventional strategy: Their oral steroids down-titrated by the respiratory physician at their monthly visit. The physicians treated the participants based on GINA guidelines for patients with severe asthma
Outcomes	Primary outcomes: Cumulative sparing of oral corticosteroids (actual cumulative dose minus the expected cumulative dose), ACT, and AQLQ Secondary outcomes: Global satisfaction scale, FEV_1, number of exacerbations, and days of hospitalisation
Notes	No information provided on how successful the daily monitoring was and how compliant participants were with daily tasks Funding: This study was funded by the Netherlands Organisation for Health Research and Development (ZonMw). Equipment for the analysis of nitric oxide was provided by Aerocrine AB. The funding sources had no role in the study design, data collection, analysis or interpretation, or in the decision to submit this article for publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	'Unblinded after randomisation'; implies it was concealed, but no details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Non blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Non blinded therefore high risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data reported
Selective reporting (reporting bias)	Low risk	All data reported

Hashimoto 2011 *(Continued)*

Other bias	Unclear risk	Nil information provided in the published article regarding success in obtaining FeNO on each visit

Honkoop 2014

Methods	3-armed cluster randomised trial comparing 3 strategies aiming at either partially controlled asthma (PCa), controlled asthma (Ca), or FeNO-driven controlled asthma (FCa) . Cluster randomisation was performed at the general-practice level to prevent intervention contamination within practices. Participants visited the practice every 3 months for 1 year and had their current medication assessed, asthma control assessed using ACT, lung function and FeNO performed in the FCa group only There was no blinding. There were 31 dropouts prior to any interventions: 12 in PCa group, 6 in Ca group, and 13 in FCa group. In addition to these dropouts, 5 participants attended only once
Participants	3662 adults were assessed for eligibility, 647 of which were randomised PCa group N = 219; mean age 39 (SD 9), 150 female, 69 males. Ca group N = 203; mean age 40 (SD 10), 134 female, 69 males. FCa group N = 189; mean age 39 (SD 9), 137 female, 62 males. All participants were attending general practices in the regions of Amsterdam, Leiden, and Nijmegen in the Netherlands Inclusion criteria: Aged 18 to 50 years, doctor-diagnosed asthma according to Dutch national guidelines, prescribed ICS for at least 3 months in the previous 12 months, and asthma being managed in primary care Exclusion criteria: Significant comorbidity (at the doctor's discretion), inability to understand Dutch, and a prescription for oral corticosteroids in the previous month
Interventions	At each visit the participant's asthma control was assessed based on the ACT score as controlled (≤ 0.75), partly controlled (0.75 to 1.5), or uncontrolled (> 1.5). Additionally, participants in the FCa group were categorised based on FeNO levels as: low/absence of airway inflammation ≤ 25 ppb, intermediate 26 to 50 ppb, and high/presence of airway inflammation > 50 ppb. Treatment decisions were based on an algorithm for each strategy, with an online decision support tool for implementing the strategy
Outcomes	Primary outcome: societal costs per quality-adjusted life year (QALY) gained Secondary outcomes: asthma control, asthma-related quality of life, number of days with asthma-related limitations of activity, medication adherence, severe exacerbation rate, lung function, FeNO value, and total medication use
Notes	Control group used for analysis in this review was the controlled asthma (Ca) group Funding: This study was supported by the Netherlands Organisation for Health Research and Development and by the Netherlands Asthma Foundation. Aerocrine (Solna, Sweden) provided 20 of a total of 40 fraction of exhaled nitric oxide meters for free

Risk of bias

Honkoop 2014 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent researcher randomly allocated the general practice to 1 of the 3 treatment strategies. Stratified according to region, urbanisation grade (rural versus urban), and practice nurse's level of experience with asthma management (> 1 year or < 1 year)
Allocation concealment (selection bias)	Unclear risk	Authors stated that "allocation was applied to both the cluster and participant levels". However, it is unclear in the published article how this was achieved
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data reported and analysed as ITT
Selective reporting (reporting bias)	Low risk	All data presented and analysed as ITT
Other bias	Unclear risk	Nil information provided in the published article regarding success in obtaining FeNO on each visit

Powell 2011

Methods	Randomised, parallel, double-blind controlled trial of FeNO-guided therapy in 2 antenatal clinics. Expectant mothers were randomised to a FeNO-guided algorithm for adjusting asthma therapy or a clinical-guideline algorithm. The randomisation was stratified by maintenance budesonide dose (< 800 ug per day or > 800 ug per day) The participant, research assistant, and investigators were blinded to the randomisation group There were 17 dropouts, 11 in the FeNO group and 6 in the control group The women were reviewed monthly until delivery
Participants	242 women were recruited, of which 220 were randomised. FeNO group N = 111; mean age 28 (range 27 to 29). Control group N = 109; mean age 29 (range 28 to 30). Attending antenatal clinics at 2 hospitals in New South Wales, Australia Inclusion: Non-smoking pregnant women (aged > 18 years) with asthma using inhaled

Powell 2011 *(Continued)*

	therapy and attending the clinic. They were recruited at between 12 and 20 weeks' gestation
Interventions	The women were seen monthly until they delivered. Clinical-symptom data, ACT score, present treatment, FeNO, and FEV_1 were collected at each visit. ACT score, FeNO levels, and current treatment were sent to the algorithm keeper via facsimile for treatment recommendations FeNO group: Sequential process, first FeNO concentrations used to adjust ICS dose, and second ACT score used to adjust the LABA dose Clinical group: Based on asthma control using Juniper ACT with cutoff points defined as: well-controlled asthma (ACT < 0.75), partially controlled asthma (0.75 to 1.50), and uncontrolled asthma (> 1.5)
Outcomes	Primary outcome: Total number of asthma exacerbations (i.e. moderate and severe) Secondary outcomes: QoL, asthma treatment, and fetal outcomes
Notes	Funding: This study was funded by the National Health and Medical Research Council of Australia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was completed in blocks of 4 with an equal treatment allocation ratio
Allocation concealment (selection bias)	Low risk	A statistician used computer-generated random number list for randomisation and stratified by maintenance budesonide dose at visit two (< 800 ug per day or ≥ 800 ug per day)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind. The use of an algorithm keeper was not masked but was not directly involved in the care or assessment of the participant
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment of asthma control was made by investigators who were blinded to the participant's randomisation group. The algorithm keeper received the ACT score, FeNO level and current treatment via facsimile and applied the appropriate algorithm and sent the treatment recommendation to the research assistant who informed the participant
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data presented

Powell 2011 *(Continued)*

Selective reporting (reporting bias)	Low risk	All data presented
Other bias	Unclear risk	Nil information provided in the published article regarding success in obtaining FeNO on each visit

Shaw 2007

Methods	Randomised, single-blind controlled trial comparing exacerbation frequency and corticosteroid dosage in people 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 participants were blinded to which group they were randomised to. At completion, the participants were asked to record which randomisation group they thought they had been assigned to There were 15 dropouts, 6 in FeNO group and 9 in control group The study ran for 12 months, and the participants 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 to 75), 27 males, 31 females Control group N = 60; median age 52 (range 24 to 81), 27 males, 33 females Attending a general practice in Leicester, UK. Inclusion: > 18 years old, diagnosis of asthma and at least 1 prescription for anti-asthma medication in the past 12 months Exclusion: Current smokers, past smoking history of > 10 pack-years, or physician determines that they are poorly compliant
Interventions	Participants were seen at baseline, 2 weeks, month: 1, 2, 3, 4, 6, 8, 10, and 12 FEV_1, FeNO, and Juniper asthma control score (JACS) were undertaken at each visit. Methacholine challenge for 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: When FeNO > 26 ppb, ICS was increased. If < 16 ppb, or < 26 ppb on 2 separate occasions, treatment was decreased
Outcomes	Primary outcome: Number of exacerbations. Secondary outcome: Total ICS dose
Notes	Funding: This study was supported by a grant from Asthma UK

