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FeNO and Asthma Treatment in Children

A Systematic Review and Meta-Analysis

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Abstract: Traditional asthma treatments are typically adjusted in children with asthma using symptoms and spirometry. Treatments tailored in accordance to inflammatory markers, such as fraction of exhaled nitric oxide (FeNO) or sputum eosinophils, are increasing in use.

This meta-analysis evaluated the potential benefit of incorporating the use of monitoring FeNO with guideline-based management in treating children with asthma.

PubMed and Cochrane CENTRAL databases were searched until November 2013 for randomized control trials that investigated the use of FeNO compared with conventional monitoring in managing asthma in children.

Included studies had at least 2 intervention groups: one that utilized FeNO and the other that utilized only conventional or standard methods (eg, spirometry, symptoms, and others) to guide treatment.

Six studies were included in the meta-analysis comprising 506 subjects whose treatment was monitored using FeNO and 511 subjects who were managed using conventional methods. We found no difference between the FeNO and the conventional groups in FeNO value (95% confidence interval [CI]: −0.31, 0.1), change from baseline in FEV_1 (95% CI: −0.07, 0.20), or steroid use (95% CI: −0.67, 1.80). However, the FeNO group was associated with a lower frequency of >1 asthma exacerbation (95% CI: 0.532, 0.895).

This meta-analysis suggests that using FeNO to guide treatment decisions has little clinical benefit, although may result in a decrease in asthma exacerbations. Our findings support the use of guideline-based asthma management and diagnosis.

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Abbreviations: CI = confidence interval, FeNO = fraction of exhaled nitric oxide, FEV_1 = forced expiratory volume in 1 second, ICS = inhaled coritcosteroids, IQR = interquartile range, NO = nitric oxide, SD = standard deviation.

INTRODUCTION

The monitoring and treatment of asthma in children is often based on the presence of symptoms associated with airway hyperresponsiveness, airway inflammation, and variable airflow obstruction.[1] Inhaled coritcosteroids (ICS) are the treatment of choice for treating asthma but do not always provide good asthma control.[1] Clinical studies indicate that asthma outcomes can be improved when airway inflammation is considered that can result in reduced ICS use, lower rate of exacerbations, improved lung function, and reduced airway hyperresponsiveness.[2–6]

There are several biomarkers that are used to monitor airway inflammation and include eosinophils in induced sputum and the fraction of exhaled nitric oxide (FeNO). Because, at least in part, of the fact that it is easy to assess and is an inexpensive assay, FeNO measurements are increasingly used to diagnose asthma and guiding treatment.[7–10] Increases in FeNO are associated with deterioration in asthma control and the levels drop in a dose-dependent fashion with anti-inflammatory treatment.[9,11] However, some studies have found that FeNO values do not always correlate with markers of eosinophilic airway inflammation, and FeNO is typically elevated in only patients with atopic asthma and positively correlates with the number of sensitizations in nonasthmatic children.[12–17] Moreover, corticosteroids may dissociate the relationship of FeNO with inflammation since corticosteroids inhibit the expression of the nitric oxide (NO) synthases.[12]

The ambiguity of the association of a direct relationship of airway inflammation and asthma in all children raises the question of the value of using FeNO to tailor the dose of corticosteroids in treating asthma. Only a limited number of randomized controlled studies have assessed the benefit of monitoring FeNO to guide asthma treatment decisions. The aim of this meta-analysis was to assess whether follow-up FeNO monitoring gave additional benefit over guideline-based management of treating children with asthma.

MATERIAL AND METHODS

Search Strategy

PubMed and Cochrane CENTRAL databases were searched until November 2013 for randomized control trials that investigated the use of FeNO compared with treatment guidelines in monitoring and treating children with asthma. Studies were identified using the following search terms: asthma, FeNO, nitric oxide, management, and randomized controlled trials. Included studies had at least 2 intervention groups: one that utilized FeNO and the other that utilized conventional or standard methods (eg, spirometry, symptoms, and others) to guide treatment. Single-arm studies, non-English publications, published letters, editorials, and case reports were excluded from the analysis. The list of potential studies was

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screened by 2 independent reviewers and a third resolved any disagreements.

Data Extraction and Analysis

The following information was extracted from the included studies: name of first author, type of study (ie, single or double-blind), number of patients, age, gender, length of treatment, and length of follow-up posttreatment.

