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SYSTEMATIC REVIEW

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Effectiveness of FeNO-guided treatment in adult asthma patients: A systematic review and meta-analysis

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Abstract

Objective: Asthma control is generally monitored by assessing symptoms and lung function. However, optimal treatment is also dependent on the type and extent of airway inflammation. Fraction of exhaled Nitric Oxide (FeNO) is a noninvasive biomarker of type 2 airway inflammation, but its effectiveness in guiding asthma treatment remains disputed. We performed a systematic review and meta-analysis to obtain summary estimates of the effectiveness of FeNO-guided asthma treatment.

Design: We updated a Cochrane systematic review from 2016. Cochrane Risk of Bias tool was used to assess risk of bias. Inverse-variance random-effects meta-analysis was performed. Certainty of evidence was assessed using GRADE. Subgroup analyses were performed based on asthma severity, asthma control, allergy/atopy, pregnancy and obesity.

Data Sources: The Cochrane Airways Group Trials Register was searched on 9 May 2023.

Eligibility Criteria: We included randomized controlled trials (RCTs) comparing the effectiveness of a FeNO-guided treatment versus usual (symptom-guided) treatment in adult asthma patients.

Results: We included 12 RCTs (2,116 patients), all showing high or unclear risk of bias in at least one domain. Five RCTs reported support from a FeNO manufacturer. FeNO-guided treatment probably reduces the number of patients having ≥1 exacerbation (OR = 0.61; 95%CI 0.44 to 0.83; six RCTs; GRADE moderate certainty) and exacerbation rate (RR = 0.67; 95%CI 0.54 to 0.82; six RCTs; moderate certainty), and may slightly improve Asthma Control Questionnaire score (MD = −0.10; 95%CI −0.18 to −0.02, six RCTs; low certainty), however, this change is unlikely to be clinically important. An effect on severe exacerbations, quality of life, FEV1, treatment dosage and FeNO values could not be demonstrated. There were no indications that effectiveness is different in subgroups of patients, although evidence for subgroup analysis was limited.

Conclusions: FeNO-guided asthma treatment probably results in fewer exacerbations but may not have clinically important effects on other asthma outcomes.

KEYWORDS
asthma, eosinophils, Fraction of exhaled Nitric Oxide, meta-analysis, systematic review

1 | INTRODUCTION

Asthma is a chronic airway disease, characterized by airway inflammation and variable expiratory airflow limitation.[1] The goal of asthma treatment is to minimize symptoms, optimize lung function, and prevent acute exacerbations. The cornerstone of treatment consists of corticosteroids, preferably in inhaled form (ICS), combined with bronchodilators. International guidelines recommend to treat asthma using a stepwise approach: treatment is increased (i.e., by adding a medicine or increasing dosage) if disease is insufficiently controlled, and treatment is maintained or decreased when disease is stable.[1,2] Asthma control is commonly monitored by assessing symptoms, sometimes in combination with lung function testing. However, increasing evidence is emerging that asthma is a heterogenous disease with different inflammatory endotypes.[3] In most patients, asthma is predominantly driven by type 2 airway inflammation, with high levels of eosinophils. In others, type 2 inflammation plays a smaller, or no role at all, and these tend to respond poorly to corticosteroid therapy. Ideally, asthma treatment is tailored in accordance with the type and extent of airway inflammation.

It has been shown that the frequency of asthma exacerbations is significantly lower in patients in whom the dose of ICS is guided by sputum eosinophil levels, as compared with those in whom management is based on usual methods of asthma monitoring.[4] Unfortunately, sputum induction requires experienced laboratory personnel, is time-consuming, does not provide immediate results, and is not feasible in every patient.[5,6] An alternative could be Fraction of exhaled Nitric Oxide (FeNO), which strongly correlates with sputum eosinophils, is noninvasive and quick.[7–11] However, a Cochrane systematic review by Petsky and colleagues from 2016 found only limited evidence in favour of FeNO-guided asthma treatment.[12] Since then, several new studies have appeared. In addition, that Cochrane systematic review focused on asthma control in the overall population, without looking at specific subgroups.

We performed a systematic review and meta-analysis to summarize the effectiveness of FeNO-guided asthma treatment compared to usual (symptom-guided) treatment in (specific subgroups of) adult asthma patients.

Key messages

- FeNO-guided asthma treatment probably reduces the number of asthma exacerbations.
- No effect was found on severe exacerbations, quality of life, FEV1 and treatment dosage.
- There were no indications that effectiveness is different in subgroups of asthma patients.

2 | METHODS

2.1 | Search and selection

The abovementioned Cochrane systematic review by Petsky and colleagues on the effectiveness of FeNO-guided treatment in adult asthma patients (which included seven randomized controlled trials (RCTs); searches were performed in June 2016) served as our starting point.[12] The exact same search was used to identify studies published since then, that is, between 1 January 2016 and 9 May 2023. We searched the Cochrane Airways Group Trials Register (composed of airway-related RCTs identified through systematic searches in MEDLINE, Embase, Cochrane CENTRAL, PsycINFO and CINAHL databases, and through handsearching of respiratory medicine journals and conference abstracts). The full search strategy is reported in Data S1—Supplementary Material 1.

Study selection was independently performed by two reviewers. First, titles and abstracts were screened and disagreements were discussed between the two reviewers. All abstracts deemed potentially relevant were assessed for inclusion on full texts. Differences in the full-text assessment between the reviewers were discussed. In case of disagreement, a third reviewer made the final decision. Studies were included if they were RCTs (*study design*) comparing the effectiveness of FeNO-guided treatment (*intervention*) versus usual treatment (*control*) in adult asthma patients (*study population*), or specific subgroups thereof. FeNO-guided treatment could be tailored by FeNO results alone, or in combination with other measures of asthma control, such as symptoms, lung function or other biomarkers of type 2 airway inflammation, such as blood eosinophils or periostin.[9] Usual treatment could be tailored by clinical asthma symptoms alone, or in combination with other variables such as lung function. Studies were only included if they reported on any of the following outcomes: asthma exacerbations (≥1 exacerbation during the study period, or exacerbation rate), asthma control (assessed by Asthma Control Questionnaire (ACQ) or Asthma Control Test (ACT)), quality of life (assessed by Asthma Quality of Life Questionnaire (AQLQ)), lung function (Forced Expiratory Volume in 1 second (FEV1) % predicted), medication use (dosage of ICS) or FeNO. We excluded nonrandomized studies, such as observational studies and literature reviews. We also excluded studies in children and studies only reported as conference abstracts. We included studies written in English, Dutch, French, German or Spanish. In addition to database searching, we also scanned reference lists of included articles for RCTs potentially missed in our search and selection process. We did not search trial registers for ongoing studies.[13,14]

