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Effectiveness of Fractional Exhaled Nitric Oxide for Asthma Management in Children: A Systematic Review and Meta-analysis

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ppul.24898.

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(I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: Xia Wang and Xiangsheng Tan; (IV) Collection and assembly of data: Xia Wang and Xiangsheng Tan; (V) Data analysis and interpretation: Xia Wang and Xiangsheng Tan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Keywords: Fractional exhaled nitric oxide; asthma; children; airway inflammation; meta-analysis

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Abstract

Background: Fractional exhaled nitric oxide (FENO) is a non-invasive strategy for diagnosing and managing asthma, but limited evidence is available for the effects of FENO-guided asthma management in children. This meta-analysis aimed to evaluate the effectiveness of fractional exhaled nitric oxide for asthma management in children.

Methods: In total, 6 databases were searched, and 23 randomized controlled trials that compared the effects of FENO-guided asthma management with those not using FENO in pediatric asthma were included. Methodological quality was assessed using the Cochrane risk-of-bias tool. Data for relevant endpoint were extracted and analyzed.

Results: Our meta-analysis of the effectiveness of fractional exhaled nitric oxide for asthma management in children showed that FENO-guided asthma management helped reduce the numbers of children with asthma exacerbations (risk ratio (RR) 0.73, 95% confidence interval (CI) 0.63 to 0.84; $P < 0.0001$) and the exacerbation frequency (standardized mean difference (SMD) -1.57, 95% CI -2.25 to -0.88; $P < 0.00001$). Furthermore, it improved the predicted forced

expiratory volume in 1 minute (FEV1%pred) (weighted mean difference (WMD) 3.67, 95% CI 0.91 to 6.43; P = 0.009), and was also found to be associated with an increase of daily inhaled corticosteroid (ICS) dose (WMD 64.17μg，95% CI 53.59 to 74.75; P < 0.00001).

Conclusions: This meta-analysis indicated that the FENO-guided asthma management strategy could partially improve the outcomes of pediatric asthma at the expense of increased ICS use.

1 | INTRODUCTION

Asthma is a heterogeneous disease that is characterized by chronic airway inflammation. It is defined by a history of respiratory symptoms including wheezing, shortness of breath, chest tightness, cough varying in intensity over time, and variable expiratory airflow limitation.[1] The prevalence of asthma in children varies across different countries, but shows a globally increased incidence.[2] In China, three epidemiological surveys on pediatric asthma found that the prevalence has continued to increase at a rate of more than 50% every 10 years within the past 20 years.[3,4] Poorly controlled asthma can have a significant impacts on the quality of life of the affected individuals and their families and is costly to healthcare systems, putting considerable stress on health care providers and society.[5]

Traditional asthma management strategies have included question series for clinical assessment, diary cards, quality of life (QoL) questionnaires, along with measurements of peak flow, spirometry, and degree of airway hyperresponsiveness;[6] however, none of these accurately reflect airway inflammation. Fractional exhaled nitric oxide (FENO) is a non-invasive biomarker of airway inflammation that can be used for diagnosing and managing asthma and has been recommended by some scholars.[7-9] High levels of FENO in patients with asthma are correlated with eosinophilic airway inflammation, which usually responds well to inhaled corticosteroid (ICS) treatment compared with non-eosinophilic airway inflammation.[7] However, at present, the existing guidelines[1,8,10,11] offer no specific recommendation for routine FENO monitoring in pediatric asthma. The effectiveness of FENO-guided asthma management in children has been widely discussed in original studies and systematic reviews, but opinions still conflict. Some studies have suggested that FENO monitoring yields better asthma outcomes by reducing asthma exacerbations[12-15] and ICS dosage,[7] while improving lung function,[16] symptoms and airway responsiveness.[17] However, some scholars have remained skeptical of these conclusions or oppose this view.[18,19] This lack of consensus can be partially attributed to the small sample sizes of the relevant studies and reviews, making outcomes difficult to gauge

accurately. Therefore, more comprehensive evidence for FENO monitoring in pediatric asthma is urgently needed.