The main outcomes for this analysis included FeNO value (ppb), percentage of predicted forced expiratory volume in 1 second (FEV_1), dose of inhaled corticosteroids (ICS) (mcg or μg), and percentage of patients with >1 exacerbations. For FeNO, FEV_1, and ICS dose, values were transformed to mean ± standard deviation (SD) since in the original studies they were reported in multiple ways, that is, SD, median (interquartile range [IQR]: 1st quartiles, 3rd quartiles), mean (range: minimum, maximum), or median (range: minimum, maximum), using the methods of Hozo et al.[18] For continuous variables, the difference in change from baseline between FeNO and control groups was compared following treatments. The standardized (Std) difference (diff) in mean change with corresponding 95% confidence interval (CI) was calculated for each individual study and for the studies combined; a Std diff in means of change in outcomes >0 indicated the FeNO group may have a greater change in the particular outcome than the control standard treatment group; a Std diff in means of change in outcomes <0 indicated the FeNO group may have a lower change in the particular outcome than the control standard treatment group; a Std diff in means of change in outcomes =0 indicated the change was similar between FeNO group and control standard treatment group. For percentage of patients with >1 asthma exacerbation, an odds ratio with 95% CI was determined for each study; an odds ratio >1 indicated that patients in FeNO group may have a greater chance of having an exacerbations after treatments than control group; inversely, an odds ratio <1 indicated that patients in FeNO group may have a lower chance of having an exacerbations after treatments than control group; odds ratio =1 indicated that patients in FeNO group or in control group may have a similar chance of having an exacerbations after treatments. A χ^2-based test of homogeneity was performed using Cochran Q statistic and I^2. I^2 illustrates the percentage of the total variability in effect estimates among trials that is due to heterogeneity rather than chance. Random-effects models of analysis was used if heterogeneity was detected ($I^2 > 50\%$), otherwise fixed-effects models were used. Pooled Std diff in means of change and event rates were calculated and a 2-sided P value <0.05 indicated statistical significance.

Sensitivity analysis was carried out for each outcomes using the leave-one-out approach. Publication bias was assessed by constructing funnel plots for ICS and exacerbation rates by Egger test. The absence of publication bias was indicated by the data points forming a symmetric funnel-shaped distribution and 1-tailed significance level $P > 0.05$ in the Egger test. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

RESULTS

The search identified 265 potential studies of which 252 were excluded for not being relevant to this analysis (Figure 1). The 13 remaining studies were fully evaluated for inclusion and 7 were excluded because of not being designed to utilize FeNO measurements to guide treatment (n = 4), the full text was not available (n = 1), and the patients were not children (n = 2). Six studies were included in the analysis.[4,5,19–22]

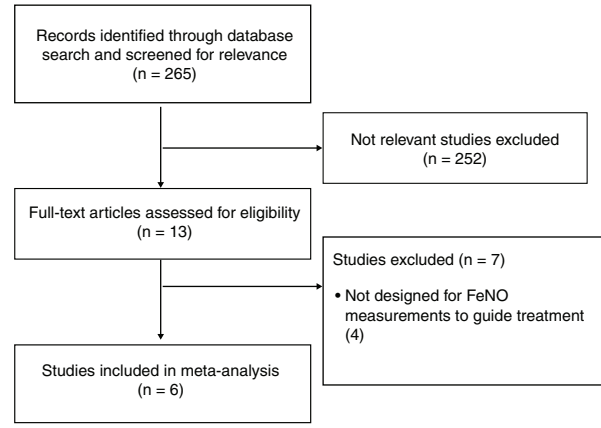


FIGURE 1. Flow diagram of study selection.

The 6 studies differed in their randomization procedures and in study design: 1 was an open-label,[19] 2 were single-blind,[5,20] and 3 were double-blind studies (Table 1).[4,21,22] The number of patients across the studies ranged from 22 to 276 in the FeNO groups (total = 507) and from 25 to 270 in the control groups (total = 511). Among the studies, the mean age of patients ranged from about 10 to 14 years in both the groups, and generally, more than half of the patients were male (Table 1). The length of treatment ranged from 24 weeks to 12 months and the posttreatment follow-up ranged from 24 weeks to 12 months (Table 1).