2.2 | Data extraction and quality assessment

For each included study, descriptive data were collected regarding patient characteristics, intervention (i.e., FeNO-guided asthma treatment), control (i.e., usual treatment) and outcomes. The methodological quality of each study was assessed using the Cochrane Risk of Bias tool for RCTs.[15] Data extraction and quality assessment were performed by two reviewers independently, where differences were discussed. If necessary, a third reviewer made the final decision. For the meta-analyses, data extraction and quality assessment were performed exclusively on newly identified RCTs; for the seven RCTs already included in the Cochrane systematic review by Petsky and colleagues, we used the results that were previously extracted and presented in their review report.[12]

2.3 | Statistical analysis

If possible, results were pooled using inverse-variance random-effects meta-analysis, accounting for differences between studies. Studies for which insufficient data were presented and outcomes for which insufficient studies were available (two or fewer) were described qualitatively. The following predefined subgroups were evaluated: asthma severity (mild–moderate vs. severe), asthma control (controlled vs. uncontrolled), allergy/atopy (allergic/atopic vs. nonallergic/non-atopic asthma), pregnancy and obesity. Analyses were performed in Review Manager.[16]

2.4 | Grading the evidence

For each outcome, two investigators independently assigned the certainty of the evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology, whereby the scientific evidence is assessed using five established criteria (study design, risk of bias, imprecision, inconsistency and reporting bias). Based on this, a final 'level of certainty' is attributed to the evidence, which can be high, moderate, low or very low.[17]

2.5 | Funding and registration

This systematic review was part of a wider literature investigation of the usefulness of FeNO in the diagnosis and treatment of specific groups of asthma patients, performed by Cochrane Netherlands commissioned by the Dutch National Health Care Institute, for which the full report was published online in Dutch in June 2020.[18] Updated results are reported in the current article. The review protocol was inspired by the abovementioned prior Cochrane systematic review by Petsky and colleagues, but was not identical (e.g., the same search strategy was used, but the subgroup analyses were newly added). Our protocol was finalized and submitted to the Dutch National Health Care Institute prior to initiation of the searches and study selection process, and can be accessed at https://osf.io/ycxt7/. The current review has not been published in the Cochrane Library, and the authors of the previous Cochrane systematic review by Petsky and colleagues were not involved in this updated systematic review, but were contacted for clarification of some of the reported data.

3 | RESULTS

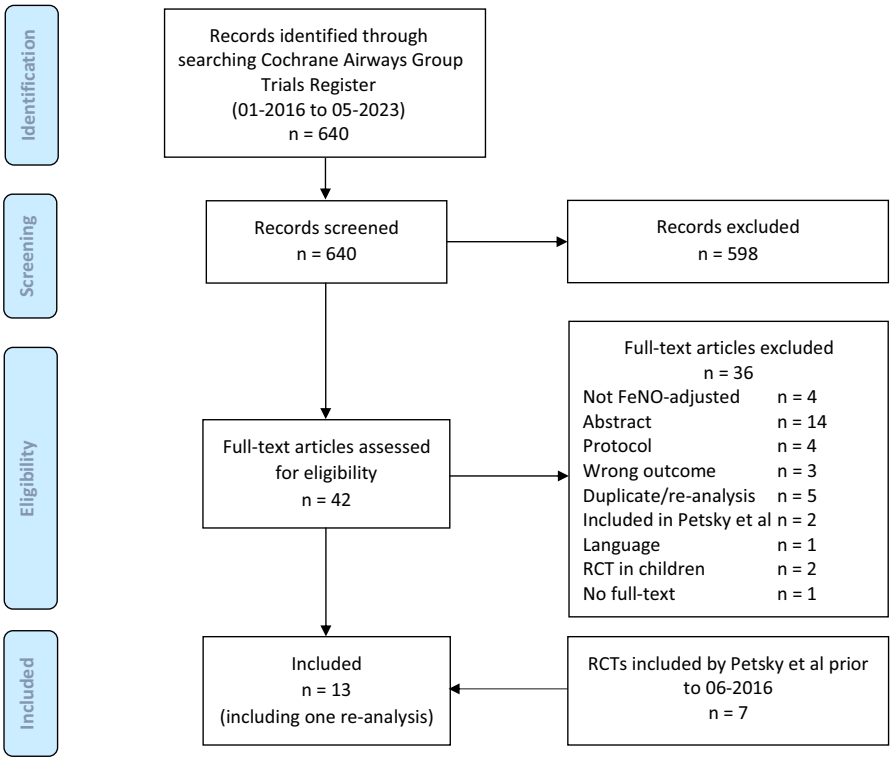
3.1 | Study selection

The Cochrane systematic review by Petsky and colleagues identified seven RCTs up to June 2016.[12,19–25] In our update of the search, we identified 640 records (Figure 1). Of these, 598 could be excluded after screening titles and abstracts. For the remaining 42 records, full texts were assessed, of which 36 were excluded (Data S1—Supplementary Material 2). Of the remaining studies, five were RCTs that fulfilled the inclusion criteria,[26–30] and one was a reanalysis of an RCT already included in the Cochrane systematic review.[31] So in total, we included 12 RCTs (and one reanalysis) on the effectiveness of FeNO-guided asthma treatment, covering 2,116 randomized asthma patients. No protocols of, or conference abstracts corresponding to, ongoing studies were identified in our literature searches.