The aim of this systematic review and meta-analysis was to summarize the evidence and evaluate the effectiveness of fractional exhaled nitric oxide for asthma management in children. The findings from this study are expected to provide insight into the clinical management of children with asthma.

2 | METHOD

This meta-analysis was prepared in compliance with the Cochrane Handbook for Systematic Reviews of Interventions and reported according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement.[20]

2.1 | Search strategy

Two researchers (X Wang and X Tan) comprehensively searched the following electronic databases from their start date to March 31, 2020: PubMed, Web of Science, Cochrane Library, China Biology Medicine (CBM) Database, and China National Knowledge Infrastructure (CNKI), and Wanfang Data. Google Scholar was also searched for any relevant articles. In addition, reference lists of relevant systematic reviews were searched for further potential studies. The detailed search strategy can be found in ***Appendix 1***.

2.2 | Eligibility of studies

We included all studies of randomized controlled trials (RCTs) that compared the effects of FENO-guided asthma management with those of non-FENO management methods that used clinical symptoms, spirometry and asthma guidelines. Conference articles, reviews, case reports, duplicates, and non-English- or Chinese-language texts were excluded, along with literature with only partial text available or missing data.

We included research on child patients (age < 18 years old) diagnosed with asthma, with no restrictions on gender, race, and geographical location or setting. Asthma was defined according to the published guidelines.[1,11] Patients with the following comorbidities were also excluded: asthma-related to an underlying pulmonary disease such as bronchiectasis, bronchiolitis obliterans, and chronic obstructive pulmonary disease; and asthma-related to certain drugs, or diagnosed as bronchitis-induced wheezing illness and eosinophilic bronchitis.

The primary outcomes were asthma exacerbations and inhaled corticosteroid dose. Asthma exacerbations were defined as any types including patients needing oral steroids, asthma-related hospitalization, asthma-related emergency admission, asthma-related school missed or off-scheduled visit, increase of asthma symptoms and decline of lung function. The secondary outcomes included asthma symptoms

(as determined by the Asthma Control Test (ACT), Children Asthma Control Test (C-ACT), or Asthma Severity Score (ASS)); quality of life (as determined by the Pediatric Asthma-Related Quality of Life Questionnaire, PAQLQ); short-acting beta2-agonists (SABA) courses; and lung function. The priority of outcomes was adjusted for different studies if necessary.

2.3 | Selection of studies

After eliminating duplicates, two researchers (X Wang and X Tan) independently screened the titles, abstracts, and potentially relevant full-texts by using the predefined criteria, and any discrepancies were discussed. Prior to the formal selection, a training exercise of a random sample of 100 references was conducted. All reasons for the exclusion of ineligible studies were recorded, and the process of study selection was documented using a PRISMA flow diagram.

2.4 | Data extraction

The two researchers (X Wang and X Tan) independently extracted data by using a standard sheet, and any disagreement was resolved by consensus. Pilot-test was conducted to check the applicability and comprehensiveness of the extraction sheet. The following data were extracted: 1) basic information, including title, authors, publication year, funding, study design, study sample size, participants' characteristics; 2) details of the intervention and control strategies; 3) outcomes,

including those of continuous data, means, standard deviations (SD) or interquartile range (IQR), while dichotomous data was used for the number of events.

2.5 | Quality assessment of included studies

The two researchers (X Wang and X Tan) independently performed bias assessment of included studies, and any disagreements were resolved by discussion. We used the Cochrane risk-of-bias tool[21] which consists of 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases. We graded the risk of bias of each domain as “low”, “unclear”, or “high”, and the overall risk of bias within each study was based on the combined results of the individual domains.