Overall, changes in FeNO and FEV_1 from baseline were similar between the FeNO and the control groups across the studies (Table 2). Four of the 6 studies found no difference between FeNO and control groups in ICS use; however, Peirsman et al[20] and Szefler et al[22] found that the FeNO cohort was associated with higher ICS use than the control groups ($P \leq 0.016$). In 3 of the studies,[4,19,20] the FeNO group was associated with lower rates of exacerbations than in the control groups.

FeNO Evaluation

Three[19–21] of the 6 included studies had reported sufficient information for FeNO to determine the change from baseline in FeNO between the FeNO and the control groups (Table 2). The data from Szefler et al[22] were only presented in a figure as geometric mean that precluded the study from being included in the analysis. A fixed effects analysis was applied because there was no evidence of heterogeneity among the studies (Q statistic = 1.51, $I^2 = 0\%$, $P = 0.471$). The Std diff in means of change of FeNO was similar between the FeNO and the control groups (Std diff in means of change of FeNO = −0.10; 95% CI: −0.31, 0.12; $P = 0.369$) (Figure 2A).

Percent FEV_1

Four of the studies[4,19,20,22] reported FEV_1 at both baseline and final visit for the FeNO and the control groups, and hence were used for analysis. A fixed-effects analysis was applied as there was no evidence of heterogeneity among the studies (Q statistic = 0.360, $I^2 = 0\%$, $P = 0.948$). The Std diff in means of change of FEV_1 % was similar between the FeNO and the

TABLE 1. Baseline Characteristics Among Studies

1st Author (Year)	Type of Study	FeNO Group: Number of Patients	FeNO Group: Age, Mean ± SD, y	FeNO Group: Sex, Males (n, %)	Control Group: Number of Patients	Control Group: Age, Mean ± SD (yrs)	Control Group: Sex, males (n, %)	Length of Treatment	Length of Follow-Up After Treatments
Peirsman (2013)	Single-blind RCT	49	10.6 ± 2.2	33 (67%)	50	10.7 ± 2.1	33 (66%)	NA	52 wk
Pike (2012)	Double-blind RCT	44	10.51 ± 2.62	21 (47.7%)	46	11.42 ± 2.69	30 (65.2%)	12 mo	12 mo
de Jongste (2009)	Open label RCT	77	11.6 ± 2.6	46 (60%)	74	11.8 ± 4.3	54 (73%)	30 wk	30 wk
Szefler (2008)	Double-blind RCT	276	14.4 ± 2.1	146 (53%)	270	14.4 ± 2.1	142 (53%)	46 wk	46 wk
Fritsch (2006)	Single-blind RCT	22	11.3 ± 3.4	14 (64%)	25	12.1 ± 2.8	14 (56%)	24 wk	24 wk
Pijnenburg (2005)	Double-blind RCT	39	11.9 ± 2.9	25 (64%)	46	12.6 ± 2.8	30 (65%)	12 mo	12 mo

NA = not available, RCT = randomized controlled trial, SD = standard deviation.