Risk of bias

Bias	Authors' judgement	Support for judgement

Shaw 2007 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Insufficient information provided in published article
Allocation concealment (selection bias)	Low risk	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 of participants and personnel (performance bias) All outcomes	Low risk	Single blind. Participants were assessed at completion of study regarding the group they thought they were assigned to, 49% were unsure of which group they were assigned. 33% correctly identified their group, and 18% incorrectly identified their group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment of asthma control was made by investigators who were blinded to the participant's randomisation group. A separate unblinded physician communicated to the patient the correct treatment decision
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Low risk	Measurement of FeNO was successful on every occasion

Smith 2005

Methods	Randomised, placebo-controlled, single-blind study. This was a 2-phase study, with phase 1 varying in duration (3 to 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 Participants were blinded to which group they were assigned to In phase 1 there were 16 dropouts, 13 during run-in and 3 during follow-up. Phase 2 had 5 dropouts during the 12 months
Participants	97 participants were randomised from 110 participants recruited, mean age of 44.8 years (range 12 to 73) and 41 males, 69 females FeNO group N = 46 Control group N = 48 Inclusion criteria: Inhaled corticosteroids for 6 months with no dose change in previous 6 weeks

Smith 2005 (*Continued*)

	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 750 ug/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 < 15 ppb at 250 mL/sec Control group: Dose adjustment based on asthma symptoms, nighttime waking, bronchodilator use, variation in PEFR and FEV_1. 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 ICS
Notes	Funding: This study was funded by the Otago Medical Research Foundation, the Dean's Fund of the Dunedin School of Medicine, and a grant from the University of Otago. Supplies of fluticasone were provided by GlaxoSmithKline (New Zealand). Equipment for the analysis of nitric oxide in other studies was provided by Aerocrine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information of randomisation and sequence generation in published article
Allocation concealment (selection bias)	Unclear risk	Insufficient information of randomisation in published article
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single blind. All treatment orders were verified independently by an investigator who was blinded to treatment group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Single blind. All treatment orders were verified independently by an investigator who was blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data has been imputed using appropriate methods
Selective reporting (reporting bias)	Unclear risk	Insufficient information provided in published article

Smith 2005   *(Continued)*

Other bias	Unclear risk	Nil information provided in published article regarding success of measuring FeNO

Syk 2013

Methods	Multicentred, open-label, parallel RCT comparing a FeNO-guided strategy versus usual care to adjust anti-inflammatory treatment to improve asthma-related QoL and asthma symptoms whilst reducing asthma exacerbations in atopic participants with asthma in primary care
Participants	165 participants completed the study from 187 randomised. FeNO group N = 87, mean age 40.9 (SD 11.8), 48 males, 39 females Control group N = 78, mean age 41.1 (SD 12.9), 46 males, 32 females They attended 1 of 17 primary healthcare centres in 7 different autonomous healthcare regions in Sweden Inclusion criteria: aged 18 to 64 years, physician's diagnosis of asthma, prescribed ICS for > 6 months, confirmed IgE sensitisation to ≥ 1 major airborne perennial allergen (dog, cat, or mite) Exclusion criteria: pregnancy or breastfeeding, participation in another study, unstable asthma, smokers, solely on montelukast or in combination with budesonide equivalent dose 0 to 400 mcg
Interventions	Participants were seen at enrolment, baseline (2 to 4 weeks later), month 2, month 4, month 8, and month 12 (final visit) FeNO, ACT, and registration of exacerbations were undertaken at each visit. mAQLQ and GQLI were attended at baseline, month 4, and month 12 only FeNO group: Treatment was adjusted according to a FeNO algorithm and 6 fixed treatment steps Control group: Treatment was adjusted according to usual care including patient-reported symptoms, SABA use, physical examination, and lung functions results
Outcomes	Primary outcome: change in mAQLQ score during the study. Secondary outcome: changes in ACT score, exacerbation frequency, lung function, generic QoL score, and overall medication use
Notes	Funding: This study was funded by the Stockholm county council (PickUP), Centre for Allergy Research, Karolinska Institute, and the Research Foundation of the Swedish Asthma and Allergy Association. Support was also received from Aerocrine AB (NIOX MINO instruments), Phadia AB (ImmunoCAP Rapid), Meda AB (Buventol Easyhaler) , and MSD Sweden (small grant)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prepared by the study coordinator outside the primary health care centre. However,

Syk 2013 *(Continued)*

		unclear how sequence was generated
Allocation concealment (selection bias)	Low risk	Envelopes used in lottery randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label. FeNO analyser screen was covered for control group, therefore study staff member nor participant knew the result. However, the FeNO analyser screen was not covered in FeNO group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Regarding FeNO as the FeNO group was not blinded to FeNO results which could influence their symptom scores
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcome data reported
Selective reporting (reporting bias)	Low risk	The named outcomes were well reported in the paper and the study protocol was prospectively registered. Additional data were provided by study authors
Other bias	Unclear risk	One of the authors (Alving K) was an employee and stock holder of Aerocrine (manufacturer of FeNO analysers)

ACT: Asthma Control Test
AQLQ: Asthma Quality of Life Questionnaire
ATS: American Thoracic Society
BBA: biomarker-based adjustment
FeNO: fractional exhaled nitric oxide
FEV1: forced expiratory volume in 1 second
GINA: Global Initiative for Asthma
GQLI: Göteborg Quality of Life Instrument
ICS: inhaled corticosteroids
IgE: immunoglobulin E
ITT: intention-to-treat
LABA: long-acting beta-agonist
mAQLQ: mini-Asthma Quality of Life Questionnaire
QoL: quality of life
PABA: physician assessment-based adjustment
PEFR: peak expiratory flow rate
RCT: randomised controlled trial
SABA: short-acting beta-agonist
SBA: symptom-based adjustment
SD: standard deviation

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

Study	Reason for exclusion
Anderson 2012	Excluded as treatment not adjusted according to FeNO. Randomised, cross-over trial evaluating the dose response of ICS in people with asthma and elevated FeNO
de Jongste 2009	Excluded as study did not include adults but based instead in paediatric population. Included in paediatric systematic review by same authors
Fritsch 2006	Excluded as study did not include adults but based instead in paediatric population. Included in paediatric systematic review by same authors
Gelb 2006	Not a RCT, treatment not based on FeNO. Prospective study to assess FeNO and spirometry to predict asthma exacerbations
Griese 2000	Not a RCT, treatment not based on FeNO. Prospective study to assess FeNO in comparison to symptoms adjusted using clinical symptoms
Gruchalla 2009	Excluded as treatment not adjusted according to FeNO. Same dataset as paediatric included study (Szefler 2008)
Jatakanon 1999	Excluded as treatment not based on FeNO. Randomised into 2 double-blind, placebo-controlled studies (1 parallel study involving 3 groups receiving either budesonide 110 ug/day, budesonide 400 ug/day, or placebo; the second was a cross-over randomised study to receive budesonide 1600 ug or placebo)
Jones 2001	Non-RCT. Observational study to determine if FeNO is useful in diagnosing and predicting loss of asthma control. Participants had ICS withdrawn until loss of control or for a maximum of 6 weeks
Jones 2002	Excluded as treatment not based on FeNO. Double-blind, parallel-group, placebo-controlled trial of 50, 100, 200, or 500 ug budesonide per day
Kharitonov 1996	Non-RCT. Observational study of the effect of increasing and then reducing the dose of ICS on FeNO, lung function, and symptoms in people with asthma
Kharitonov 2002	Excluded as treatment not adjusted according to FeNO. Double-blind, placebo-controlled, parallel-group study of 100 or 400 ug budesonide or placebo in participants with mild asthma
Lim 1998	Excluded as treatment not adjusted according to FeNO. Randomised, longitudinal study monitoring the effect of increasing anti-inflammatory medication or to continue unchanged using conventional measures of lung function, symptom scores, medication usage, and peak expiratory flow rate variability
Malerba 2008	Excluded as non-randomised. Prospective observational study including 14 participants with asthma who had asthma treatment adjusted based on sputum eosinophil counts and FeNO
Peirsman 2014	Excluded as study did not include adults but based instead in paediatric population. Included in paediatric systematic review by same authors