2.6 | Statistical analysis

We conducted a meta-analysis of outcomes for which the data were sufficiently compatible. Otherwise, a qualitative synthesis was performed. For dichotomous data, we analyzed risk ratios (RR) with 95% confidence intervals (CI); for continuous data, we analyzed weighted mean difference (WMD) or standardized mean difference (SMD) with 95% CI. A random-effects model or fixed-effects model was used, and data were processed according to the Cochrane Handbook for Systematic Reviews of Interventions.[20] A P value < 0.05 was considered to be

statistically significant. Heterogeneity was assessed by forest plot and I^2 statistic, with values higher than 50% indicating substantial heterogeneity. Subgroup analysis was conducted to assess possible sources of heterogeneity. Significant heterogeneity between subgroups indicated that the subgroup factor could explain part of the total heterogeneity. Sensitivity analysis was carried out to check the stability and reliability of the merged effects. All statistical analyses were performed by using Review Manager 5.3[22] and Stata 15.1 software.[23]

3 | RESULTS

3.1 | Search results

In total, 4185 records were identified from the databases, 1509 duplicates were excluded, and 2676 records were considered to be potentially relevant. After screening the titles, abstracts, and full texts, a total of 23 eligible studies were finally included (***Appendix 2***).

3.2 | Characteristics of included studies

This meta-analysis included 23 RCTs comprising 2723 pediatric patients with asthma (1360 in the intervention group vs. 1363 in the control group). All studies were carried out between 2005 and 2020. Eleven studies were presented in English;[6,7,13,17-19,24-28] the remaining studies were presented in Chinese.[16,29-39] The

age of patients ranged from 0.6 to 16.5 years. Sample sizes ranged from 41 to 546. The severity of asthma ranged from mild to severe. Most of the studies evaluated lung function and FENO at baseline. The baseline values of predicted forced expiratory volume in 1 minute (FEV1%pred) were beyond 80% in most studies, and 2 were below 80%.[7,29] Median of FENO baseline levels ranged from 13.78 ppb to 77.4 ppb, and there was no statistical difference in baseline between groups. The median frequency of FENO assessment was about 2.75 months. Strategies of asthma management were based on symptoms, spirometry, need for rescue treatment, exacerbations, activity, and guidelines for the control group compared with FENO-guided alone or plus any of the above for the intervention group. The duration of intervention ranged from 3 months to 2 years. More details are shown in ***Appendix 3*** and ***Appendix 4***.

3.3 | Methodological quality

The quality of the literature was variable. Overall, only one study was rated low risk of bias on every domain,[6] nine studies were rated as high risk of bias,[7,19,24,26-29,35,38] and the remaining were rated as unclear risk of bias, which including nine Chinese articles and four English articles. There was considerable uncertainty concerning selective bias and performance bias since the majority of studies did not provide sufficient information to judge the potential bias on any of these domains. The details of methodological quality are shown in Fig.1.

3.4 | Effectiveness evaluation

3.4.1 | Exacerbation

Twenty studies provided some data on asthma exacerbations, using a wide variety of definitions. Studies with similar definitions were grouped in the following meta-analysis or qualitative synthesis.

Eight trials (n = 1167 patients) reported the effects of FENO monitoring on the numbers of children with asthma exacerbations.[6,13,17,19,24,25,27,28] The meta-analysis showed that FENO-guided asthma management versus control could significantly reduce the proportion of children with asthma exacerbations (RR = 0.73, 95% CI 0.63 to 0.84, P < 0.0001, I^2 = 61%) (Fig.2). Five trials (n = 954 patients) reported the effects of FENO monitoring on exacerbation frequency (per person-year).[7,16,25,28,34] The meta-analysis showed a significantly lower frequency of asthma exacerbations in the FENO group (SMD = -1.57, 95% CI -2.25 to -0.88, P < 0.00001, I^2 = 94%) (Fig.3). Seven trials (n = 863 patients) compared the total exacerbations between the FENO group and control group,[26,30,32,33,35,36,39] but the data could not be merged for methodological reasons. Overall, no significant difference was observed except for one study,[36] which showed fewer total exacerbations in the FENO group (2 vs. 8, P < 0.05) (***Appendix 4***).