TABLE 2. Summary of the Outcomes for Each Study

1st Author (Year)	Group	FeNO Value, ppb: Baseline	FeNO Value, ppb: Final Visit	FeNO Value, ppb: Change From Baseline	FEV_1, %: Baseline	FEV_1, %: Final Visit	ICS, mcg or μg: Baseline	ICS, mcg or μg: Final Visit	ICS, mcg or μg: Change From Baseline	Rate of Patients With Exacerbations ≥1, n (%)
Peirsman (2013)	FeNO	32.5 (13.8, 72.0)*	22.5 (17.5, 55)*		92.9 ± 12.2	93.9 ± 15.5	320 (160, 400)*		100 (0, 400)*	11 (23.9%)
	Control	27.5 (16.3, 47.3)*	27.5 (18.5, 57.5)*		89.0 ± 16.2	91.2 ± 12.3	320 (14, 400)*		0 (−200, 80)*	22 (47.8%)
Pike (2012)	FeNO			3.1 (−5.5, 11.6)†	87.2 ± 15.3		750 (400–1000)*	800 (400, 1000)*	0 (−200, 300)*	37 (84.1%)
	Control			3.3 (−8.5, 15.1)†	91.1 ± 13.2		800 (400–1000)*	500 (400, 1000)*	0 (−300, 0)*	38 (82.6%)
de Jongste (2009)	FeNO	27.5 (15.0, 54.0)*	33.8 (23.8)‡		88 ± 15	95 ± 14	400 (250, 1000)*	200 (0, 500)*		9 (11.7%)
	Control	32.0 (15.0, 59.0)*	38.8 (31.4)‡		88 ± 12	94 ± 14	400 (250, 600)*	200 (100, 500)*		12 (16.2%)
Szefler (2008)	FeNO	20.5 (11.5, 45.3)§	26.5 (25, 28)§		95.9 ± 15.5	96.3 ± 7	560 ± 40	550 ± 50		102 (37%)
	Control	19.7 (10.9, 38.0)§	27 (24, 30)§		95.7 ± 15.9	95.5 ± 6.7	550 ± 30	420 ± 40		118 (43.6%)
Fritsch (2006)	FeNO	34.6 (17.5, 58.6)*			101 (91.1, 107.5)*		230 (100, 400)*	316 (200, 500)*		17 (18.2%)
	Control	31 (20.8, 54.8)*			93.7 (83.8, 99.6)*		140 (0, 400)*	241 (26, 607)*		22 (21.2%)
Pijnenburg (2005)	FeNO	26.4 (5.6, 134.9)§	25.1 (2.7)‡		96 ± 14	100.3 ± 13.74	762 ± 335	935 ± 655.7		8 (20.5%)
	Control	29.8 (3.1, 117.5)§	36.7 (4.5)‡		99 ± 20	100.3 ± 15.6	746 ± 410	910 ± 678.2		18 (39.1%)

*Median (IQR: Q1, Q3). †Mean (95% CI). ‡Mean ± SD. §Geometric mean (95% CI). CI = confidence interval, FeNO = fraction of exhaled nitric oxide, FEV_1 = forced expiratory volume in 1 second, ICS = inhaled coritcosteroids, IQR = interquartile range.