3.2 | Description of included RCTs

An overview of characteristics of included RCTs is provided in Table 1. The majority was conducted in Europe ($n=6$) or Asia ($n=3$), sample size ranged from 72 to 392 patients (median 162), and mean age ranged from 28 to 58 years. Study duration varied from 18 weeks to 1 year. Seven RCTs included participants with asthma regardless of control or severity, whereas the others included patients with mild–moderate asthma ($n=2$), moderate–severe asthma ($n=1$) or severe asthma ($n=2$). Two other RCTs were performed in primary care, where it can be expected that only patients with mild–moderate asthma were included. One RCT only included pregnant asthma patients. In four RCTs, the treatment decision was based on the FeNO value alone in the FeNO-guided asthma treatment group, while in the remaining studies FeNO was combined with other characteristics or tools, such as ACQ ($n=5$), GINA (Global Initiative for Asthma) guidelines ($n=2$) or other biomarkers of type 2 airway inflammation ($n=1$). The cut-off values of FeNO used to adjust treatment also differed between RCTs. Two RCTs used a single cut-off value, that is, either 15 or 25 ppb. If the FeNO value was above this cut-off value, increasing treatment was considered, whereas treatment was adjusted downwards if FeNO was below this value. Eight RCTs used two or even three cut-off values; if the FeNO value was between these cut-off values, treatment was not adjusted. Finally, two RCTs used the relative change in FeNO from the previous measurement to adjust treatment. Usual treatment in the control group was in most cases guided by ACQ ($n=5$) or according to the

FIGURE 1 Study selection.



GINA guidelines ($n=4$). Five RCTs reported support from a FeNO manufacturer.[20,21,24,25,28]

An overview of the risk of bias assessment is provided in Table 2. Risk of bias was high in at least one domain for five RCTs (only one of them being among the five newly identified RCTs); for the remaining seven RCTs, risk of bias was unclear in at least one domain. Nine RCTs had an unclear risk of bias in the randomization procedure (i.e., unclear random sequence generation and/or allocation concealment). Four RCTs had a high risk of bias because staff and participants were not blinded, and this was unclear in three. Three RCTs had a high risk of bias because outcome assessors were not blinded, and this was unclear in six. In one RCT, risk of bias due to incomplete outcome data was unclear. In one RCT, there was high risk of selective reporting, and this was unclear in five.

3.3 | Asthma exacerbations

Meta-analysis results are shown in Figure 2, with detailed GRADE summary of findings tables in Data S1—Supplementary Material 3. The definition of asthma exacerbation varied across studies, which is illustrated in Data S1—Supplementary Material 4. Six RCTs reported on the number of patients with ≥1 exacerbation during the study period. Although most of these found no significant difference, in meta-analysis a statistically significantly lower odds of having ≥1 exacerbation was found for FeNO-guided treatment compared to usual treatment in meta-analysis (OR = 0.61 (95%CI 0.44 to 0.83); GRADE moderate level of evidence; Figure 2A). Ten RCTs reported on exacerbation rate (i.e., the number of exacerbations per year), of which six could be included in meta-analysis. A statistically significantly lower exacerbation rate for FeNO-guided treatment was found (RR = 0.67 (95%CI 0.54 to 0.82); GRADE moderate level of evidence; Figure 2B). The remaining four RCTs reported no significant difference in median incidence of exacerbations per year (absolute difference = −0.14 in favour of FeNO-guided treatment; $p=.95$),[20] in mean exacerbation rate per patient per year (0.19 (95%CI 0.11 to 0.29) for FeNO-guided treatment versus 0.29 (95%CI 0.17 to 0.40) for usual treatment),[21] in total number of exacerbations requiring treatment throughout the course of the study ($n=20$ for FeNO-guided treatment vs. $n=25$ for usual treatment ($p=.6$)),[26] and in mean exacerbation rate per patient per year (0.3 (95%CI 0.145–0.455) for FeNO-guided treatment vs. 0.4 (95%CI 0.228–0.572) for usual treatment ($p=.387$)).[27]

Five RCTs reported on the number of exacerbations requiring treatment with oral corticosteroids (OCS) during the study period, of which three could be included in meta-analysis. No significant difference between groups was found (OR = 0.86 (95%CI 0.50 to 1.48); GRADE low level of evidence; Figure 2C). In the fourth RCT, the total number of OCS-requiring exacerbations throughout the study course was similar ($n=4$ for FeNO-guided treatment vs. $n=6$ for usual treatment; no p-value reported). In the fifth RCT, the total number of severe asthma exacerbations (requiring OCS treatment and/or hospitalization) was not significantly different between FeNO-guided treatment versus usual treatment (OR 0.64 (95%CI 0.27–1.56)).[21] Additionally, six RCTs reported on the number of patients with exacerbations requiring hospitalization during the study period. Three of these could be included in meta-analysis, but in two of these, the outcome was not observed at all, and in one of these, the outcome was also infrequent and no significant difference was found (OR = 0.14 (95%CI 0.01 to 2.67); GRADE very low level of evidence; Figure 2D). In the fourth

TABLE 1 Characteristics of included RCTs.