Petsky 2015a	Excluded as study did not include adults but based instead in paediatric population. Included in paediatric systematic review by same authors
Pijnenburg 2005	Excluded as study did not include adults but based instead in paediatric population. Included in paediatric systematic review by same authors
Pike 2013	Excluded as study did not include adults but based instead in paediatric population. Included in paediatric systematic review by same authors
Powell 2015	Excluded as reporting results regarding rhinitis from participants in an included study (Powell 2011)
Szefler 2008	Excluded as study did not include adults but based instead in paediatric population. Included in paediatric systematic review by same authors
Verini 2010	Excluded as study did not include adults but based instead in paediatric population. Included in paediatric systematic review by same authors
Voorend-van Bergen 2013	Excluded as study did not include adults but based instead in paediatric population. Included in paediatric systematic review by same authors
Zacharasiewicz 2005	Non-RCT. Prospective and observation study in children using non-invasive measures (FeNO, induced sputum, and exhaled breath condensate) to monitor airway inflammation to result in optimal treatment

FeNO: fractional exhaled nitric oxide
ICS: inhaled corticosteroids
RCT: randomised controlled trial

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

Duong-Quy 2015

Trial name or title	Exhaled NO (FeNO) measurement used to determine asthma control, dose of inhaled corticosteroid and cost in a developing country
Methods	People with uncontrolled asthma with FeNO > 25 ppb were included in this study. They were classified into 3 groups according to the intervention used to determine therapy: group 1 (Gr1): used GINA guidelines, group 2 (Gr2): used GINA plus FeNO, and group 3 (Gr3): used only FeNO
Participants	Unknown
Interventions	Group 1 (Gr1): used GINA guidelines, Group 2 (Gr2): used GINA plus FeNO, and Group 3 (Gr3): used only FeNO
Outcomes	ICS dose, exacerbations, cost

Duong-Quy 2015   (*Continued*)

Starting date	Unknown
Contact information	Sy Duong-Quy <sduongquy.jfvp@gmail.com>
Notes	Prof Duong-Quy was contacted January 2016, when he stated that the article will be submitted in the near future

FeNO: fractional exhaled nitric oxide
GINA: Global Initiative for Asthma
ICS: inhaled corticosteroids

DATA AND ANALYSES

Comparison 1.   Asthma treatment tailored on FeNO versus clinical symptoms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who had ≥ 1 exacerbations over study period	5	1005	Odds Ratio (Fixed, 95% CI)	0.60 [0.43, 0.84]
2 Number of exacerbations per 52 weeks (exacerbation rates)	5	842	Rate Ratio (Fixed, 95% CI)	0.59 [0.45, 0.77]
3 Severe exacerbations requiring oral corticosteroids	3	495	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.50, 1.48]
4 Severe exacerbations requiring hospitalisation	3	488	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.67]
5 FEV$_1$% pred at final visit	4	802	Mean Difference (Fixed, 95% CI)	0.11 [-1.15, 1.37]
6 FeNO level at final visit	5	668	Std. Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.16, 0.15]
7 Symptom score as per Asthma Control Test	4	707	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.18, 0.01]
8 Symptom score as per AQLQ	2		Mean Difference (Fixed, 95% CI)	0.00 [-0.10, 0.10]
9 ICS dose at final visit (microgram per day)	4	582	Mean Difference (IV, Random, 95% CI)	-147.15 [-380.85, 86.56]
10 Subgroup (control guideline use): Number of participants who had ≥ 1 exacerbations over study period	5		Odds Ratio (Fixed, 95% CI)	0.60 [0.43, 0.84]
10.1 Guideline control	2		Odds Ratio (Fixed, 95% CI)	0.87 [0.47, 1.61]
10.2 Other control	3		Odds Ratio (Fixed, 95% CI)	0.51 [0.34, 0.76]
11 Subgroup (control guideline use): Number of exacerbations per 52 weeks (exacerbation rates)	5		Rate Ratio (Fixed, 95% CI)	0.59 [0.45, 0.77]
11.1 Guideline control	3		Rate Ratio (Fixed, 95% CI)	0.76 [0.48, 1.19]
11.2 Other control	2		Rate Ratio (Fixed, 95% CI)	0.51 [0.37, 0.71]

Analysis 1.1. Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 1 Number of participants who had ≥ 1 exacerbations over study period.

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

Outcome: 1 Number of participants who had ≥ 1 exacerbations over study period

Study or subgroup	FeNO strategy N	Control strategy N	log [Odds Ratio] (SE)	Odds Ratio IV,Fixed,95% CI	Weight	Odds Ratio IV,Fixed,95% CI
Honkoop 2014	189	203	-0.4463 (0.4546)		14.3 %	0.64 [0.26, 1.56]
Powell 2011	111	109	-0.7344 (0.2926)		34.4 %	0.48 [0.27, 0.85]
Shaw 2007	58	60	-0.5746 (0.4267)		16.2 %	0.56 [0.24, 1.30]
Smith 2005	46	48	0.3863 (0.4697)		13.4 %	1.47 [0.59, 3.69]
Syk 2013	93	88	-0.7244 (0.3679)		21.8 %	0.48 [0.24, 1.00]
Total (95% CI)	**497**	**508**			**100.0 %**	**0.60 [0.43, 0.84]**

Heterogeneity: Chi² = 4.61, df = 4 (P = 0.33); I² =13%

Test for overall effect: Z = 3.00 (P = 0.0027)

Test for subgroup differences: Not applicable

```
       0.01    0.1     1     10    100
   Favours FeNO strategy    Favours control strategy
```
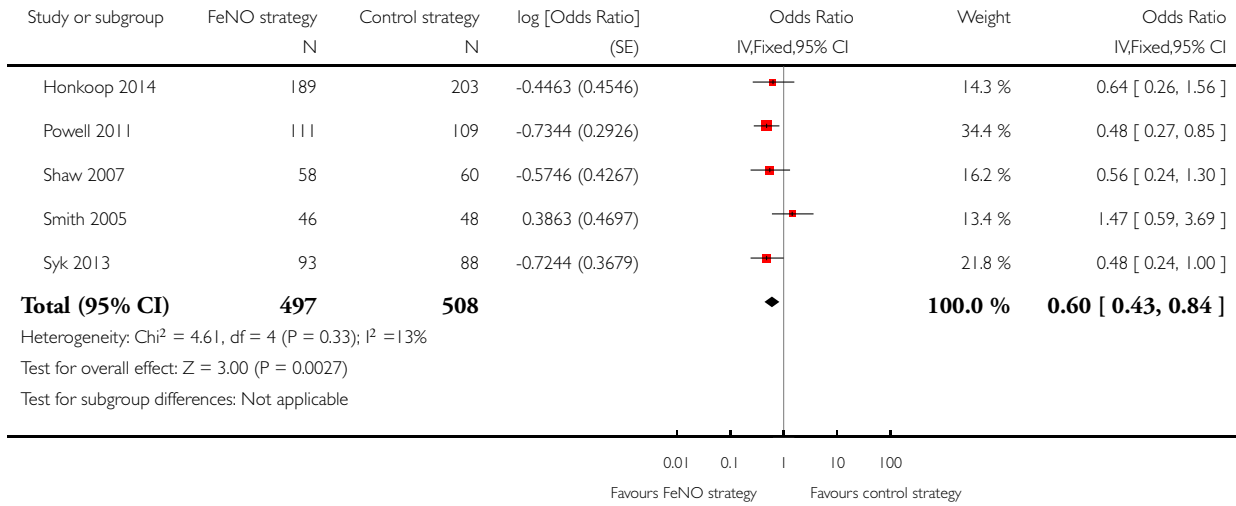
Analysis 1.2. Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 2 Number of exacerbations per 52 weeks (exacerbation rates).