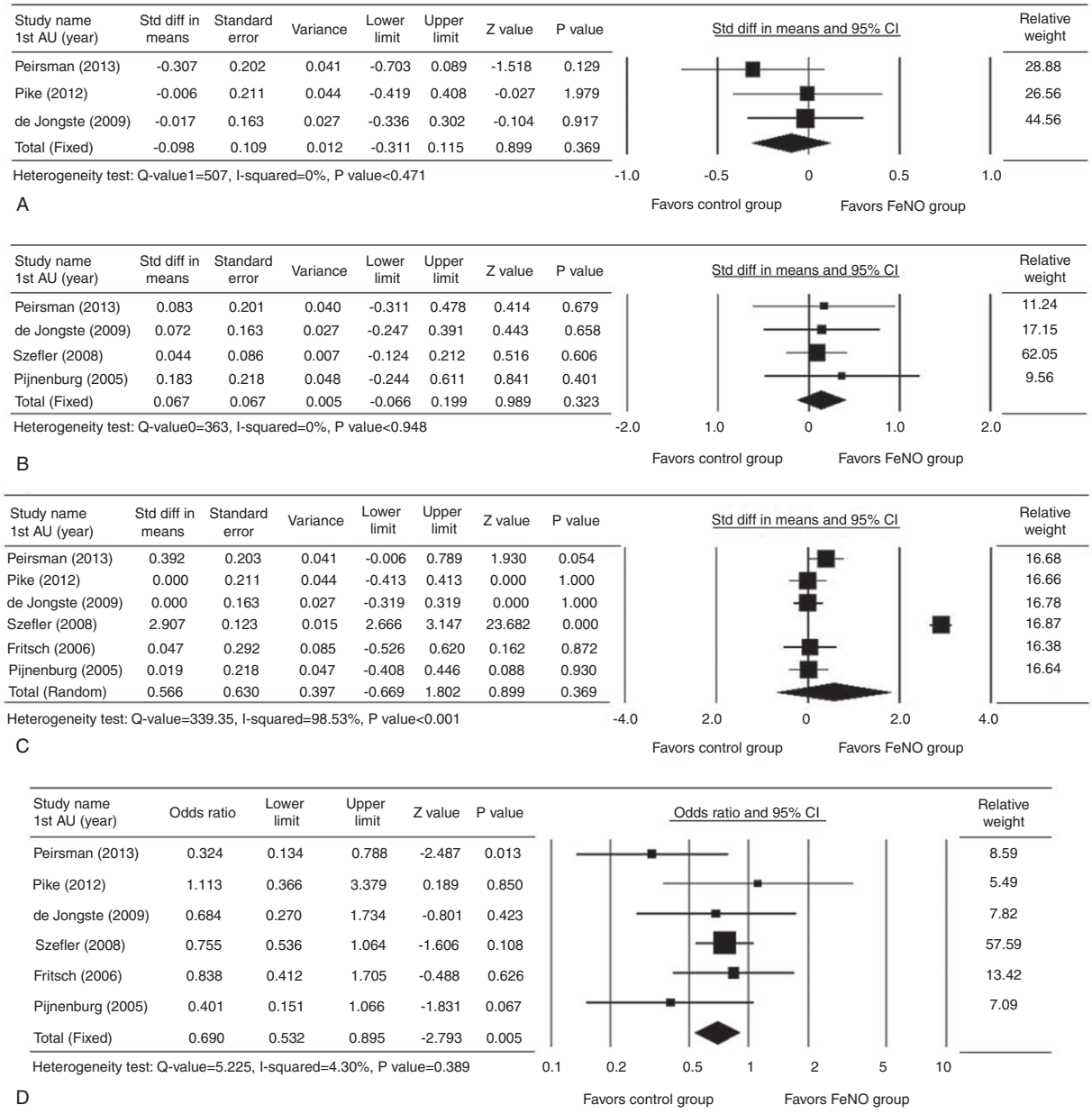


FIGURE 2. Forest plot evaluating the (A) FeNO value, (B) FEV_1 %, (C) ICS value, and (D) rate of exacerbations ≥1 represented for participants between FeNO and control groups. 1st AU = first author, CI = confidence interval, FeNO = fraction of exhaled nitric oxide, FEV_1 = forced expiratory volume in 1 second, Lower limit = lower bound of the 95% CI, Std diff = standardized difference, Upper limit = upper bound of the 95% CI.

control groups (Std diff in means of change of FEV_1 % = 0.07, 95% CI: −0.07, 0.20; $P = 0.323$) (Figure 2B).

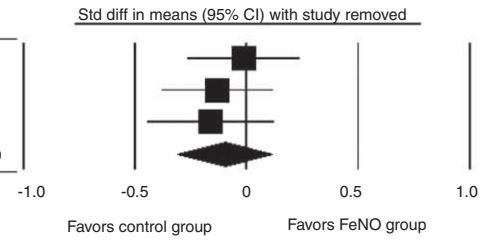
ICS Use

All 6 studies presented both baseline and final visit ICS dose and consequently were used in the analysis. A random-effects analysis was applied since there was evidence of heterogeneity among the studies (Q statistic = 339.35, $I^2 = 98.35\%$, $P < 0.001$). The Std diff in means of change of use of ICS indicated that the FeNO group may be associated with greater ICS use than the control group, although this did not reach statistical significance (Std diff in means of change of use of ICS = 0.57, 95% CI: −0.67, 1.80; $P = 0.369$) (Figure 2C).

Percentage of Subjects >1 Asthma Exacerbation

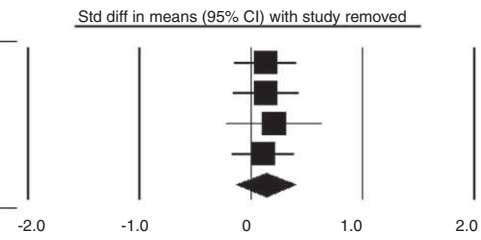
All the 6 studies reported the percentage of patients that had >1 exacerbation during the study and hence were used in this analysis. Since there was no evidence of heterogeneity among the studies (Q statistic = 5.225, $I^2 = 4.30\%$, $P = 0.389$), a fixed-effects analysis was used. The overall event rate of patients experiencing >1 asthma exacerbations over the time courses studied was significantly lower for the FeNO group