Reference	Sample size	Mean age (years) (intervention versus control)	Study duration	Asthma population	Intervention	FeNO cut-off	Control
Bernholm 2018[26] Denmark	72	42 vs 30	36 weeks	Asthma	FeNO + ACQ	<16 and >29 ppb	ACQ
Calhoun 2012[a19] USA	229	35 vs 34	9 months	Mild–moderate asthma, well or partially controlled	FeNO	<22 and >35 ppb	NHLBI guidelines (FEV1, symptoms)
Garg 2020[27] India	100	41 vs 38	12 months	Mild–moderate asthma	FeNO	Relative: change of >20% or 10 ppb	GINA (clinical symptoms and spirometry)
Hashimoto 2011[a20] Netherlands	89	49 vs 52	6 months	Severe refractory asthma, uncontrolled	FeNO + ACQ	Relative: change of >10% or 10 ppb	GINA
Heaney 2020[28] UK	301	55 vs 58	48 weeks	Severe asthma	FeNO + blood eosinophils + serum periostin	<15 and >30 ppb	ACQ and recent exacerbation history
Honkoop 2014[a21] Netherlands	392	39 vs 40	12 months	Asthma Performed in primary care	FeNO + ACQ	<25 and >50 ppb	ACQ
Powell 2011[a22] Murphy 2019[31] Australia	220	28 vs 29	Mean 18–19 weeks	Asthma, pregnant women	FeNO + ACQ	<16 and >29 ppb	ACQ
Shaw 2007[a23] UK	118	50 vs 52	12 months	Asthma	FeNO + ACQ	<16 and >26 ppb	ACQ
Smith 2005[a24] New Zealand	94	Overall 45	12 months	Asthma	FeNO	15 ppb	Symptoms, nighttime waking, bronchodilator use, variation in PEFR and FEV_1
Syk 2013[a25] Sweden	165	41 vs 41	12 months	Asthma Performed in primary care	FeNO	Women: <19, ≥24, ≥30 ppb Men: <21, ≥26, ≥32 ppb	Swedish MPA guidelines (symptoms, SABA use, physical examination, lung function)
Truong-Thanh 2020[29] Vietnam	176	36 vs 34	9 months	Moderate–severe asthma, uncontrolled	FeNO + GINA	<25 and >50 ppb	GINA
Wang 2019[30] China	160	40 vs 40	12 months	Mild–moderate–severe asthma, persistent	FeNO + GINA	25 ppb	GINA

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; FeNO, Fraction of exhaled Nitric Oxide; FEV_1, Forced Expiratory Volume in 1 second; GINA, Global Initiative for Asthma; MPA, Medical Product Agency; NHLBI, National Heart, Lung, and Blood Institute; PEFR, peak expiratory flow rate; ppb, parts per billion; SABA, short-acting β-agonist.

[a]Identified from Petsky et al.

TABLE 2 Risk of bias of included RCTs.

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other
Bernholm 2018[26]	Low	Low	Unclear	Unclear	Low	Low	Low
Calhoun 2012[a19]	Unclear	Unclear	Unclear	Unclear	Low	High	Unclear
Garg 2020[27]	Low	Low	Low	Unclear	Low	Unclear	Low
Hashimoto 2011[a20]	Low	Unclear	High	High	Low	Low	Unclear
Heaney 2020[28]	Low	Unclear	Low	Unclear	Low	Low	Low
Honkoop 2014[a21]	Low	Unclear	High	High	Low	Low	Unclear
Powell 2011[a22] Murphy 2019[31]	Low	Low	Low	Low	Low	Low	Unclear
Shaw 2007[a23]	Unclear	Low	Low	Low	Low	Unclear	Low
Smith 2005[a24]	Unclear	Unclear	Low	Low	Low	Unclear	Unclear
Syk 2013[a25]	Unclear	Low	High	High	Low	Low	Unclear
Truong-Thanh 2020[29]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Wang 2019[30]	Unclear	Unclear	High	Unclear	Unclear	Unclear	Low

[a]Risk of bias obtained from Petsky et al.

RCT, no significant difference was found in the annual hospitalization rate (RR = 0.77 (95%CI 0.32 to 1.84)).[28] In the fifth RCT, no significant difference was found in median days of hospitalization per patient (absolute difference = 0; $p = .25$).[20] In the sixth RCT, the number of hospitalizations was similar ($n = 3$ for FeNO-guided treatment vs. $n = 2$ for usual care; no p-value reported).[21]

3.4 | Asthma control

Nine RCTs reported on asthma control measured by ACQ (where lower scores indicate better asthma control) at final visit, of which six could be included in meta-analysis. Although none of these found a significant difference, in meta-analysis a statistically significantly lower ACQ was found for FeNO-guided treatment (MD = −0.10 (95%CI -0.18 to −0.02); GRADE low level of evidence; Figure 2E). In the seventh RCT, no significant difference in mean ACQ change from baseline was observed (MD = 0.14 (95%CI −0.14 to 0.42); $p = .37$).[20] In the eighth RCT, no significant difference was found in mean ACQ (MD = −0.05 (95%CI −0.15 to 0.06)).[21] In the ninth RCT, no significant difference was found in median ACQ score (FeNO group: 0.8 (IQR 0.4 to 1.8); control group: 0.8 (IQR 0.4 to 2); $p = .7$).[26] In addition, one RCT reported on asthma control measured by ACT (where higher scores indicate better asthma control) at final visit, and found no significant difference in mean scores (MD = −1 (95%CI −2.63 to 0.63)).[29]

3.5 | Quality of life

Seven RCTs reported on quality of life measured by AQLQ (where lower scores indicate higher quality of life) at final visit, of which three could be included in meta-analysis, but no significant difference was found (MD = 0.02 (95%CI −0.10 to 0.14); GRADE low level of evidence; Figure 2F). In the fourth RCT, no difference was found in mean AQLQ change from baseline to final visit between groups (FeNO: −0.03 (SE 0.10); control −0.14 (SE 0.13); $p = .30$).[20] In the fifth RCT, no difference was found in median score on MiniAQLQ at final visit (FeNO: 6.2 (IQR 5.3 to 6.6), control: 6.2 (IQR 5.3 to 6.6); $p = .5$).[26] In the sixth RCT, the median overall MiniAQLQ score did not significantly improve more in the FeNO-guided group (0.23 (IQR, 0.07–0.73) vs. 0.07 (IQR, −0.20 to 0.80); $p = .197$).[25] In the seventh RCT, no significant difference was found in MiniAQLQ between the FeNO-guided and control group (0.75 (IQR 0.38 to 1.25) vs. 0.81 (IQR 0.38 to 1.63); $p = .54$).[22]

3.6 | Lung function

Eleven RCTs reported FEV1% predicted at final visit, of which eight could be included in meta-analysis, but no significant difference was found (MD = 0.14; 95%CI −0.98 to 1.26; GRADE low level of evidence; Figure 2G). In the remaining three RCTs, it was reported that there was no difference in FEV1 between groups over the duration of the study,[23] that no significant differences in FEV1 were observed between groups,[19] and that changes in FEV1 were not significantly different between the two groups,[20] without additional data reported.

