ORIGINAL ARTICLE

Tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils): a systematic review and meta-analysis

Helen L Petsky,[1] Chris J Cates,[2] Kayleigh M Kew,[3] Anne B Chang[4,5]

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[1]School of Nursing and Midwifery, Griffith University and Menzies Health Institute Queensland, Brisbane, Queensland, Australia
[2]Population Health Research Institute, St George's, University of London, London, UK
[3]British Medical Journal Technology Assessment Group (BMJ-TAG), BMJ, London, UK
[4]Child Health Division, Menzies School of Health Research, Darwin, Australia
[5]Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia

Correspondence to
Dr Helen L Petsky, School of Nursing and Midwifery, Griffith University and Menzies Health Institute Queensland, Brisbane, Australia;
helenpetsky@gmail.com

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ABSTRACT

Background Asthma guidelines guide health practitioners to adjust treatments to the minimum level required for asthma control. As many people with asthma have an eosinophilic endotype, tailoring asthma medications based on airway eosinophilic levels (sputum eosinophils or exhaled nitric oxide, FeNO) may improve asthma outcomes.

Objective To synthesise the evidence from our updated Cochrane systematic reviews, for tailoring asthma medication based on eosinophilic inflammatory markers (sputum analysis and FeNO) for improving asthma-related outcomes in children and adults.

Data sources Cochrane reviews with standardised searches up to February 2017.

Study selection The Cochrane reviews included randomised controlled comparisons of tailoring asthma medications based on sputum analysis or FeNO compared with controls (primarily clinical symptoms and/or spirometry/peak flow).

Results The 16 included studies of FeNO-based management (seven in adults) and 6 of sputum-based management (five in adults) were clinically heterogeneous. On follow-up, participants randomised to the sputum eosinophils strategy (compared with controls) were significantly less likely to have exacerbations (62 vs 82/100 participants with ≥1 exacerbation; OR 0.36, 95% CI 0.21 to 0.62). For the FeNO strategy, the respective numbers were adults OR 0.60 (95% CI 0.43 to 0.84) and children 0.58 (95% CI 0.45 to 0.75). However, there were no significant group differences for either strategy on daily inhaled corticosteroids dose (at end of study), asthma control or lung function.

Conclusion Adjusting treatment based on airway eosinophilic markers reduced the likelihood of asthma exacerbations but had no significant impact on asthma control or lung function.

Key messages

What is the key question?

► What is the overall outcome of trials that use eosinophilic markers (sputum eosinophil counts or exhaled nitric oxide levels) to tailor asthma treatment in children and adults?

What is the bottom line?

► Treatment tailored using eosinophilic markers results in fewer asthma attacks when compared with traditional management but did not impact on day-to-day reported symptoms, lung function or final daily inhaled corticosteroid doses.

Why read on?

► This systematic review combines 3 Cochrane reviews with 22 included studies, examining the updated evidence for objectively measuring inflammatory markers to personalise asthma management.

INTRODUCTION

The main aim of asthma guidelines is to provide an evidence-based approach to assist health professionals improve their patients' asthma management, which involve using the minimal amount of medications to optimise asthma outcomes (minimal symptoms and exacerbations and high quality of life).[1–3] Exacerbations are important as they cause anxiety to patients and are associated with increased healthcare cost.[4] Monitoring asthma control is important in asthma management, although there is no single outcome measure that can adequately assess asthma control.[5] Subjective measures usually involve a series of questions used for clinical assessment, and can include diary cards and quality of life (QoL) questionnaires. Traditional objective methods used to monitor asthma (but not control) include indices of spirometry/peak flow and airway hyper-responsiveness (AHR).[6] Newer methods include measurement of airway inflammation, such as airway cellularity in induced sputum or fractional exhaled nitric oxide (FeNO), as phenotypes/endotypes of asthma are increasingly appreciated.[7]

The inflammation in airways of people with asthma can be predominantly eosinophilic or non-eosinophilic (including neutrophilic).[8] Irrespective of the type of airway inflammation, inhaled corticosteroids (ICS) remain the major preventer therapy to control asthma symptoms, other than for children with mild intermittent asthma.[2] However, ICS are more effective in reducing symptoms in patients with eosinophilic inflammation than those with neutrophilic inflammation.[9] Thus, treatment tailoring based on objective eosinophilic inflammation data may be helpful in improving asthma outcomes. Currently, clinically available techniques are assessing airway cellularity and FeNO.[10]