Removed study 1st AU (year)	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z value	P value
Peirsman (2013)	-0.013	0.129	0.017	-0.265	0.240	-0.099	0.921
Pike(2012)	-0.131	0.127	0.016	-0.380	0.118	-1.033	0.302
de Jongste (2009)	-0.163	0.146	0.021	-0.449	0.123	-1.114	0.265
Total (Fixed)	-0.098	0.109	0.012	-0.311	0.115	-0.899	0.369



A

Removed study 1st AU (year)	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z value	P value
Peirsman (2013)	0.065	0.072	0.005	-0.076	0.205	0.902	0.367
de Jongste (2009)	0.066	0.074	0.005	-0.080	0.211	0.884	0.376
Szefler (2008)	0.103	0.109	0.012	-0.111	0.318	0.945	0.344
Pijnenburg (2005)	0.054	0.071	0.005	-0.085	0.193	0.766	0.443
Total (Fixed)	0.067	0.067	0.005	-0.066	0.199	0.989	0.323



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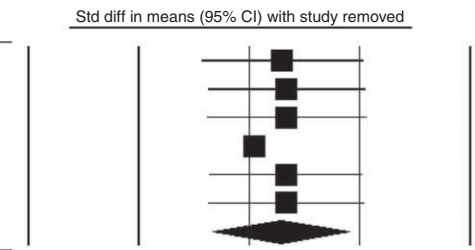
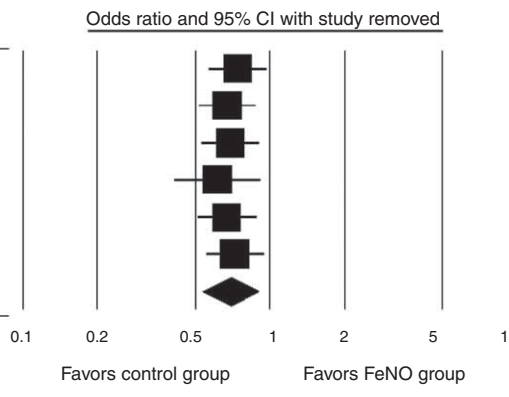
Removed study 1st AU (year)	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z value	P value
Peirsman (2013)	0.600	0.750	0.562	-0.869	2.070	0.801	0.423
Pike (2012)	0.679	0.724	0.525	-0.741	2.099	0.937	0.349
de Jongste (2009)	0.680	0.735	0.541	-0.762	2.121	0.924	0.355
Szefler (2008)	0.089	0.092	0.009	-0.092	0.270	0.966	0.334
Fritsch (2006)	0.668	0.710	0.505	-0.724	2.060	0.940	0.347
Pijnenburg (2005)	0.675	0.724	0.524	-0.744	2.094	0.933	0.351
Total (Random)	0.566	0.630	0.397	-0.669	1.802	0.899	0.369



C

Removed study 1st AU (year)	Odds ratio	Lower limit	Upper limit	Z value	P value
Peirsman (2013)	0.741	0.564	0.973	-2.159	0.031
Pike (2012)	0.671	0.514	0.877	-2.919	0.004
de Jongste (2009)	0.691	0.527	0.906	-2.676	0.007
Szefler (2008)	0.611	0.410	0.911	-2.418	0.016
Fritsch (2006)	0.670	0.506	0.886	-2.810	0.005
Pijnenburg (2005)	0.719	0.549	0.942	-2.392	0.017
Total (Fixed)	0.690	0.532	0.895	-2.793	0.005



D

FIGURE 3. Sensitivity analysis of the influence of each study on the pooled estimate for (A) FeNO value, (B) FEV_1 %, (C) ICS value, and (D) rate of exacerbations ≥1. The leave-one-out approach was used. 1st AU = first author, CI = confidence interval, FENO = fraction of exhaled nitric oxide, FEV_1 = forced expiratory volume in 1 second, Lower limit = lower bound of the 95% CI, Std diff = standardized difference, Upper limit = upper bound of the 95% CI.

compared with the control groups (odds ratio = 0.690, 95% CI: 0.532, 0.895; $P = 0.005$) (Figure 2D).

Sensitivity Analysis and Publication Bias

Sensitivity analysis was performed using leave-one-out approach for the different outcomes that we assessed. The findings did not significantly differ when each study was left out in turn (Figure 3) except for exacerbations in which the findings were significantly influenced by the removal of each study ($P = 0.005$) (Figure 3D).