3.7 | Medication use

Nine RCTs reported on the dosage of ICS (budesonide variant) at final visit, of which seven could be included in meta-analysis, but no significant difference was found (MD = −57 μg/day; 95%CI −135 to 20; GRADE low level of evidence; Figure 2H). In the eighth RCT, no significant difference was found in the median dose of ICS (FeNO:

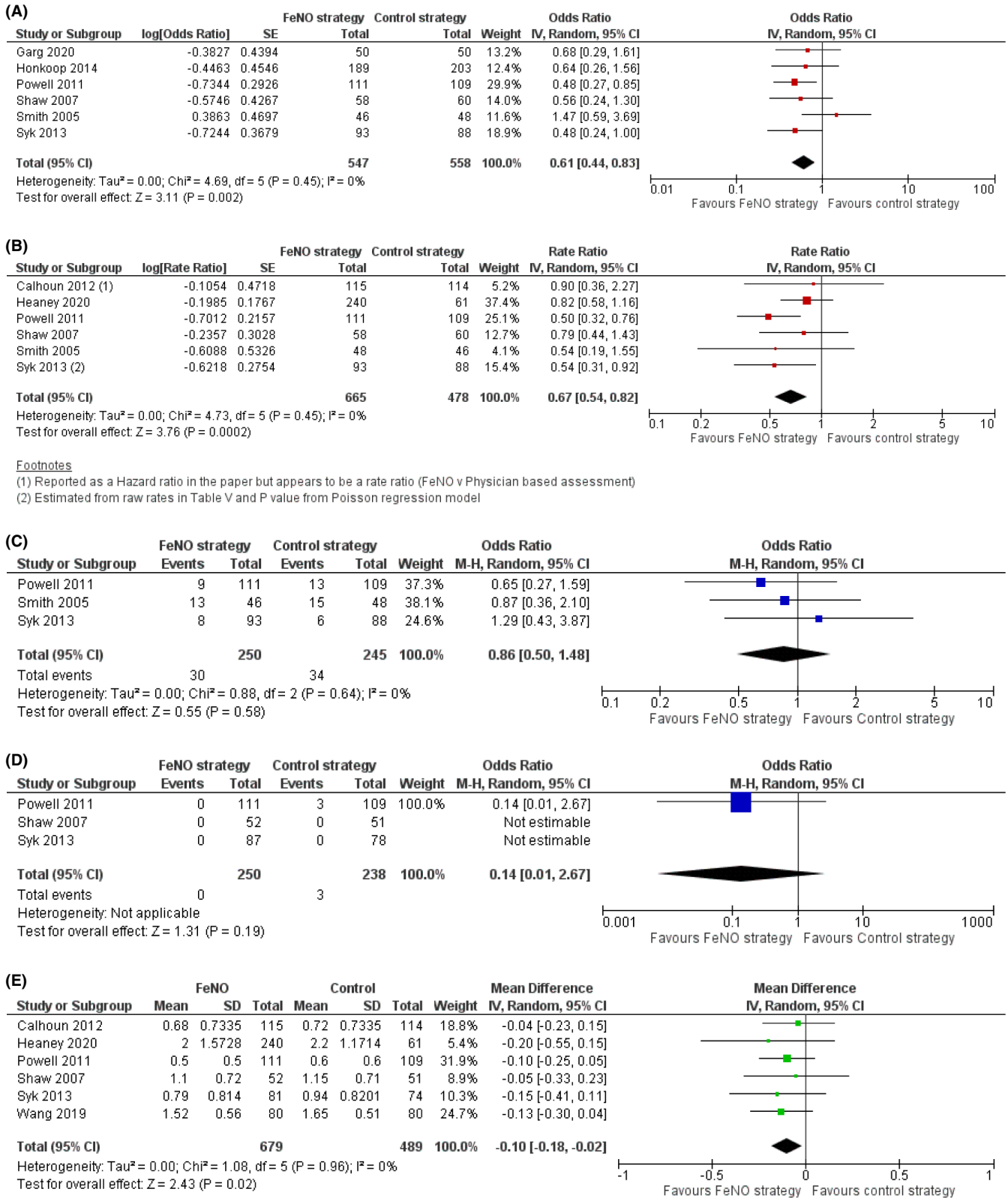


FIGURE 2 Forest plots and meta-analyses of RCTs comparing FeNO-guided treatment versus usual (symptom guided) treatment in adult asthma patients. (A) ≥1 Asthma exacerbation during the study period. (B) Exacerbation rate (number of exacerbations per 52 weeks). (C) ≥1 Asthma exacerbation requiring treatment with oral corticosteroids during the study period. (D) Asthma exacerbation requiring hospitalization during the study period. (E) Asthma control assessed by Asthma Control Questionnaire (ACQ) at final visit. (F) Quality of life assessed by Asthma Quality of Life Questionnaire (AQLQ) at final visit. (G) FEV1% predicted at final visit. (H) Dosage of inhaled corticosteroids (in μg/day) at final visit. (I) FeNO value in parts per billion (PPB) at final visit.