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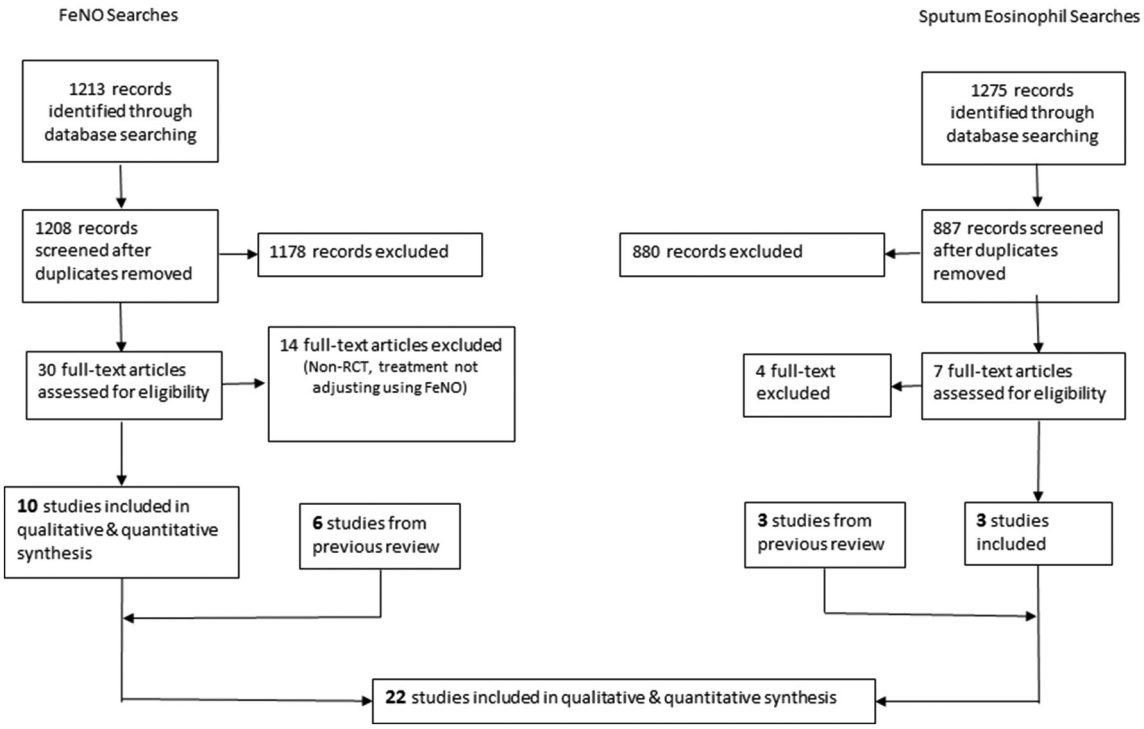

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart. FeNO, fractional exhaled nitric oxide; RCT, randomised controlled trial.

The increased attention to personalised medicine, which for asthma includes basing treatment on objective airway inflammation,[11] is reflected by interest in our previous systematic review.[12] We present an update to our previous review[12] by providing an overview of three recent related Cochrane reviews,[13–15] each of which addressed a different question as per the Participants Intervention Camparator Outcomes (PICO) framework. The objective of our systematic review is to evaluate the efficacy of tailoring asthma medications based on FeNO or sputum eosinophils (ie, eosinophilic-based strategy) in comparison with controls (clinical symptoms with or without spirometry/peak flow) for asthma-related outcomes in children and adults.

METHODS

Inclusion criteria, outcomes and analyses were a priori specified and documented in Cochrane review protocols and in the first versions of the three reviews on *The Cochrane Library*.[13–15]

Eligibility, information sources, search strategy and study selection

We used Cochrane methods and searched (up to February 2017) for eligible randomised controlled trials (RCTs) that compared adjustment of asthma medications based on sputum eosinophils or FeNO levels with adjustment according to clinical symptoms (with or without spirometry/peak flow). As outlined in the reviews,[13–15] searches used keywords in electronic sources (Cochrane Airways Group Specialised Register of Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, EMBASE) and reference hand searching. Searches of bibliographies and texts were conducted to identify additional studies. Trials that included the use of other interventions were included if all participants had equal access to such interventions.

Participant inclusion criteria were children and adults with a diagnosis of asthma according to a guideline-defined criteria. Exclusion criteria were as follows: eosinophilic bronchitis, asthma related to an underlying lung disease such as bronchiectasis and chronic obstructive airway disease, or diagnostic categories such as 'cough variant asthma' and 'wheezy bronchitis' where controversies exist.

Data extraction

Titles and abstracts of all records returned by the literature search were reviewed independently in duplicate to identify potentially relevant trials. Searches of bibliographies and texts were conducted to identify additional studies. Using the prespecified criteria, two reviewers independently reviewed full texts to select trials for inclusion. There was no disagreement although it was planned that disagreement would have been resolved by third-party adjudication. We extracted information from each trial on (1) study characteristics, (2) intervention type and (3) outcomes, as described in our Cochrane reviews.[13–15]

Risk of bias

Risk of bias for each included study was assessed using the Cochrane Risk of Bias tool available in the RevMan5 software. Seven components were assessed in duplicate as low, unclear or high risk of bias: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.

Summary (outcome) measures

Primary outcomes were indices reflective of asthma exacerbations (defined by study authors) during the follow-up period. Secondary outcomes were mean differences (MDs) between