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

Outcome: 2 Number of exacerbations per 52 weeks (exacerbation rates)

Study or subgroup	FeNO strategy N	Control strategy N	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
Calhoun 2012 (1)	115	114	-0.1054 (0.4718)		8.4 %	0.90 [0.36, 2.27]
Powell 2011	111	109	-0.7012 (0.2157)		40.1 %	0.50 [0.32, 0.76]
Shaw 2007	58	60	-0.2357 (0.3028)		20.3 %	0.79 [0.44, 1.43]
Smith 2005	48	46	-0.6088 (0.5326)		6.6 %	0.54 [0.19, 1.55]
Syk 2013 (2)	93	88	-0.6218 (0.2754)		24.6 %	0.54 [0.31, 0.92]
Total (95% CI)	**425**	**417**			**100.0 %**	**0.59 [0.45, 0.77]**

Heterogeneity: Chi² = 2.52, df = 4 (P = 0.64); I² =0.0%

Test for overall effect: Z = 3.89 (P = 0.00010)

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10

Favours FeNO strategy   Favours control strategy
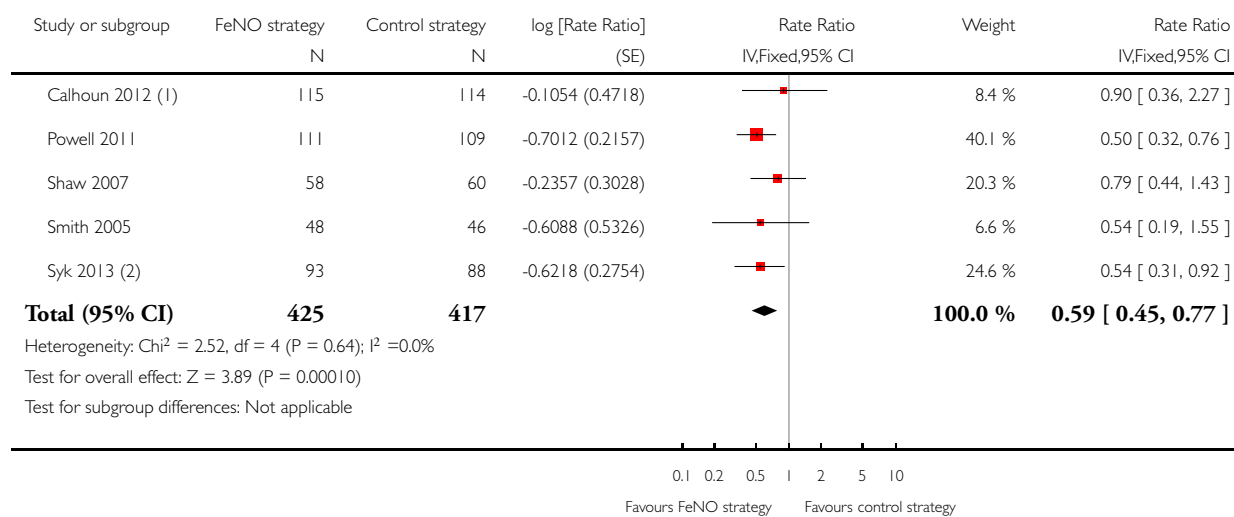
(1) Reported as a Hazard ratio in the paper but appears to be a rate ratio (FeNO v Physician based assessment)

(2) Estimated from raw rates in Table V and P value from Poisson regression model

Analysis 1.3. Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 3 Severe exacerbations requiring oral corticosteroids.

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

Outcome: 3 Severe exacerbations requiring oral corticosteroids

Study or subgroup	FeNO strategy	Control strategy	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
	n/N	n/N			
Powell 2011	9/111	13/109		37.3 %	0.65 [0.27, 1.59]
Smith 2005	13/46	15/48		38.1 %	0.87 [0.36, 2.10]
Syk 2013	8/93	6/88		24.6 %	1.29 [0.43, 3.87]
Total (95% CI)	**250**	**245**		**100.0 %**	**0.86 [0.50, 1.48]**

Total events: 30 (FeNO strategy), 34 (Control strategy)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.88, df = 2 (P = 0.64); I^2 =0.0%

Test for overall effect: Z = 0.55 (P = 0.58)

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10

Favours FeNO strategy   Favours Control strategy
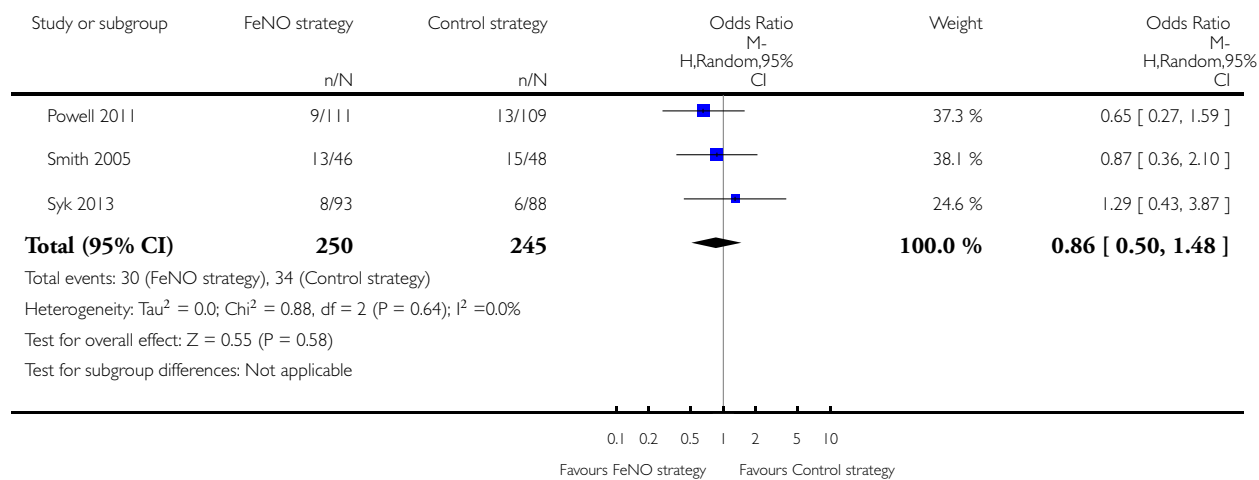
Analysis 1.4.   Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 4 Severe exacerbations requiring hospitalisation.