We evaluated the possibility of publication bias for the use of ICS and the percentage of patients who experienced >1 asthma exacerbation. We did not evaluate FeNO or FEV_1 as >5

studies are required to detect funnel plot asymmetry.[23] Publication bias was apparent for ICS use ($t = 2.55$, 1-tailed $P = 0.032$) (Figure 4A) but was not present for the proportion of patients experiencing >1 asthma exacerbation ($t = 0.77$, 1-tailed $P = 0.244$) (Figure 4B).

DISCUSSION

This meta-analysis assessed whether incorporation of FeNO with guideline-based management added benefit in monitoring and treating children with asthma. Six studies were included in the analysis in which subjects were randomized into 2 groups: one in which asthma therapy (eg, ICS, long-acting bronchodilators, and others) was altered according to FeNO levels along with conventional monitoring or conventional monitoring alone. Our analysis found that monitoring FeNO to adjust treatment did not have a meaningful impact on FeNO levels, FEV_1, or ICS dose. However, there was a lower frequency of >1 asthma exacerbation over the time frames studied in the FeNO group compared with the conventional group. A caveat to the interpretation of the exacerbation findings is that sensitivity analysis indicated the removal of any one of the studies influenced the findings, although the directionality of the findings did not change. Our findings suggest that there is limited benefit in advocating the routine use of FeNO in guiding treatment for children with asthma.

Prior meta-analyses have also indicated that using FeNO to tailor treatment intervention adds little benefit in managing pediatric asthma.[24–26] One meta-analysis that included 4 studies (2 adult and 2 pediatric) with 356 randomized patients found that there was no difference between the groups whose treatments were tailored using FeNO compared with traditional methods in regard to ICS use or frequency of asthma exacerbations.[24] They did find in a post hoc analysis that the mean daily dose of ICS per adult was increased in the FeNO group. Another meta-analysis that included 9 studies (5 adult and