Table 1 Characteristics of included studies

Study	Sample size	Description of intervention and control arms
Calhoun *et al*[35]	FeNO group n=115 Control group n=114	Control group: National Heart, Lung and Blood Institute guidelines FeNO group: <22 ppb treatment stepped down 22 to 35 maintain treatment >35 increase treatment
Cao *et al*[22]	EOS strategy n=20 Control group n=21	Control strategy: 'Standard clinical guidelines' EOS strategy: decrease ICS <1% eosinophils, keep ICS the same 1%–3% eosinophils, increase ICS if eosinophils >3%
Chlumsky *et al*[23]	EOS strategy n=30 Standard strategy n=25	Standard strategy arm: GINA guidelines EOS strategy: decrease ICS if ≤3%, keep same if 4%–8%, increase ICS if ≥8%
de Jongste *et al*[30]	FeNO group n=75 Symptom group n=72	All participants scored asthma symptoms in an electronic diary over 30 weeks. Aim to keep FeNO <20 ppb Symptom group based on symptom score: below range (<10)=step down/discontinue, range 10 to 60=no change and range >60=step up
Fleming *et al*[26]	Inflammatory group n=27 Symptom group n=28	Symptom group: based on number of major exacerbations in the preceding 3 months and SABA use in preceding 2 weeks Inflammatory group: treatment aimed to keep sputum eosinophil counts <2.5%
Fritsch *et al*[19]	FeNO group n=22 Control group n=25	FeNO group: therapy was based on symptoms, beta-agonist use, lung function and FeNO Control group: therapy based on symptoms, beta-agonists and lung function only
Green *et al*[24]	Sputum management group n=37 BTS group n=37	Sputum management group: anti-inflammatory treatment was based on maintenance of sputum eosinophil count below 3% with a minimum dose of anti-inflammatory treatment BTS management group: BTS/SIGN guidelines
Hashimoto *et al*[36]	Internet strategy n=51 Conventional strategy n=38	Internet strategy: had steroid dose adjusted based on the three components: electronic diary, in-built algorithm (which includes FeNO levels) and monitoring support Conventional strategy: GINA guidelines for the treatment of severe asthma
Honkoop *et al*[37]	FeNO group n=189 Controlled asthma group n=203	Cluster randomisation (at general practice level) FeNO strategy: treatment targeted to keep FeNO <50 ppb Symptom strategy: ACT used including lung function
Jayaram *et al*[31]	Sputum strategy group n=50 Clinical strategy group n=52	Sputum strategy: guided solely by induced sputum eosinophils to keep <2% Clinical strategy: Canadian Asthma Consensus Group Guidelines
Malerba *et al*[25]	Sputum strategy n=14 Clinical strategy n=14	Sputum strategy: treatment based on sputum eosinophil (%) and FeNO (ppb) Decrease ICS <2% and ≤10 pbb Keep same 2%–3% and 11–20 ppb Increase ICS >3% and ≥20 ppb Symptom strategy: symptom scores, use of SABA and night-time symptoms
Peirsman *et al*[34]	FeNO group n=49 Control group n=50	FeNO group: treatment aimed to keep FeNO below 20 ppb Control group: GINA guidelines
Petsky *et al*[28]	FeNO group n=31 Symptom group n=32	FeNO group: treatment adjusted based on FeNO level and atopy status Elevated FeNO defined as: ≥10 ppb with no positive SPT ≥12 ppb with one positive SPT ≥20 ppb with ≥2 positive SPT Control group: symptom diary cards
Pijnenburg *et al*[18]	FeNO group n=39 Symptom group n=46	FeNO group: FeNO guided ICS dosing according to predetermined algorithm Symptom group: symptom scores influenced ICS dosing
Pike *et al*[32]	FeNO group n=44 Standard management group n=46	FeNO group: FeNO measurements and symptom control Standard management group: symptom control as per blinded clinician (reliever use, FEV_1)
Powell *et al*[27]	FeNO group n=111 Control group n=109	FeNO group: sequential process, first FeNO concentrations used to adjust ICS dose, and second ACT score used to adjust the LABA dose Clinical group: Juniper ACT cut-off points defined as well-controlled asthma (ACT<0.75), partially controlled asthma (0.75 to 1.50) and uncontrolled asthma (>1.5)
Shaw *et al*[38]	FeNO group n=58 Control group n=60	FeNO group: FeNO >26 ppb, ICS was increased. If FeNO <16 ppb or <26 ppb on two separate occasions, treatment was decreased Control group: treatment was doubled if Juniper Asthma Control Score (JACS) >1.57 and treatment halved if JACS <1.57 for two consecutive months
Smith *et al*[21]	97 patients randomised from 110 patients	FeNO group: based to keep FeNO <15 ppb at 250 mL/s Control group: dose adjustment based on asthma symptoms, night-time waking, bronchodilator use, variation in PEFR and FEV_1
Syk *et al*[39]	FeNO group n=87 Control group n=78	FeNO group: keep FeNO level <24 ppb for women and <26 ppb for men Control group: treatment adjusted based on patient-reported symptoms, SABA use, physical examination and spirometry results
Szefler *et al*[29]	FeNO group n=276 Control group n=270	FeNO group: standard treatment modified on the basis of measurements of FeNO Control group: National Asthma Education and Prevention Programme guidelines

Continued

Table 1 Continued

Study	Sample size	Description of intervention and control arms
Verini *et al*[20]	FeNO group n=32 GINA group n=32	FeNO group at 6-month visit only: step treatment up if >12 ppb Control group: GINA guidelines
Voorend-van Bergen *et al*[33]	FeNO group n=92 Standard care group n=89	FeNO group: treatment adjusted according to FeNO levels and ACT results If ACT ≥20 and: FeNO <25=step down FeNO ≥25 to <50=no change FeNO ≥50= step up If ACT <20 and: FeNO ≥25=step up FeNO <25=no change Control group: treatment adjusted based on ACT results <20=step up ≥20=no change or step down

ACT, Asthma Control Test; BTS, British Thoracic Society; EOS, eosinophils; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long acting beta-agonist; PEFR, peak expiratory flow rate; SABA, short acting beta-agonist; SIGN, Scottish Intercollegiate Guidelines Network; SPT, skin prick test.

groups in objective measurements of asthma (FEV_1, peak flow, airway hyper-responsiveness), FeNO level, symptoms of asthma (as reported in Asthma Control Test (ACT) or asthma-related QoL score) and ICS dose at final visit.

Methods of analyses

The results from studies that met the inclusion criteria and reported any of the outcomes of interest were included in the subsequent meta-analyses. We a priori separated children from adult studies. All data were double entered (HLP/ABC or HLP/KK) and triple checked (CJC). We combined data for meta-analyses only where it was meaningful (ie, based on clinical and statistical criteria). We analysed dichotomous data as ORs and continuous data as MD, or as standardised MD if different measurement scales were used across studies. For dichotomous data, we reported the proportion of participants contributing to each outcome in comparison with the total number randomised. Generic inverse variance was used for rate ratio (RR) analysis of common events, where one subject may have more than one event. The RRs were taken from the published papers and SEs of the log RR were calculated from CIs or p values published in the papers. Numbers needed to treat (NNT) were calculated from the pooled OR and its 95% CI applied to a specified baseline risk using an online calculator.[16] Fixed effects were used throughout unless stated otherwise.