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

Outcome: 4 Severe exacerbations requiring hospitalisation

Study or subgroup	FeNO strategy	Control strategy	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Powell 2011	0/111	3/109		100.0 %	0.14 [0.01, 2.67]
Shaw 2007	0/52	0/51			Not estimable
Syk 2013	0/87	0/78			Not estimable
Total (95% CI)	**250**	**238**		**100.0 %**	**0.14 [0.01, 2.67]**

Total events: 0 (FeNO strategy), 3 (Control strategy)

Heterogeneity: not applicable

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Not applicable

0.001 0.01 0.1   1   10   100 1000

Favours FeNO strategy   Favours Control strategy
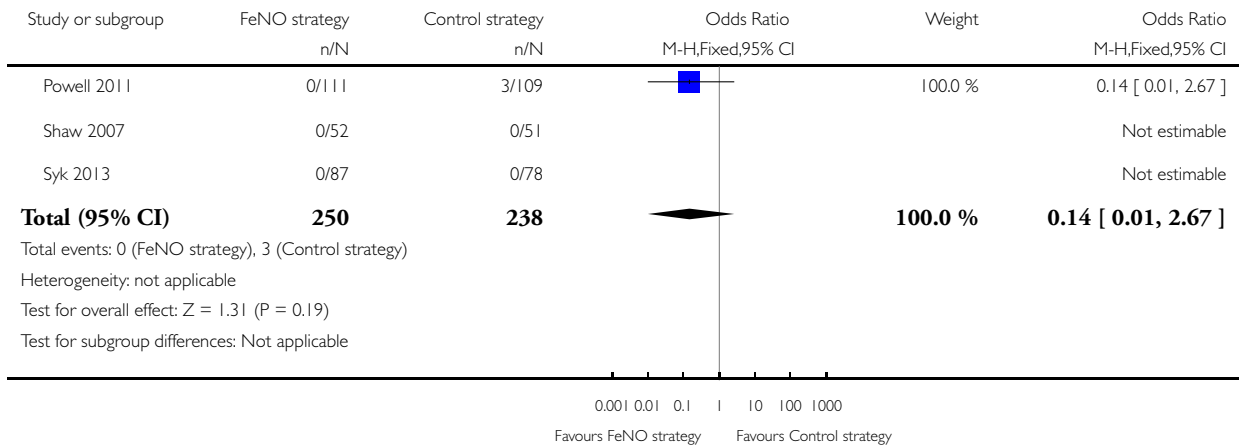
Analysis 1.5. Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 5 FEV1% pred at final visit.

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

Outcome: 5 FEV$_1$% pred at final visit

Study or subgroup	FeNO strategy	Control strategy	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
	N	N				
Honkoop 2014	189	203	0.04 (0.7347)		76.3 %	0.04 [-1.40, 1.48]
Powell 2011	73	78	0.19 (1.902)		11.4 %	0.19 [-3.54, 3.92]
Smith 2005	46	48	3.8 (4.2329)		2.3 %	3.80 [-4.50, 12.10]
Syk 2013	87	78	-0.3 (2.0265)		10.0 %	-0.30 [-4.27, 3.67]
Total (95% CI)	**395**	**407**			**100.0 %**	**0.11 [-1.15, 1.37]**

Heterogeneity: Chi^2 = 0.81, df = 3 (P = 0.85); I^2 =0.0%

Test for overall effect: Z = 0.17 (P = 0.86)

Test for subgroup differences: Not applicable

-10   -5   0   5   10

Favours FeNO strategy   Favours Control strategy
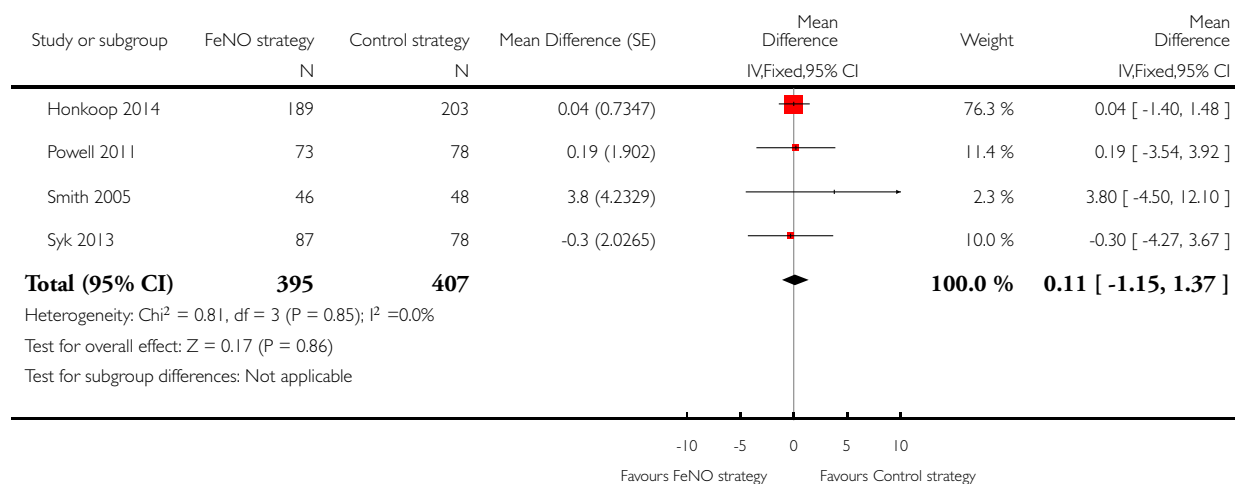
Analysis 1.6. Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 6 FeNO level at final visit.

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

Outcome: 6 FeNO level at final visit

Study or subgroup	FeNO strategy		Control strategy		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Hashimoto 2011	51	58 (50.72)	38	58 (49.8)		13.1 %	0.0 [-0.42, 0.42]
Powell 2011	110	18.62 (34.97)	107	17.44 (19.03)		32.7 %	0.04 [-0.22, 0.31]
Shaw 2007	52	24.5 (14.42)	51	27 (17.85)		15.5 %	-0.15 [-0.54, 0.23]
Smith 2005	46	8.6 (4.04)	48	7.6 (4.64)		14.0 %	0.23 [-0.18, 0.63]
Syk 2013	87	25 (14.5452)	78	27.1 (23.507)		24.7 %	-0.11 [-0.41, 0.20]
Total (95% CI)	**346**		**322**			**100.0 %**	**0.00 [-0.16, 0.15]**

Heterogeneity: Chi² = 2.38, df = 4 (P = 0.67); I² =0.0%

Test for overall effect: Z = 0.06 (P = 0.95)

Test for subgroup differences: Not applicable

```
        -1   -0.5    0    0.5    1
   Favours FeNO strategy    Favours Control strategy
```

Analysis 1.7. Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 7 Symptom score as per Asthma Control Test.

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

Outcome: 7 Symptom score as per Asthma Control Test

Study or subgroup	FeNO		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Calhoun 2012	115	0.68 (0.7335)	114	0.72 (0.7335)		27.0 %	-0.04 [-0.23, 0.15]
Powell 2011	111	0.5 (0.5)	109	0.6 (0.6)		45.6 %	-0.10 [-0.25, 0.05]
Shaw 2007	52	1.1 (0.72)	51	1.15 (0.71)		12.8 %	-0.05 [-0.33, 0.23]
Syk 2013	81	0.79 (0.814)	74	0.94 (0.8201)		14.7 %	-0.15 [-0.41, 0.11]
Total (95% CI)	**359**		**348**			**100.0 %**	**-0.08 [-0.18, 0.01]**

Heterogeneity: Chi^2 = 0.56, df = 3 (P = 0.91); I^2 =0.0%

Test for overall effect: Z = 1.68 (P = 0.092)

Test for subgroup differences: Not applicable

-1   -0.5   0   0.5   1

Favours FeNO strategy   Favours control strategy

Analysis 1.8. Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 8 Symptom score as per AQLQ.

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

Outcome: 8 Symptom score as per AQLQ

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Calhoun 2012	0 (0.1122)		20.3 %	0.0 [-0.22, 0.22]
Honkoop 2014	0.001 (0.0566)		79.7 %	0.00 [-0.11, 0.11]
Total (95% CI)			**100.0 %**	**0.00 [-0.10, 0.10]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² =0.0%

Test for overall effect: Z = 0.02 (P = 0.99)

Test for subgroup differences: Not applicable

```
        -1    -0.5    0    0.5    1
    Favours FeNO strategy    Favours Control strategy
```

Analysis 1.9. Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 9 ICS dose at final visit (microgram per day).