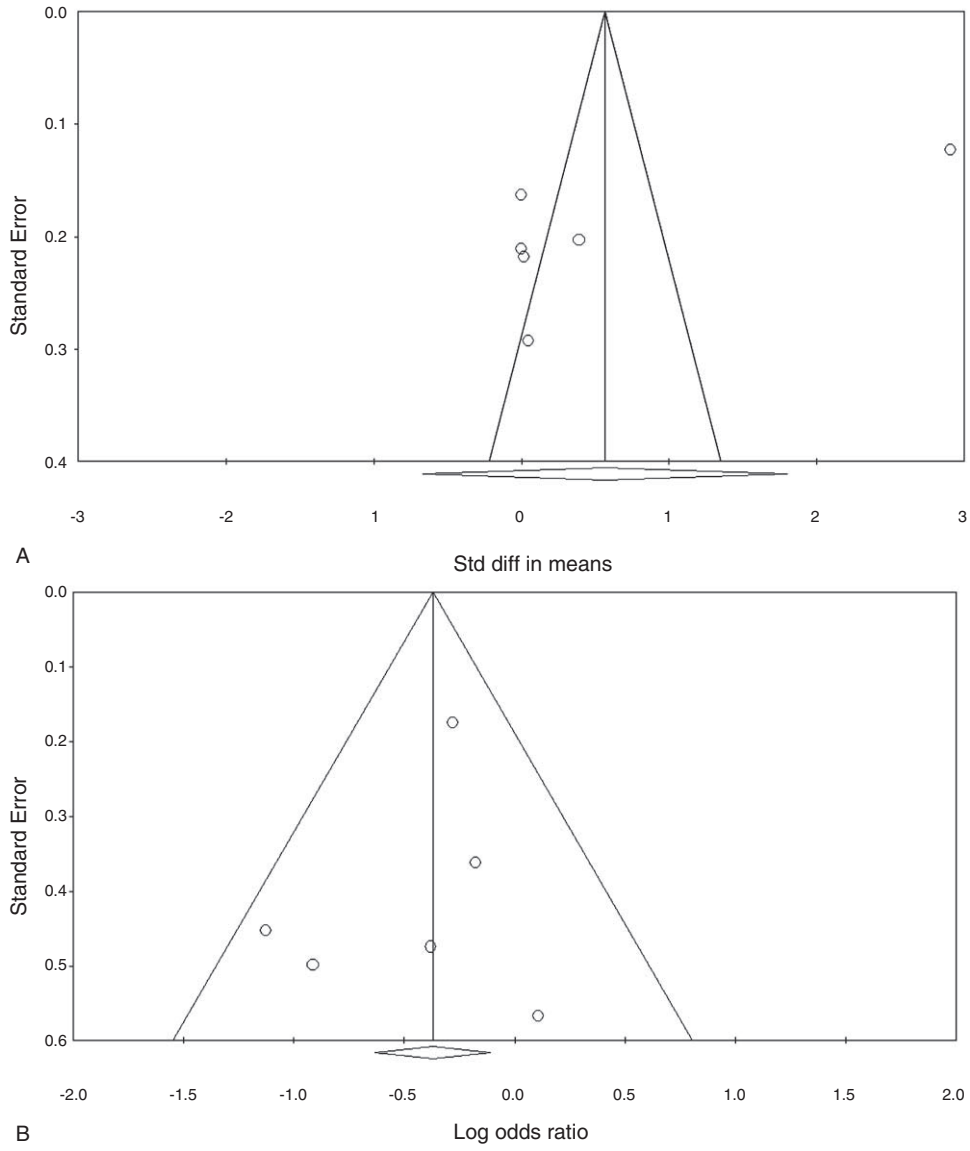


FIGURE 4. Funnel plots for (A) ICS value and (B) rate of exacerbations ≥1 among the studies.

4 pediatric) and 1299 subjects (389 children) found no difference in ICS dose between the group of subjects whose treatment was guided by FeNO compared to the groups whose treatment was based primarily on clinical symptoms.[26] However, in children/adolescence, they found a lower frequency of exacerbations in the FeNO group, although this did not reach statistical significance and came at the expense of increased ICS use.[26] They found no difference between the groups in FEV_1, symptom score, airway hyperresponsiveness, and β-agonist use.[26] The statistical significant lower rate of exacerbations with FeNO monitoring seen in our study may reflect that our population consisted entirely of children as well as differences in study designs across the included studies.

Jartti et al[25] performed a meta-analysis that evaluated the clinical value of FeNO in the management of pediatric asthma. Their meta-analysis used 4 studies,[4,5,19,22] all of which were included in our meta-analysis. They found that FeNO monitoring compared with conventional asthma monitoring was associated with increased dose of ICS, a decrease in FeNO, but had no meaningful influence on FEV_1 and did not alter the rate of exacerbations.[25] The discrepancy between our analysis and that of Jartti et al[25] may reflect differences in the studies included in evaluating each outcome. For example, we also included ICS values and frequency of asthma exacerbations from the study by Peirsman et al[20] and Pike et al[21] that likely influenced the findings. The frequency of asthma exacerbations was particular high (84.1% and 82.6% for the FeNO and the control groups, respectively) in the study by Pike et al[21] compared with the other studies where the frequency ranged from about 12% to 48%. It is not clear why the exacerbation rate was so high in the study by Pike et al.

The 6 pediatric studies included in our analysis varied in study design including where FeNO was measured. For example, de Jongste et al[19] had the subjects assess their FeNO at home while the others evaluated in the clinic. Also, some of the values used in this meta-analysis, as well as earlier ones,[25] were extrapolated from figures likely causing differences in the values used in a given analysis. Other factors that may have influenced the findings are the percentage of subjects in each study who had atopic asthma, as there is an association of atopic asthma and increased FeNO.[1] In addition, height, age, sex, nasal inflammation, respiratory tract infection, and medications also influence FeNO levels.[25] The difference among the studies in regard to these factors may have confounded the results. Specific phenotypes of patients that may benefit from FeNO is not well studied and well-designed clinical studies are needed to address this issue. Finally, we did not assess whether monitoring FeNO levels could be useful for different stages of asthma. It was not possible to address this question because of the fact that the number of studies included and asthma stages investigated were too small. Also the guidelines used for diagnosing the stage of asthma differed across the studies that would have resulted in a large degree of heterogeneity in the data.

In summary, our meta-analysis suggests that using FeNO to guide treatment decisions has little clinical benefit. Our findings support the use of guideline-based asthma management and diagnosis, and that clinicians should be aware of confounding factors that may influence FeNO levels.

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