Any heterogeneity between the study results was described and tested to see if it reached statistical significance using a χ^2 test. We included the 95% CI estimated using a random-effects model whenever there were concerns about statistical heterogeneity. Heterogeneity was considered significant when the p value was <0.100.[17] We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (>50%), we reported it and explored possible causes. Subgroup analysis was planned for (1) basis for adjustment of ICS in the control group (guideline-driven monitoring vs non-guideline driven); (2) use of spirometry or peak flow as an adjunctive monitoring tool for adjustment of medications (vs non-use of spirometry or peak flow); (3) baseline ICS dose at commencement of intervention (<800 µg/day vs >800 µg/day budesonide equivalent); (4) cut-offs for adjustment of medications.

We used the five Grading of Recommendations Assessment, Development and Evaluatation (GRADE) considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it

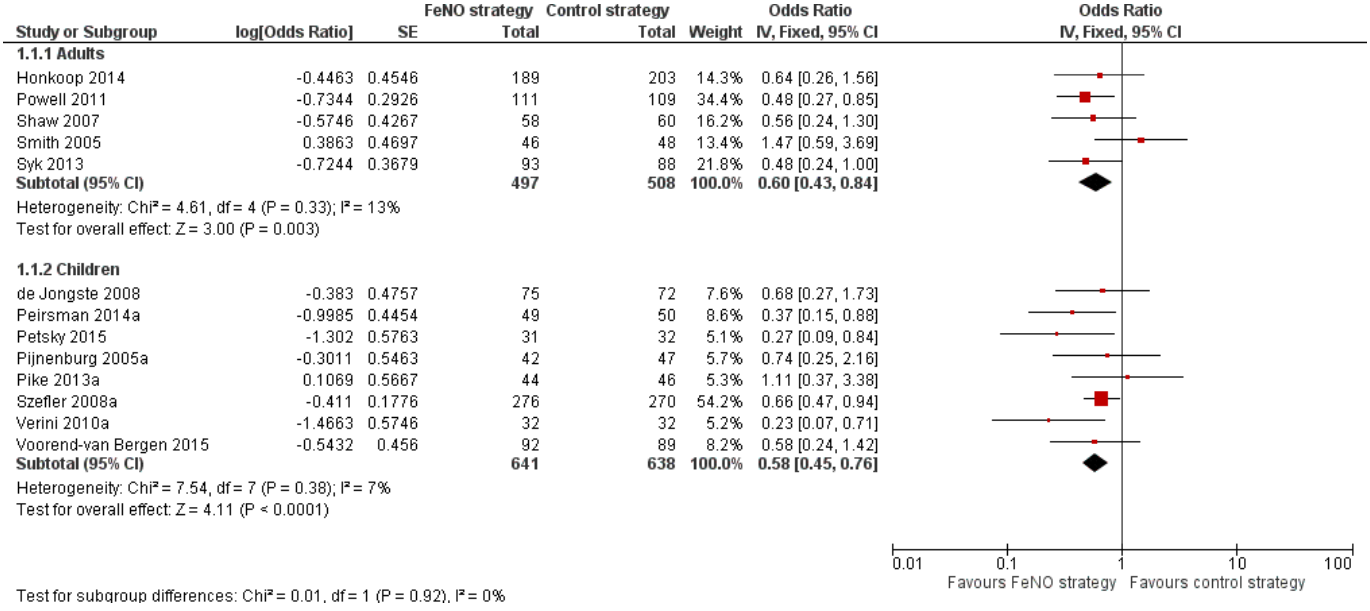

Figure 2 Number of subjects who had ≥1 exacerbation over the study period (FeNO).

Table 2 Number of participants who had ≥1 exacerbation over the study period (FeNO)

	FeNO group		Control group	
Adult studies	N with exacerbation	N of group	N with exacerbation	N of group
Honkoop *et al*[37]	23	189	30	203
Powell *et al*[27]	28	111	45	109
Berry *et al*[9]	12	58	19	60
Smith *et al*[21]	14	46	11	48
Syk *et al*[39]	15	93	25	88
Paediatric studies				
de Jongste *et al*[30]	9	75	12	72
Peirsman *et al*[34]	11	49	22	50
Petsky *et al*[28]	6	31	15	32
Pijnenburg *et al*[18]	7	42	10	47
Pike *et al*[32]	37	44	38	46
Szefler *et al*[29]	91	276	115	270
Verini *et al*[20]	16	32	26	32
Voorend-van Bergen *et al*[33]	9	92	14	89

FeNO, fractional exhaled nitric oxide.

relates to the studies that contributed data to the meta-analyses for the prespecified outcomes.

RESULTS

Study selection and study characteristics

The searches in 2017 identified 1208 publications for FeNO-based strategy and 1213 for sputum. After screening, 30 and 7 papers respectively were retrieved but only 16 and 6, respectively, fulfilled the inclusion criteria (figure 1), including the nine studies from the previous review.[12] The 22 studies consisted of 16 FeNO-based trials (seven adults, nine children) and six sputum-based trials (five adults, one children), which included a total of 3500 participants, of whom 3208 completed the studies (91.7%).

Of the 22 studies included (table 1, online supplementary Table 1), 9 were single-centre studies,[18–26] 2 were dual-centred[27 28] and 11 were multicentred.[29–39] Ten studies were in children or adolescents,[18–20 26 28–30 32–34] and 12 involved adult participants.[21–25 27 31 35–39] We classified studies into children/adolescent studies based on the mean age reported as opposed to the entry criteria. Nine studies were double-blind, parallel group trials,[18 24 26–29 31 32 35] seven were single-blind, parallel group trials,[19 21 22 25 33 34 38] and six studies had no blinding.[20 23 30 36 37 39] Twenty-one papers were published in English and one was translated from Chinese.[22] Seven studies were supported by Aerocrine, the manufacturer of FeNO analyser (online supplementary Table 1).