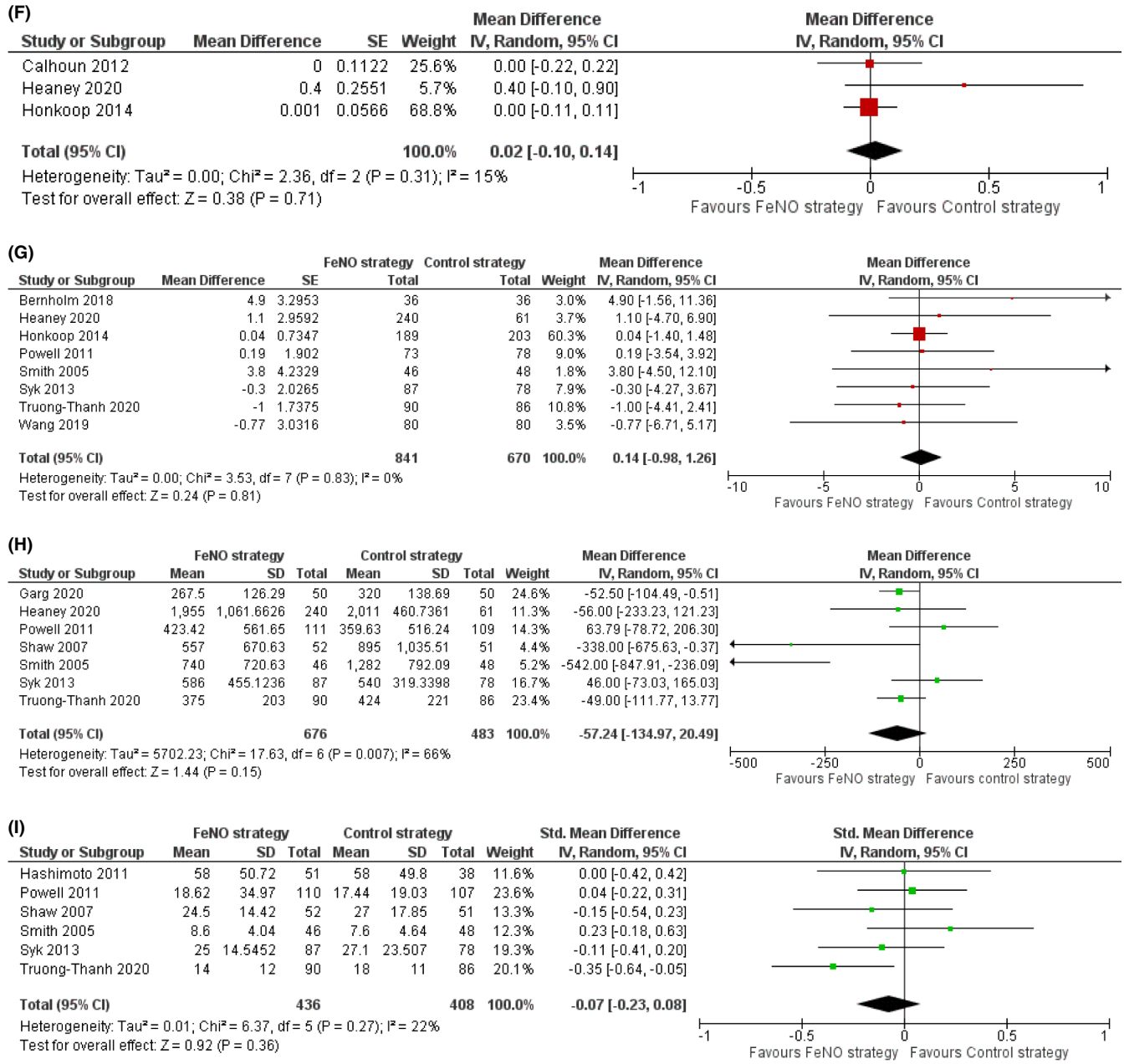


FIGURE 2 (Continued)

100 μg/day (IQR 0–600); control: 0 μg/day (IQR 0–800); $p = .8$).[26] In the ninth RCT, the median change in ICS dose showed no change in the FeNO-guided group (range 0 to 250 μg/day), and was 125 μg/day (range −250 to 250 μg/day) in the control group ($p < .01$).[20]

3.8 | FeNO values

Nine RCTs reported on FeNO values at final visit, of which six could be included in the meta-analysis, but no significant difference was found (SMD = −0.07; 95%CI −0.23 to 0.08; GRADE low quality of evidence; Figure 2I). In the seventh RCT, a significant difference in median FeNO values was found (FeNO group: 15 (IQR 12 to 18); control group: 21 (IQR 14 to 29); $p = .03$).[26] In the eighth RCT, no significant difference was found (ratio of geometric means = 1.02; 95%CI 0.87 to 1.19).[28] In the ninth RCT, it was reported that the increase in FeNO was significantly greater in the control group than in the FeNO-guided group ($p = .007$).[19]

3.9 | Subgroups based on asthma severity, asthma control, atopic asthma, pregnancy and obesity

Results on subgroup analyses are reported in Data S1—Supplementary Material 5. Regarding asthma severity, there are no indications that the effectiveness of a FeNO-tailored treatment is

considerably different in studies with patients with mild−-moderate asthma patients,[19,21,25,27] compared to studies with patients with (moderate−)severe asthma,[20,28,29] or compared to the other studies that included patients regardless of severity. The same applied to asthma control, where one RCT only included patients with well-controlled asthma only,[19] three RCTs only included patients with uncontrolled asthma,[20,29,30] and two RCTs additionally performed a subgroup analysis including only patients with uncontrolled asthma.[25,28] A single RCT evaluated atopic patients only (they had confirmed IgE sensitization to at least one major airborne perennial allergen), whereas no RCTs evaluated (subgroups of) non-atopic/allergic patients only, but results were similar compared to overall meta-analysis results. Regarding pregnancy, one RCT only included pregnant asthma patients.[22] The results from this RCT do not differ from the other studies, although the effect on exacerbations seems to be slightly stronger in this study. Regarding obesity, one study compared the effectiveness of FeNO-guided asthma treatment in three subgroups of pregnant asthma patients based on BMI, categorized as either not overweight, or overweight, or obese.[22,31] Between subgroups, there were no significant differences in terms of women with ≥1 exacerbation, number of hospital admissions, AQLQ, FEV1% predicted, dose of ICS or FeNO values.

4 | DISCUSSION

We performed a systematic review, evaluating the effectiveness of FeNO-guided treatment in adult asthma patients, and were able to include 12 RCTs covering 2,116 patients. Compared to usual (symptom-guided) treatment, the use of FeNO led to a 39% lower odds of having ≥1 exacerbation during the study period, a 33% lower exacerbation rate and a 0.1 lower ACQ score. However, an effect with regard to the number of severe exacerbations requiring OCS or hospitalization, quality of life, FEV1% predicted, dosage of ICS treatment and FeNO could neither be demonstrated nor rejected. The certainty of the evidence according to GRADE was 'moderate' for the outcomes on exacerbations, and 'low' or 'very low' for almost all other analyses, mainly due to high risk of bias and imprecision of effect estimates. Furthermore, we found no indications that the effectiveness of FeNO-guided treatment depends on asthma severity, asthma control, allergy/atopy, obesity or pregnancy, although evidence was limited or absent for most of these subgroups.