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

Outcome: 9 ICS dose at final visit (microgram per day)
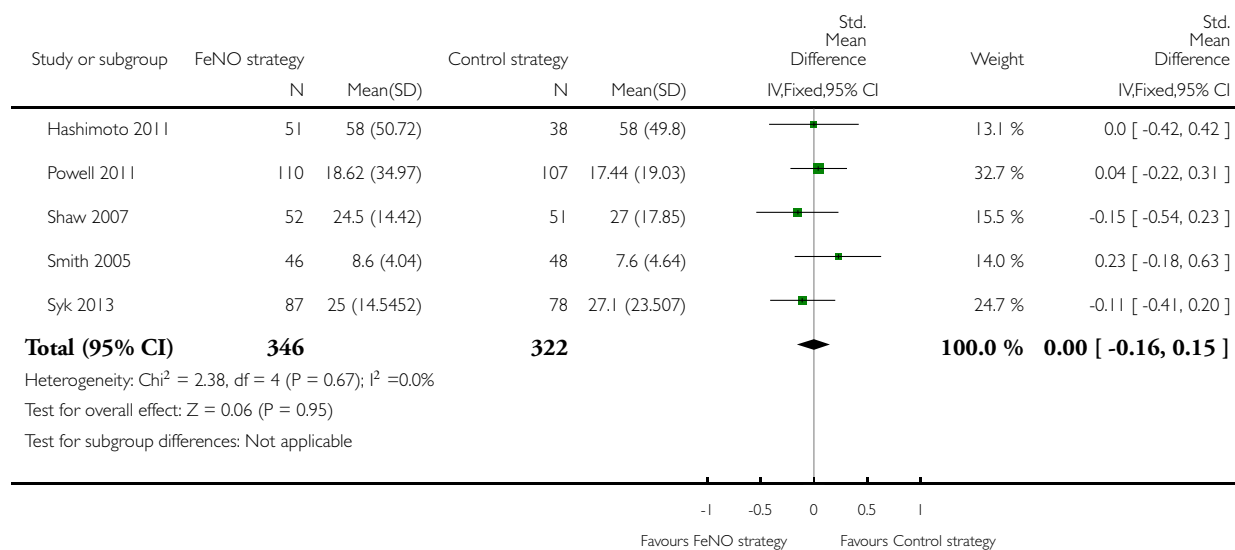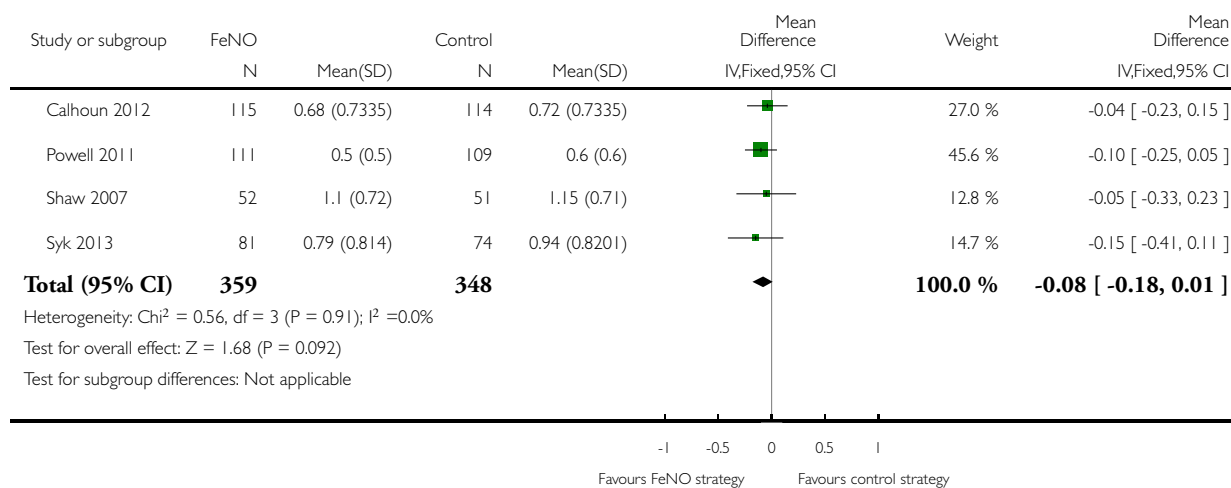
Study or subgroup	FeNO strategy N	Mean(SD)	Control strategy N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Powell 2011	111	423.42 (561.65)	109	359.63 (516.24)		29.3 %	63.79 [-78.72, 206.30]
Shaw 2007	52	557 (670.63)	51	895 (1035.51)		19.5 %	-338.00 [-675.63, -0.37]
Smith 2005	46	740 (720.63)	48	1282 (792.09)		21.0 %	-542.00 [-847.91, -236.09]
Syk 2013	87	586 (455.1236)	78	540 (319.3398)		30.3 %	46.00 [-73.03, 165.03]
Total (95% CI)	**296**		**286**			**100.0 %**	**-147.15 [-380.85, 86.56]**

Heterogeneity: Tau² = 43312.37; Chi² = 17.10, df = 3 (P = 0.00067); I² =82%

Test for overall effect: Z = 1.23 (P = 0.22)

Test for subgroup differences: Not applicable

```
        -500   -250    0    250    500
    Favours FeNO strategy    Favours control strategy
```

Analysis 1.10. Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 10 Subgroup (control guideline use): Number of participants who had ≥ 1 exacerbations over study period.

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

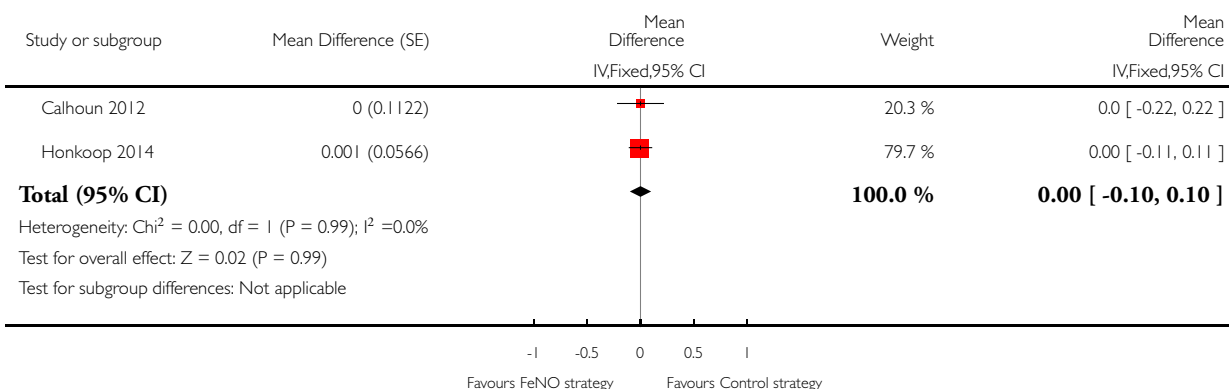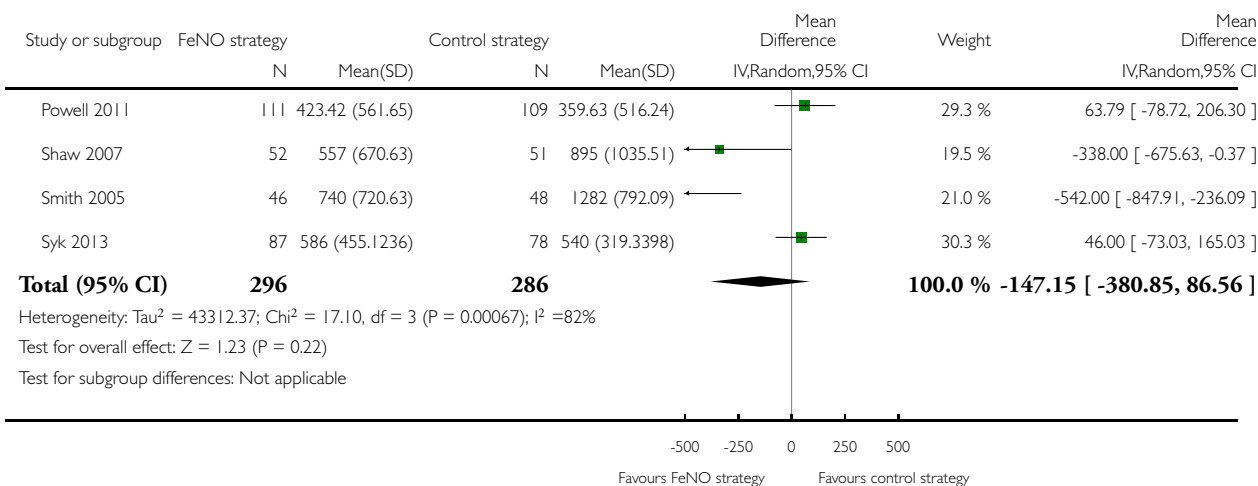Outcome: 10 Subgroup (control guideline use): Number of participants who had ≥ 1 exacerbations over study period