There was a degree of clinical heterogeneity among the studies (table 1, online supplementary Table 1), primarily with regard to the definition of an asthma exacerbation and the FeNO and sputum eosinophil cut-offs used for adjusting therapies. Although asthma exacerbations were an outcome measure in all papers, they differed in how they were defined ranging from unscheduled emergency visits[25] to defining an exacerbation using diary card data.[21 28] Two studies defined an exacerbation as a decrease in morning lung function.[24 36] Although there were variations in how exacerbations were defined, all included studies uniformly managed exacerbations with rescue oral steroids. Algorithms for adjustment of medications differed among studies and the cut-off values to step-up and down also varied across the FeNO studies (range 12[20] to 50 ppb[37]), and the sputum eosinophil percentages range from 2[31] to 8[23].

Outcomes and synthesis of results

Primary (exacerbations)

In both adults and children, the number of participants with exacerbations (during the follow-up period 18–52 weeks) in the group whose treatment was adjusted according to FeNO were significantly lower than the control group; in adults, OR was 0.60 (95% CI 0.43 to 0.84, p=0.003; participants=1005; studies=5) and in children the OR was 0.58 (95% CI 0.45 to 0.76, p<0.0001; participants=2284; studies=8) (figure 2). Based on the number of participants who had at least one exacerbation over the study period (table 2), the number needed to treat to benefit (NNTB) over 52 weeks was 12 (95% CI 8 to 32) in adults and 9 (95% CI 6 to 15) in children.

The exacerbation rate in the FeNO-strategy group was significantly lower than controls in the adult studies (RR 0.59, 95% CI 0.45 to 0.76; participants=842; studies=5). There was no significant difference between groups in the paediatric data and as statistical heterogeneity among studies was present, we used random-effects analysis to calculate the rate of exacerbations over 52 weeks (MD −0.37, 95% CI −0.8 to 0.06; participants=736; studies=4).

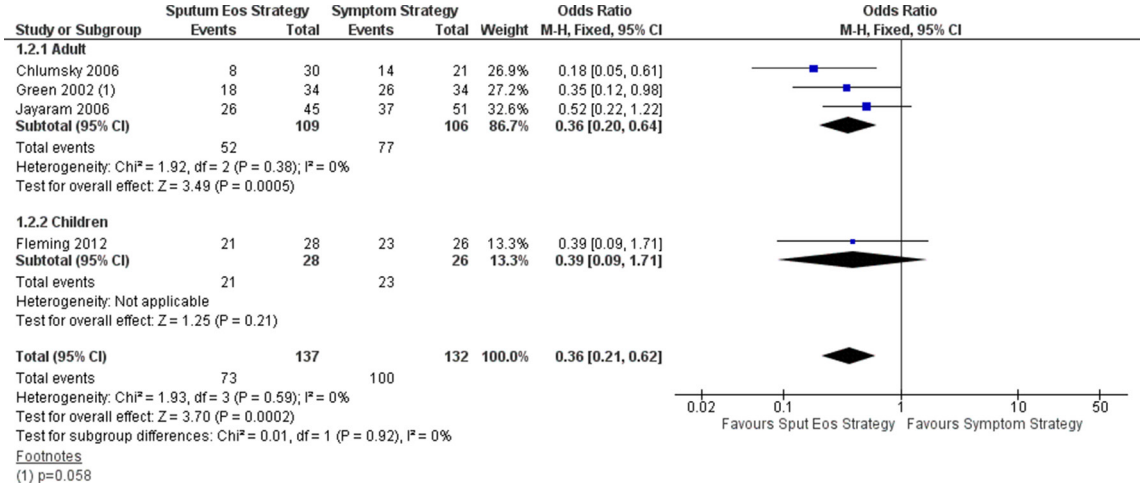

Figure 3 Number of subjects who had ≥1 exacerbation over the study period (SpEos).

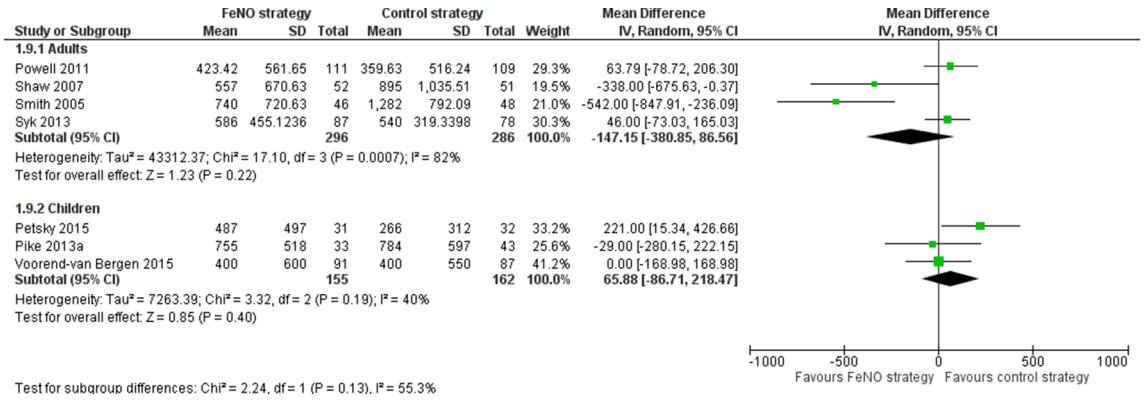

Figure 4 Inhaled corticosteroid dose at final visit (FeNO).