Several elements should be taken into account when interpreting these findings. There was considerable variation in the reported outcome measures across RCTs. Because of this, we were only able to include a fraction of all available RCTs in most meta-analyses. RCTs that could not be included in meta-analysis did not always support the findings of the main meta-analyses. For example, only six RCTs reported sufficient information to be included in the meta-analysis on exacerbation rate, and only three reported sufficient information to be included in the meta-analysis on quality of life based on AQLQ. Despite a relatively large overall number of RCTs included, there was imprecision in the estimated effect size for many outcomes, which made it difficult to generate firm recommendations regarding the use of FeNO in specific asthma subgroups. Such variations in outcome measures can be considered as a substantial source of research waste,[32] and this should be harmonized as much as possible across future studies.

A closer look at the definitions of an asthma exacerbation used in RCTs revealed that this was often a composite measure including both mild and severe exacerbations (Data S1—Supplementary Material 4). Severe exacerbations requiring OCS treatment and/or hospitalization were reported as a separate outcome by only a few RCTs. Moreover, these outcomes occurred infrequently or not at all in these studies, making it difficult to demonstrate or exclude an effect. This is unfortunate, as severe exacerbations are likely to have more impact than mild ones, in terms of medical consequences and healthcare costs. Although a significantly lower ACQ score in the FeNO-guided treatment group is reassuring, the difference of only 0.1 points compared to usual care is generally considered as clinically irrelevant and the 95%CI excludes the minimal clinically important difference of 0.5 points for ACQ.[33]

The FeNO-guided treatment protocol differed considerably across the included studies, both with regard to cut-offs used, as well as to whether or not additional measures of asthma control (e.g., ACQ) were incorporated. Despite this heterogeneity, RCT results were generally consistent for most outcomes. Still, our systematic review does not answer the question which protocol is optimal. Given the fact that it is unlikely that there is one single cut-off above which patients will, and below which patients will not, respond to treatment, a two-cut-off protocol seems rational. In the in-between group, it may be appropriate to keep medication as it is, and to monitor the patient more closely. Alternatively, the relative change in FeNO from the previous measurement could be used, which has the advantage of taking into account inter-person differences in FeNO levels due to intrinsic and extrinsic factors not related to type 2 airway inflammation.[7] For the same reason, we believe that FeNO should ideally not be used as a standalone test to make treatment decisions, but should be combined with other simple measures of asthma control (e.g., ACQ), as most studies did. Whether addition of other noninvasive markers of asthma control that are mechanistically complimentary, such as blood eosinophils, can further improve outcomes is mostly unclear.[28,34,35]

Over the past years, treatment with biologicals affecting the airway inflammatory pathways involved in asthma has rapidly emerged. These biologicals are now being used in selected patients with severe asthma that is uncontrolled under conventional treatment.[36,37] FeNO plays an important role in selecting the optimal biological in a given patient.[7] In addition, large numbers of studies have evaluated a potential role of FeNO in asthma care, not only for treatment selection, but also for, for example, diagnosis of (eosinophilic) asthma, prediction of asthma outcomes and assessing adherence to treatment.[7–10,34,35,38–40] Although FeNO has been implemented in clinical practice in many healthcare centres worldwide, discussion regarding the added value for most of these indications remains.[7,8] Our findings provide new evidence to this discussion.

Compared to the Cochrane systematic review by Petsky and colleagues from 2016,[12] we were able to almost double the number of included RCTs. Our findings confirm that FeNO can have a role in the treatment of adult asthma patients, but the added value in the general asthma population is likely to be limited. This is in line with the recommendations from most clinical guidelines and consensus documents, which generally advice against routinely using FeNO to monitor disease control in asthma patients, although most acknowledge that this can be considered in selected patients.[1,2,7,8] FeNO-guided treatment led to a reduction of asthma exacerbations, but a (clinically relevant) effect on other outcomes could not be demonstrated. Therefore, especially asthma patients with type 2 airway inflammation and frequent exacerbations may benefit, and future studies could focus specifically on the prevention of exacerbations in this subgroup of patients. Future studies on FeNO-guided treatment in the general asthma population seem futile, considering the large amount of data already available.