3.4.2 | Inhaled corticosteroids dose

Eighteen studies provided data on inhaled corticosteroids (ICS). Some data could not be merged due to using variable presentations and units of ICS. Thus, a total of seven trials (n = 773 patients) were included in the meta-analysis,[27,30,32,33,35,36,39] and the result showed that FENO-guided asthma management could significantly increase the daily dosage of ICS compared with control (WMD = 64.17μg， 95% CI 53.59 to 74.75, P < 0.00001, I^2=56%) (Fig. 4). In another six trials in which the outcome of ICS dose was presented as median and IQR, a significant increase of ICS dose was found in three of them (P < 0.05),[6,13,18] while no significant difference in the remaining trials was found[19,24,26] (***Appendix 4***).

3.4.3 | Symptom control

Fourteen trials reported the effects of FENO on asthma symptom control. Some data could not be merged due to variable scales. Thus, three trials (n = 240 patients) were included in the meta-analysis on the rate of symptom control,[30,31,38] and the result showed no significant difference between groups (RR = 1.09, 95% CI 0.99 to 1.20, P = 0.07, I^2= 70%) (Fig.5). Two trials (n = 136 patients) were included in a meta-analysis of the Asthma Severity Score (ASS).[25,37] The result showed no significant benefit of FENO-guided asthma management versus control in reducing the severity of asthma (WMD = -0.23, 95% CI -0.47 to -0.00, P = 0.05, I^2 = 0%)

(Fig.6). Moreover, three trials (n = 418 patients) indicated no statistical difference in the rate of symptom-free days between the FENO group and the control group (P > 0.05)[13,19,26] (***Appendix 4***).

3.4.4 | Other outcomes

For other outcomes, nine (n = 1508 patients) and six trials (n = 685 patients), reported the effects of FENO-guided asthma management on the end-point values of FEV1%pred[7,19,28-30,32,35,36,39] and time to SABA use,[30,32,33,35,36,39] respectively. Meta-analysis showed significantly higher values of FEV1%pred (WMD = 3.67, 95% CI 0.91 to 6.43, P = 0.009, I^2 = 94%) (Fig.7) in the FENO group, while no significant difference was found on the time to SABA use (WMD = 0.06, 95% CI -0.19 to 0.30, P = 0.65, I^2 = 0%) (Fig.8). Three trials (n = 380 patients) reported the effects of FENO on quality of life in children with asthma,[6,19,26] but no statistical difference was found between groups (P > 0.05). Two other studies showed a significant increase of leukotriene receptor antagonist use in the FENO group compared with control (P < 0.05)[13,18] (***Appendix 4***).

3.5 | Subgroup analysis and sensitivity analysis

There was significant heterogeneity of merged results in the numbers of children with asthma exacerbations, exacerbation frequency (per person-year), rate of

symptom control, and FEV1%pred. Subgroup analysis was conducted only in terms of intervention duration and the risk of bias, with limited information.

Duration of intervention

For exacerbation frequency, the overall SMDs of studies with intervention duration of 1 year[7,16,25,28] and those with intervention duration greater than 1 year[34] were –1.24 (95% CI –1.94 to –0.54, P < 0.00001, I^2 = 94%) and –3.11 (95% CI –3.88 to –2.35, P < 0.00001), respectively (Fig.3).

Risk of bias

For numbers of children with asthma exacerbations, the overall RRs of studies with low or unclear risk of bias[6,13,17,25] and those with high risk of bias[19,24,27,28] were 0.53 (95% CI 0.39 to 0.70, P < 0.0001, I^2 = 0%) and 0.82 (95% CI 0.70 to 0.96, P = 0.02, I^2 = 47%), respectively (Fig.2).