In the sputum-based meta-analysis (figure 3), significantly fewer adults and children in the sputum-based strategy had asthma exacerbations compared with the control group (73 vs 100; p=0.0002), OR 0.36 (95% CI 0.21 to 0.62); participants=173; studies=4. The NNT for one participant (adults) to avoid any exacerbations was 5 (95% CI 4 to 11) over 16 months.

Secondary outcomes

Inhaled corticosteroid (ICS) dose

For the FeNO-based studies, the meta-analysis found no significant group differences in the final ICS dose for adults or children (figure 4). In adults, the direction favoured the FeNO strategy (MD between groups was −147.15 µg budesonide equivalent; 95% CI −380.85 to 86.56; p=0.22; participants=582; studies=4), but the direction in children favoured the control strategy (MD 65.88 µg budesonide equivalent, 95% CI −86.71 to 218.47; p=0.40; participants=317; studies=3) (figure 4).

All five studies that used sputum eosinophils to adjust treatment reported no differences in doses of ICS used between groups (online supplementary figure 1). The SDs for the groups were not available in Jayaram *et al*'s paper[31] and were estimated based on the data from Green *et al*'s paper.[24] The mean dose of ICS per person per day (µg budesonide equivalent) between groups was non-significant in adult studies (MD 0.67, 95% CI −154.39 to 155.73; p=0.99; participants=262; studies=4). Likewise, there was no difference in daily ICS doses in the sole paediatric study (MD 67.0, 95% CI −264.81 to 398.81; p=0.69; participants=54).

Symptom scores and other outcomes

Symptom or ACT scores did not significantly differ between groups for FeNO studies in either adults or children (online supplementary figure 2). In adults (four studies), the direction of the difference in scores favoured the FeNO strategy, MD was −0.08 (95% CI −0.18 to 0.01; p=0.09; participants=707), but the direction in children favoured the control group: mean difference was 0.14 (95% CI −0.18 to 0.47; p=0.39; participants=724; studies=2). For the sputum-based studies, the two studies that reported on symptom scores also described no significant difference in symptom scores between groups.[23 24] Likewise, for the outcome of asthma QoL scores, there were no significant group differences for the FeNO-based studies in adults and children (online supplementary Figure 3). In adults, there were only two studies and the MD in children was 0.09 (95% CI −0.08 to 0.26; p=0.29; studies=3).

There were insufficient data reported from the individual studies to undertake a meta-analyses for the other secondary outcomes (FEV_1, AHR, rescue beta-agonist use). While FEV_1 was reported in all studies, data points were not provided; the studies described they found no difference between the participants who had treatment adjusted to inflammatory markers in comparison with the control group.

Subgroup analyses

As per table 1, 8 of the 16 FeNO-based studies[20 21 29 32 34–36 38] used guideline-driven monitoring for the control group. In this subgroup analysis based on trials that used guideline-driven monitoring, the significant difference was no longer present for the primary outcome of number of participants who had one or more exacerbations (OR 0.87, 95% CI 0.47 to 1.61) in adults (four studies) but that in children (four studies) still significantly favoured the FeNO strategy (OR 0.67, 95% CI 0.51 to 0.90). The subgroup analyses results for 'cut-off FeNO values' were similar to the main analyses; the FeNO group had significantly fewer exacerbations. As there were insufficient data, we could not undertake subgroup analyses for the other planned subgroups.

Risk of bias in individual studies

The risk of bias diagram (figure 5) shows that eight studies[18 24–28 31 34 38] were judged as having good methodological quality, but in all studies there was either insufficient details about allocation concealment and/or adequacy of blinding. Seven studies[20 23 30 33 36 37 39] were open label or single blinded (six in FeNO studies, one in sputum-driven studies). When data from the six open-label FeNO-driven studies[20 30 33 36 37 39] were removed, the primary outcome results (exacerbations) did not change. In adults, 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 rates (RR 0.61, 95% CI 0.45, 0.82; participants=661, studies=4). In children, the number of participants who had one or more exacerbations over the study period OR 0.67 (95% CI 0.50 to 0.89; participants=887, studies=5).

One sputum eosinophil-driven study[23] did not use blinding; however, removing the datum from this study did not alter the results of the primary outcome (exacerbations), occurrence of any exacerbation (RR 0.66, 95% CI 0.46, 0.93; participants=218; studies=3) or number of participants who had one or more exacerbations over the study period (OR 0.43, 95% CI 0.24 to 0.79; participants=218; studies=3).

For the FeNO-based adult papers, the quality of evidence using the GRADE approach surmises that, of the three outcomes assessed, two were of moderate quality and one (ICS dose at