AUTHOR CONTRIBUTIONS

All authors participated in the development of the protocol and interpretation of the data; RS performed the literature searches; DAK, JAD and PH did study selection, data extraction and data analysis; DAK drafted the first version of the manuscript; and all authors participated in refining the manuscript and approved with the final version.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. *Global initiative for asthma. Global Strategy for Asthma Management and Prevention*. 2021 Available at: https://ginasthma.org/
2. National Institute for Health and Clinical Excellence guideline. *Asthma: Diagnosis, Monitoring and Chronic Asthma Management*. 2017 Available at: https://wwwniceorguk/guidance/ng80
3. Hekking PP, Bel EH. Developing and emerging clinical asthma phenotypes. *J Allergy Clin Immunol Pract*. 2014;2(6):671-680.
4. Petsky HL, Li A, Chang AB. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. *Cochrane Database Syst Rev*. 2017;8:CD005603.
5. Guiot J, Demarche S, Henket M, et al. Methodology for sputum induction and laboratory processing. *J Vis Exp*. 2017;130:56612.
6. Pavord ID, Bafadhel M. Exhaled nitric oxide and blood eosinophilia: independent markers of preventable risk. *J Allergy Clin Immunol*. 2013;132(4):828-829.
7. Menzies-Gow A, Mansur AH, Brightling CE. Clinical utility of fractional exhaled nitric oxide in severe asthma management. *Eur Respir J*. 2020;55(3):1901633.
8. Chung KF. Increasing utility of FeNO as a biomarker of type-2 inflammation in severe asthma. *Lancet Respir Med*. 2021;9(10):1083-1084.
9. Korevaar DA, Westerhof GA, Wang J, et al. Diagnostic accuracy of minimally invasive markers for detection of airway eosinophilia in asthma: a systematic review and meta-analysis. *Lancet Respir Med*. 2015;3(4):290-300.
10. Westerhof GA, Korevaar DA, Amelink M, et al. Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes. *Eur Respir J*. 2015;46(3):688-696.
11. Khatri SB, Iaccarino JM, Barochia A, et al. Use of fractional exhaled nitric oxide to guide the treatment of asthma: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2021;204(10):e97-e109.
12. Petsky HL, Kew KM, Turner C, Chang AB. Exhaled nitric oxide levels to guide treatment for adults with asthma. *Cochrane Database Syst Rev*. 2016;9:CD011440.
13. Hooft L, Korevaar DA, Molenaar N, Bossuyt PM, Scholten RJ. Endorsement of ICMJE's clinical trial registration policy: a survey among journal editors. *Neth J Med*. 2014;72(7):349-355.
14. Korevaar DA, Salameh JP, Vali Y, et al. Searching practices and inclusion of unpublished studies in systematic reviews of diagnostic accuracy. *Res Synth Methods*. 2020;11(3):343-353.
15. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
16. Review Manager (RevMan). *Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration*. 2014.
17. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383-394.
18. Damen JA, Heus P, Spijker R, et al. *Nut van FeNO bij de diagnostiek en behandeling van specifieke groepen astmapatiënten/Utility of FeNO in diagnosis and treatment of specific groups of asthmatics*. 2021 Available at: https://wwwzorginstituutnederlandnl/publicaties/rapport/2021/06/09/cochrane-rapport-nut-van-feno-bij-astma
19. Calhoun WJ, Ameredes BT, King TS, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA*. 2012;308(10):987-997.
20. Hashimoto S, Brinke AT, Roldaan AC, et al. Internet-based tapering of oral corticosteroids in severe asthma: a pragmatic randomised controlled trial. *Thorax*. 2011;66(6):514-520.
21. Honkoop PJ, Loijmans RJ, Termeer EH, et al. Symptom- and Fraction of exhaled Nitric Oxide-driven strategies for asthma control: a cluster-randomized trial in primary care. *J Allergy Clin Immunol*. 2015;135(3):682-8 e11.
22. Powell H, Murphy VE, Taylor DR, et al. Management of asthma in pregnancy guided by measurement of fraction of exhaled nitric oxide: a double-blind, randomised controlled trial. *Lancet*. 2011;378(9795):983-990.
23. Shaw DE, Berry MA, Thomas M, et al. The use of exhaled nitric oxide to guide asthma management: a randomized controlled trial. *Am J Respir Crit Care Med*. 2007;176(3):231-237.
24. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med*. 2005;352(21):2163-2173.
25. Syk J, Malinovschi A, Johansson G, et al. Anti-inflammatory treatment of atopic asthma guided by exhaled nitric oxide: a randomized, controlled trial. *J Allergy Clin Immunol Pract*. 2013;1(6):639-648 e1-8.

26. Bernholm KF, Homoe AS, Meteran H, Jensen CB, Porsbjerg C, Backer V. FeNO-based asthma management results in faster improvement of airway hyperresponsiveness. *ERJ Open Res*. 2018;4(4):00147-02017.
27. Garg Y, Kakria N, Katoch CDS, Bhattacharyya D. Exhaled nitric oxide as a guiding tool for bronchial asthma: a randomised controlled trial. *Med J Armed Forces India*. 2020;76(1):17-22.
28. Heaney LG, Busby J, Hanratty CE, et al. Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial. *Lancet Respir Med*. 2021;9(1):57-68.
29. Truong-Thanh T, Vo-Thi-Kim A, Vu-Minh T, Truong-Viet D, Tran-Van H, Duong-Quy S. The beneficial role of FeNO in association with GINA guidelines for titration of inhaled corticosteroids in adult asthma: a randomized study. *Adv Med Sci*. 2020;65(2):244-251.
30. Wang X, Wu L, Zhang Z, Kong Q, Qi H, Lei H. The reliability of adjusting stepped care based on FeNO monitoring for patients with chronic persistent asthma. *Open Med*. 2019;14:217-223.
31. Murphy VE, Jensen ME, Robijn AL, et al. How maternal BMI modifies the impact of personalized asthma Management in Pregnancy. *J Allergy Clin Immunol Pract*. 2020;8(1):219-28e3.
32. Moher D, Glasziou P, Chalmers I, et al. Increasing value and reducing waste in biomedical research: who's listening? *Lancet*. 2016;387(10027):1573-1586.
33. Bonini M, Di Paolo M, Bagnasco D, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. *Eur Respir Rev*. 2020;29(156):190137.
34. Couillard S, Do WIH, Beasley R, Hinks TSC, Pavord ID. Predicting the benefits of type-2 targeted anti-inflammatory treatment with the prototype Oxford asthma attack risk scale (ORACLE). *ERJ Open Res*. 2022;8(1):00570-02021.
35. Couillard S, Shrimanker R, Lemaire-Paquette S, et al. Longitudinal changes in sputum and blood inflammatory mediators during FeNO suppression testing. *Thorax*. 2022;77(9):933-938.
36. Charles D, Shanley J, Temple SN, Rattu A, Khaleva E, Roberts G. Real-world efficacy of treatment with benralizumab, dupilumab, mepolizumab and reslizumab for severe asthma: a systematic review and meta-analysis. *Clin Exp Allergy*. 2022;52(5):616-627.
37. Upham JW, Jurak LM. How do biologicals and other novel therapies effect clinically used biomarkers in severe asthma? *Clin Exp Allergy*. 2020;50(9):994-1006.
38. Busse WW, Wenzel SE, Casale TB, et al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis. *Lancet Respir Med*. 2021;9(10):1165-1173.
39. Korevaar DA, Westerhof GA, Bel EH. Biomarkers for diagnosing asthma: a smoking gun? *Clin Exp Allergy*. 2016;46(4):516-518.
40. Louis R, Satia I, Ojanguren I, et al. European Respiratory Society guidelines for the diagnosis of asthma in adults. *Eur Respir J*. 2022;60:2101585.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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