For the rate of symptom control, the overall RRs of studies with low or unclear risk of bias[30,31] and those with high risk of bias[38] were 1.01 (95% CI 0.93 to 1.10, P = 0.79, I^2 = 0%) and 1.47 (95% CI 1.06 to 2.03, P = 0.02), respectively (Fig.5).

For FEV1%pred, the overall WMDs of studies with low or unclear risk of bias[30,32,36,39] and those with high risk of bias[7,19,28,29,35] were 7.92 (95% CI 5.91 to

9.93, P < 0.00001, I^2 = 0%) and 0.33 (95% CI –2.05 to 2.72; P = 0.79, I^2 = 91%), respectively (Fig.7).

A sensitivity analysis was conducted for all merged outcomes. Results from the sensitivity analysis did not alter direction (***Appendix 5*****).**

4 | DISCUSSION

We conducted a systematic and comprehensive meta-analysis that included 23 studies to examine the effectiveness of FENO-guided asthma management in children with asthma. Numbers of children with asthma exacerbations, exacerbation frequency (per person-year), and FEV1%pred were significantly improved in the FENO group versus the control group, while the daily ICS dose was significantly increased. No added benefit was seen in symptom control, quality of life, and SABA courses. This meta-analysis showed that FENO-guided asthma management strategy could partially improve the outcomes of pediatric asthma at the expense of increased ICS use. The main novelty of this meta-analysis is the systematic review of the Chinese literature, which comprises 1119 patients of the pooled data.

Asthma exacerbation contributes substantially to asthma mortality and health care costs.[40] It is an essential prognostic factor of pediatric asthma according to the long-term goals of asthma management in the 2019 Global Initiative for Asthma

(GINA) guidelines.[1] Published articles have indicated that exacerbation should be regarded as the primary measurable outcome of asthma.[41] Our meta-analysis showed that FENO-guided asthma management could significantly reduce exacerbations. These results were also observed by previous systematic reviews.[12,14,15] The increased asthma exacerbations are reportedly caused by poorly controlled airway inflammation,[42] with the production of FENO by the inducible nitric oxide synthase (NOS) in the lower airways being upregulated when the airway inflammation occurs.[43] Thus, FENO could be a useful early predictor for asthma exacerbations. Furthermore, it has been demonstrated that a higher level of FENO is associated with a higher incidence of exacerbations.[44] Therefore, the FENO-guided strategy may be more effective in reducing asthma exacerbations by prompt and targeted adjusting anti-inflammatory therapy. However, some other studies have pointed out that for those with asthma with a lower risk of exacerbations, the FENO-guided strategy may not have a significant benefit in improving exacerbations, but rather simply increases the economic burden.[24,45] Several independent risk factors have been identified that could increase the patient's risk of exacerbations, including poor asthma symptom control, poor adherence, incorrect inhaler technique, a history of $\geqslant$ 1 exacerbation in the previous year, decreased lung function measurements, and chronic sinusitis.[40] Therefore, we suggest strengthening the monitoring of exacerbation risks in clinic,

and using the FENO-guided strategy as a key method of treatment adjustment in pediatric asthma patients at high risk of exacerbations.

ICS is considered to be one of the most vital drugs in the treatment of asthma, but severe adverse reactions may be caused by using long-term and high-dose ICS. Previous studies reported that FENO measurement appeared to help determine the inflammatory status of the airway and predict corticosteroid compliance, and thus could be used for guiding anti-inflammatory treatment in pediatric asthma.[7,8] Our meta-analysis showed that FENO-guided asthma management could significantly increase the daily dosage of ICS, which conflicts with results of Petsky's and Lu's meta-analyses, in which no difference in ICS use was found.[14,15] As described by treatment algorithms,[19,24-27] higher FENO levels could be used to increase ICS dose even when asthma was under control, but the ICS dose could not be reduced when FENO levels were lower unless every other asthma parameter was also controlled. Therefore, it is not surprising that a higher dosage of ICS could be found in the FENO group. It is uncertain, however, whether this increase causes any relevant adverse reactions in the long term. These indicate that caution should be taken when considering the use of FENO in ICS titration in pediatric asthma. Further, multicenter, large‐scale, and long-term randomized controlled trials of pediatric asthma are warranted to explore an evidence-based algorithm of FENO-guided

strategy in order to determine which cases are suited for down-titrating or up-titrating the ICS dose.