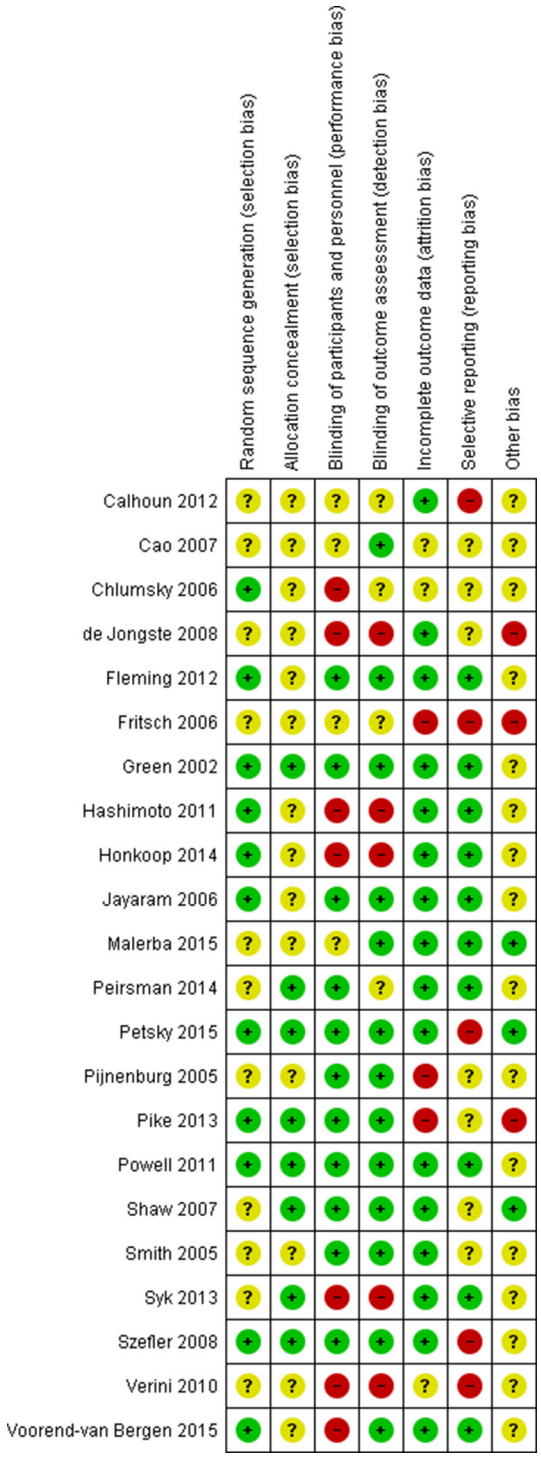

Figure 5 Risk of bias summary.

final visit) was very low quality due to wide confidence intervals and the fact that one study[39] was open labelled, as well as heterogeneity between doses (table 3). For the FeNO-based children studies, the quality was moderate for two outcomes and very low for one (exacerbation rates). This outcome was downgraded three levels for one open-labelled study,[20] imprecision and heterogeneity (I^2=67%) (table 4). For sputum-based studies, GRADE assessment shows that the quality of the three outcomes were moderate for two outcomes (exacerbations) and low (ICS dose) due to the lack of blinding in one study,[23] and the varied doses within and between studies (table 5).

DISCUSSION

In this meta-analysis, we combined data from our three Cochrane reviews[13–15] that evaluated the efficacy of tailoring asthma medications (ICS predominantly) based on airway eosinophilic markers (FeNO or sputum eosinophils) in comparison with controls (clinical symptoms with or without spirometry/peak flow) for asthma-related outcomes in children and adults. Based on 22 studies involving 3500 adults and children (3208 completed), we found that children and adults randomised to either eosinophilic marker strategy (compared with controls) were significantly less likely to experience an exacerbation during the follow-up period (4.5–24 months). The exacerbation rate was also significantly lower in adults randomised to the FeNO or sputum strategy (compared with controls) but not in children. There was not a significant difference in the final dose of ICS in either children or adults. For both FeNO and sputum-based strategies, there was no difference between groups for all secondary outcomes (FEV_1, ACT, QoL, airway hyper-responsiveness or $beta_2$ agonist use).

In this review updated from our previous combined meta-analyses,[12] the data on sputum remained unchanged, that is, using sputum to guide asthma therapies in adults is beneficial for the outcome of reducing exacerbations. The new single paediatric study[26] found no significant difference between the groups for this outcome, although it favoured the sputum-based strategy. However, the OR for the combined adult and paediatric studies remained unchanged at 0.36, but the 95% CI was marginally smaller from 0.20 to 0.64 to 0.21 to 0.62.

In contrast to the data for sputum, the additional 10 studies included in the FeNO strategy analyses altered the previous 'no benefit' found in our previous review[12] to 'some benefit' as using a FeNO-based strategy reduced the number of participants with asthma exacerbations during the follow-up period in both children and adults. However, the benefit was inconsistent as there was no longer any significant difference between groups in the sensitivity analyses for adults, while in children there were no group differences for exacerbation rate. While these new data are somewhat supportive of authors who previously advocated using FeNO levels to tailor medications,[40] we do not believe there is currently sufficient evidence to universally use FeNO to monitor airway inflammation recommended by others.[41]

In contrast to the favourable data in the outcome of exacerbations for both sputum and FeNO-based strategies, the data for other asthma outcomes (FEV_1, symptom scores, QoL and $beta_2$ agonist use) remained unchanged, that is, neither sputum and FeNO-based strategies were shown to confer any advantage over the control arms. There may be several reasons for this including the known discordance between asthma control and exacerbations.[1] While exacerbations are an important outcome, arguably subjective measures of asthma control are also important. Thus, although our findings demonstrate using airway eosinophilic markers to guide medications in future exacerbations, it is debatable whether either strategy should be universally advocated. Sputum analysis is restricted to laboratories with specific expertise, is relatively time consuming and is not always successful, particularly in young children. Use of FeNO universally will add a substantial cost to the millions of people who have asthma. Also, currently there is no evidence-based algorithm on how to adjust treatment based on FeNO levels (or indeed to sputum eosinophil levels) and the various guidelines (such as GINA,[1] BTS,[2] NAC[3]) differ on when and how to step up and down asthma therapies. Nevertheless, using airway eosinophilic markers to guide asthma therapy is most

Table 3 Summary of findings for the main comparisons: FeNO-based adult studies

Tailoring asthma treatment using FeNO vs clinical symptoms

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

	Anticipated absolute effects* (95% CI)					
Outcomes	Risk with asthma treatment tailored on clinical symptoms†	Risk with asthma treatment tailored on FeNO	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
No of participants who had ≥1 exacerbations over the 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]	–
No 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 µg	The mean ICS dose taken in the FeNO groups was 17.01 lower (101.75 lower to 67.72 more) 577 µg	–	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)

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 .
**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.
FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; MD, mean difference; RCT, randomised controlled trial.