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Fixed,95% CI	Weight	Odds Ratio IV,Fixed,95% CI
1 Guideline control				
Shaw 2007	-0.5746 (0.4267)		16.2 %	0.56 [0.24, 1.30]
Smith 2005	0.3863 (0.4697)		13.4 %	1.47 [0.59, 3.69]
Subtotal (95% CI)			**29.5 %**	**0.87 [0.47, 1.61]**
Heterogeneity: Chi² = 2.29, df = 1 (P = 0.13); I² =56%				
Test for overall effect: Z = 0.44 (P = 0.66)				
2 Other control				
Honkoop 2014	-0.4463 (0.4546)		14.3 %	0.64 [0.26, 1.56]
Powell 2011	-0.7344 (0.2926)		34.4 %	0.48 [0.27, 0.85]
Syk 2013	-0.7244 (0.3679)		21.8 %	0.48 [0.24, 1.00]
Subtotal (95% CI)			**70.5 %**	**0.51 [0.34, 0.76]**
Heterogeneity: Chi² = 0.31, df = 2 (P = 0.86); I² =0.0%				
Test for overall effect: Z = 3.29 (P = 0.0010)				
Total (95% CI)			**100.0 %**	**0.60 [0.43, 0.84]**
Heterogeneity: Chi² = 4.61, df = 4 (P = 0.33); I² =13%				
Test for overall effect: Z = 3.00 (P = 0.0027)				
Test for subgroup differences: Chi² = 2.01, df = 1 (P = 0.16), I² =50%				

0.01 0.1 1 10 100
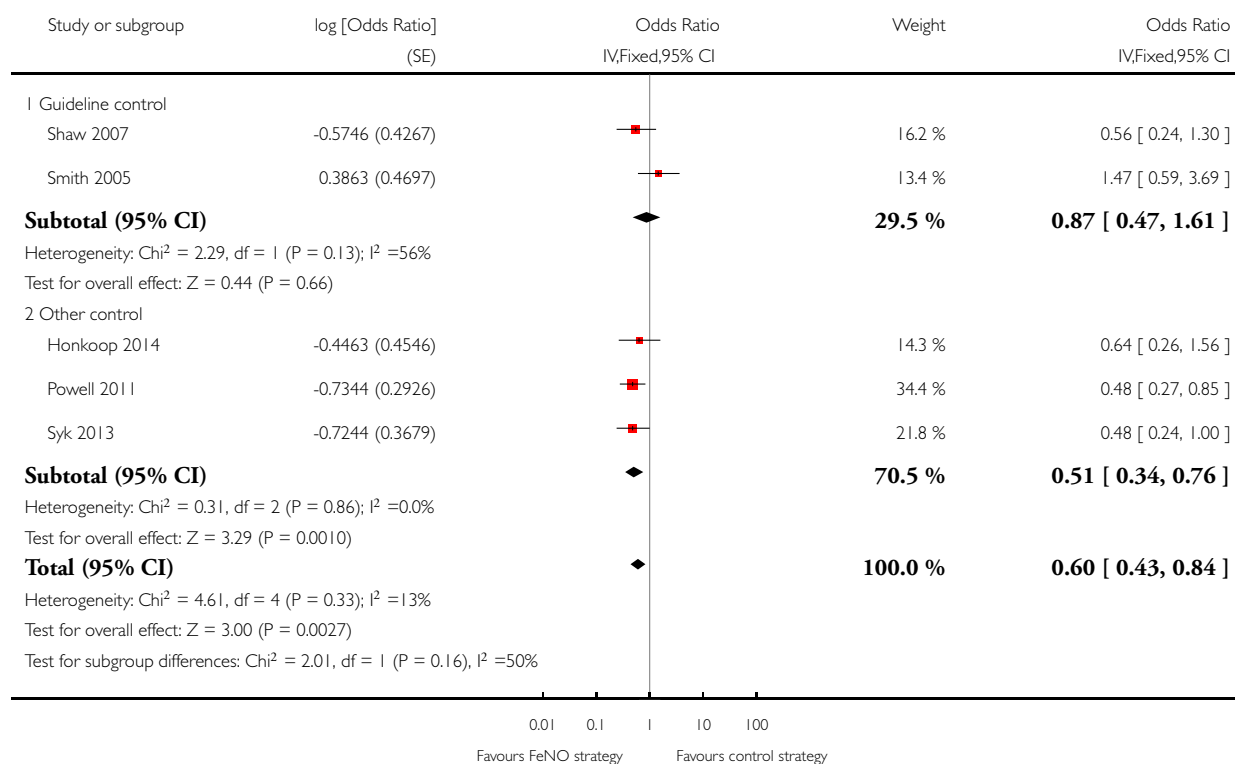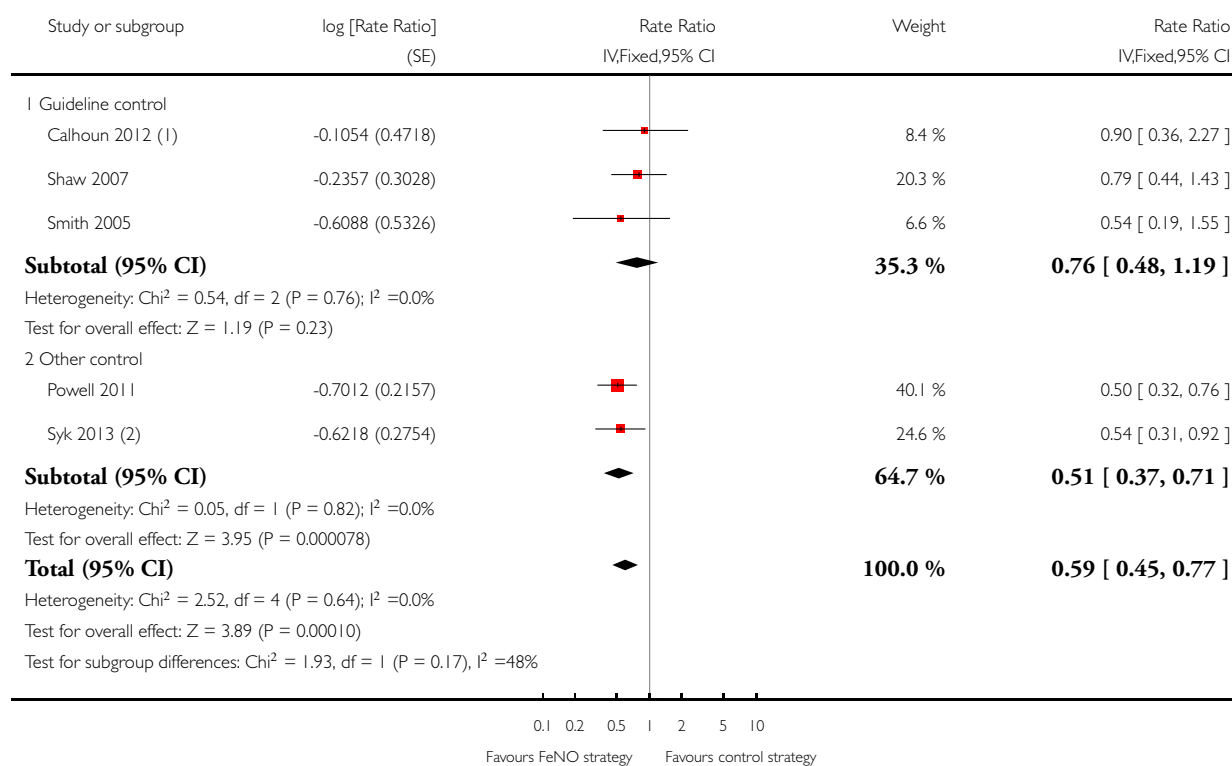
Favours FeNO strategy   Favours control strategy