Table 4 Summary of findings for the main comparisons: FeNO-based paediatric studies

Tailoring asthma treatment using fractional exhaled nitric oxide vs clinical symptoms

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

	Anticipated absolute effects* (95% CI)					
Outcomes	Risk with clinical symptoms	Risk with asthma treatment tailored on FeNO	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
No of participants who had ≥1 exacerbations over the study period (48.5 weeks)	40 per 100	28 per 100 (23 to 33)	OR 0.58 (0.45 to 0.75)	1279 (8 RCTs)	⨁⨁⨁⨀ Moderate[1]	–
No of asthma exacerbations per 52 weeks (exacerbation rate)	The mean number of asthma exacerbations per 52 weeks (exacerbation rate) was 1.66	The mean number of asthma exacerbations per 52 weeks (exacerbation rate) in the intervention group was 0.37 lower (0.8 lower to 0.06 higher)	MD −0.37 (−0.8 to 0.06)	736 (4 RCTs)	⨁⨀⨀⨀ Very low[2]	–
ICS dose at final visit (budesonide equivalent)	The mean ICS dose at final visit (budesonide equivalent) was 483 µg/day	The mean ICS dose at final visit (budesonide equivalent) in the intervention group was 63.95 µg/day higher (51.89 lower to 179.79 higher)	–	317 (3 RCTs)	⨁⨁⨁⨀ Moderate[3]	–

**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).
FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; MD, mean difference; RCT, randomised controlled trial.

Table 5 Summary of findings for the main comparisons: sputum eosinophilia-based studies

Tailored interventions based on sputum eosinophils compared with tailored interventions based on clinical symptoms for asthma in adults and children

Patient or population: adults and children with asthma
Settings: hospital outpatients
Intervention: based on sputum eosinophil count
Comparison: based on clinical symptoms

	Illustrative comparative risks* (95% CI)					
	Assumed risk at 1 year	Corresponding risk				
Outcomes	Tailored interventions based on clinical symptoms	Tailored interventions based on sputum eosinophils	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
No of participants who had one or more exacerbations over the study period Follow-up: 12 to 24 months	82 per 100	62 per 100 (49 to 74)	OR 0.36 (0.21 to 0.62)	228 (3 studies)	⊕⊕⊕⊖ Moderate[1]	
Hospitalisations Follow-up: 12 to 24 months	24 per 100	8 per 100 (3 to 21)	OR 0.28 (0.09 to 0.84)	269 (4 studies)	⊕⊕⊕⊖ Moderate[2]	
Mean dose of inhaled corticosteroids per person per day (budesonide equivalent µg/day) Follow-up: 12 to 24 months		The mean dose of inhaled corticosteroids per person per day in the intervention groups was 13 µg/day higher (128 lower to 153 higher)		316 (4 studies)	⊕⊕⊖⊖ Low[3]	

*The basis for the *assumed risk* is the mean of the two studies with a duration of 1 year. The *corresponding risk* (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).

likely to be beneficial to the subset of people with frequent asthma exacerbations.

The data on the FeNO-based studies also need to be considered in light of several issues. First, only one[28] of the 16 included studies using FeNO considered presence or severity of atopy in their algorithm of management although some but not all subjects were atopic. FeNO is higher when eosinophilic inflammation is present; however, it is also higher in other conditions (eg, atopy, allergic rhinitis, eczema).[1] Second, the cut-offs of FeNO used for stepping up or down therapy differed between studies (range 15–50 ppb). Pijnenburg *et al*'s[18] (paediatric study) subjects had the highest mean daily dose of ICS, and subjects in this study also had quite high FeNO at the final visit (approximately 25.5 pbb in FeNO group, 36.7 in controls). Disconcertingly, use of FeNO strategy did not result in a lower FeNO level at the end of trial. Moreover, some of the algorithms used a safety net to avoid excessively high doses of ICS in some participants whose FeNO remained high. Third, as reported in risk of bias table (table 2), obtaining accurate FeNO measurements at each visit could not be obtained, either due to a faulty analyser[30] or technical issues.[19] Also, many aspects need to be considered when analysing FeNO; this includes the timing of spirometry (transiently reduces FeNO), food and beverage, circadian rhythm, smoking history, ambient NO and exercise.[42] Lastly, FeNO values may not always reflect levels of airway eosinophilia as shown in a RCT using mepoluzimab.[43]

Limitations of review

This systematic review is limited to 22 studies with 3208 subjects completing the trials. While the studies share some common issues, there are also substantial differences, notably, the definition of asthma exacerbation, the participants, how the decision to prescribe oral steroids was made, the cut-off levels for FeNO and sputum eosinophils were different, the control strategies (that often used uses multiple measures) and how medications were adjusted. Also, 7 of the 16 FeNO-based studies were supported by the FeNO manufacturers, and although we are unaware of any publication bias, we cannot be certain of its existence.

CONCLUSION

Tailoring of asthma therapy based on FeNO or sputum eosinophils has been shown to be effective in decreasing asthma exacerbations in adults. Adjusting treatment based on FeNO levels for children tended to decrease asthma exacerbations at the expense of increased ICS doses. At present, despite their popularity, there is insufficient evidence to advocate their use in routine clinical practice.

Further, data starting with meta-analyses based on individual patient data (IPD) of all the studies may further inform the efficacy of strategies based on airway eosinophilic markers. If IPD meta-analysis does not shed more light, e.g., the change in FeNO before medications are adjusted, further RCTs in both adults and children are then required. Ideally, these RCTs should include stratification for example, high versus low doses of ICS, and eosinophilic versus non-eosinophilic asthma and cost-effectiveness.

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