Analysis 1.11. Comparison 1 Asthma treatment tailored on FeNO versus clinical symptoms, Outcome 11 Subgroup (control guideline use): Number of exacerbations per 52 weeks (exacerbation rates).

Review: Exhaled nitric oxide levels to guide treatment for adults with asthma

Comparison: 1 Asthma treatment tailored on FeNO versus clinical symptoms

Outcome: 11 Subgroup (control guideline use): Number of exacerbations per 52 weeks (exacerbation rates)

Study or subgroup	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
1 Guideline control				
Calhoun 2012 (1)	-0.1054 (0.4718)		8.4 %	0.90 [0.36, 2.27]
Shaw 2007	-0.2357 (0.3028)		20.3 %	0.79 [0.44, 1.43]
Smith 2005	-0.6088 (0.5326)		6.6 %	0.54 [0.19, 1.55]
Subtotal (95% CI)			**35.3 %**	**0.76 [0.48, 1.19]**
Heterogeneity: Chi² = 0.54, df = 2 (P = 0.76); I² =0.0%				
Test for overall effect: Z = 1.19 (P = 0.23)				
2 Other control				
Powell 2011	-0.7012 (0.2157)		40.1 %	0.50 [0.32, 0.76]
Syk 2013 (2)	-0.6218 (0.2754)		24.6 %	0.54 [0.31, 0.92]
Subtotal (95% CI)			**64.7 %**	**0.51 [0.37, 0.71]**
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² =0.0%				
Test for overall effect: Z = 3.95 (P = 0.000078)				
Total (95% CI)			**100.0 %**	**0.59 [0.45, 0.77]**
Heterogeneity: Chi² = 2.52, df = 4 (P = 0.64); I² =0.0%				
Test for overall effect: Z = 3.89 (P = 0.00010)				
Test for subgroup differences: Chi² = 1.93, df = 1 (P = 0.17), I² =48%				

```
        0.1  0.2   0.5   1    2    5   10
       Favours FeNO strategy   Favours control strategy
```

(1) Reported as a Hazard ratio in the paper but appears to be a rate ratio (FeNO v Physician based assessment)

(2) Estimated from raw rates in Table V and P value from Poisson regression model

ADDITIONAL TABLES

Table 1. Included studies definitions

Study ID	Exacerbation definition	FeNO cutoff (ppb)	Symptom strategy	Duration
Calhoun 2012	Increased asthma symptoms resulting in use of oral corticosteroids, increased ICS, or additional asthma medications	< 22 decrease 22 to 35 maintain > 35 increase	Based on National Heart, Lung, and Blood Institute guidelines	9 months

Table 1. Included studies definitions (*Continued*)

Hashimoto 2011	Decrease in morning $FEV_1 > 10\%$ compared to mean FEV_1 from week before, increase in symptoms requiring increased prednisolone > 10 mg/day, or course of antibiotics, regardless of hospitalisations	> +10 ppb & > 10% increase > +10 ppb & ≤ 10% maintain minus ≥10 & ≤ 10 maintain < -10 ppb decrease	Based on Global Initiative for Asthma (GINA) guidelines for treatment of severe asthma	6 months
Honkoop 2014	Severe exacerbations defined as hospitalisation, emergency department visit because of asthma, or use of oral corticosteroids for 3 or more days	< 25 decrease 25 to 50 no change > 50 increase	Asthma Control Test, 7 items which includes lung function	12 months
Powell 2011	Events for which the participant sought medical attention (unscheduled doctor visit, emergency department visit, hospital admission, or when oral corticosteroids were used to treat increase in asthma symptoms)	< 16 decrease 16 to 29 maintain > 29 increase	Asthma Control Test	4 months
Shaw 2007	Increasing asthma symptoms requiring course of oral steroids or antibiotics	< 16 once or 16 to 26 second decrease > 26 increase	BTS and Asthma Control Test	12 months
Smith 2005	Minor exacerbation: global daily asthma score of 2 on ≥ 2 consecutive days Major exacerbation: global daily asthma score of 3 on ≥ 2 consecutive days	< 15 maintain ≥ 15 increase (250 mL/sec)	GINA guidelines	12 months (Phase 2)
Syk 2013	Increasing symptoms requiring a course of oral corticosteroids	Women < 19 decrease step 19 to 23 maintain ≥ 24 increase 1 step ≥ 30 increase 2 steps Men < 21 decrease step	Based on patient-reported symptoms, SABA use, physical examination, and spirometry results	12 months

Table 1. Included studies definitions *(Continued)*

		21 to 25 maintain $\geq$ 26 increase 1 step $\geq$ 32 increase 2 steps		

FeNO: fractional exhaled nitric oxide
FEV1: forced expiratory volume in 1 second
ICS: inhaled corticosteroids
SABA: short-acting beta-agonist

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.

8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11
The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to identify relevant trials from the CAGR

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Nitric Oxide
#6 nitric* NEXT oxide*
#7 FeNO
#8 eNO
#9 "airway inflammation"
#10 "exhaled NO"
#11 biomarker*:ti,ab
#12 #5 or #6 or #7 or #8 or #9 or #10 or #11
#13 #4 and #12
[*Note: in search line #1, MISC1 denotes the field in which the reference has been coded for condition, in this case, asthma*]

Appendix 3. Search strategy to identify relevant trials from ClinicalTrials.gov and WHO trials portal

"exhaled nitric oxide" AND "asthma" AND "clinical trials"

CONTRIBUTIONS OF AUTHORS

All review authors reviewed the manuscript. HP and KK extracted the data and performed the analysis. HP and AC wrote the manuscript.

DECLARATIONS OF INTEREST

Some of the review authors (HP, AC, CT) have conducted a randomised controlled trial in children on this subject.

KK: none known

SOURCES OF SUPPORT

D I F F E R E N C E S   B E T W E E N   P R O T O C O L   A N D   R E V I E W

After retrieving articles to include in the review that reported Asthma Control Test score, we added an additional secondary outcome: symptoms of asthma as reported in Asthma Control Test.

We conducted a post hoc sensitivity analysis to remove the study that included pregnant women only (Powell 2011).