The condition of asthma control may be directly reflected by an asthma symptom, which is a subjective outcome. Poor symptom control is burdensome to quality of life and increases the risk of exacerbations. Our review showed no significant benefit of FENO-guided asthma management on symptom control compared with the control group. A relatively small sample size was included in the meta-analysis due to using variable scales. However, as such it is not surprising that FENO, which is a biomarker of airway inflammation that might be discordant with symptoms, was not found to be beneficial. Further, it may be necessary to not overemphasize the role of FENO levels in asthma symptoms control, and to pay more attention to children's subjective feelings in clinical practice.

Lung function always plays a vital role in asthma diagnosis and management. FEV1%pred has long been recommended as a marker of grading asthma severity.[1,46] Our meta-analysis showed higher end-point values of FEV1%pred in FENO group compared with control. The difference reached statistical significance. It has already been established that there is a negative correlation between the levels of FEV1%pred and asthma exacerbations. Thus, the levels of FEV1%pred were significantly improved as exacerbations in the FENO group decline.[47] As such a slight difference seems clinically insignificant. However, it's

worth noticing that lung function is a long-term prognostic indicator of pediatric asthma. A clinically significant effect of FENO-guided strategy on FEV1%pred might not be observed based on evidence of short-term RCTs.

Substantial heterogeneity was observed across the included studies. Duration of intervention, methodological quality, baseline severity of asthma, definitions of exacerbation, treatment algorithms, population, FENO cutoff values and atopy, might have contributed to the heterogeneity in the meta-analysis. Results from the sensitivity analysis did not alter direction. Thus, the conclusions in this review are still reliable. However, these factors should be considered, and a consistent methodology should be adopted in future research to decrease heterogeneity across studies and produce reliable results for evidence-based exploration.

There are several clear strengths in our research. First, this systematic review, to our knowledge, has the largest sample size involving a total of 2723 pediatric patients, for a study focusing on the effectiveness of fractional exhaled nitric oxide in pediatric asthma management. It can, therefore, be considered to constitute the best evidence for the management of pediatric asthma thus far. Second, a substantive discussion on the application of FENO-guided asthma management was undertaken and offers useful advice on how to apply FENO monitoring in clinical practice. Third, this meta-analysis included only RCTs, which limited the selection and observational bias. Fourth, a subgroup analysis was carried out to

explain the observed heterogeneity, and sensitivity analysis was conducted to check the stability and reliability of the results. Fifth, our meta-analysis was conducted and reported with strict adherence to the Cochrane handbook and PRISMA checklist. There are, however, some limitations to this analysis. First, most of included studies were rated as unclear risk of bias or high risk of bias, thus, caution is warranted in interpretation of our results to clinical practice. Second, potentially unknown publication bias was retained in the results, which we were unable to detect without additional information. Third, heterogeneity was detected in our meta-analysis for methodological diversity. Consequently, we look forward to future efforts and explorations in this field to overcome these deficiencies.

In conclusions, our meta-analysis of the effectiveness of fractional exhaled nitric oxide for asthma management in children indicates that FENO-guided asthma management helps reduce exacerbations and improve lung function, but is also associated with an increase of ICS dose. Based on the current evidence, we suggest strengthening the use of FENO monitoring in the treatment of pediatric asthma for individuals with high risks of exacerbations rather than using it as for the general asthma population.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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Figures

Fig.1: Risk of bias summary of included studies.

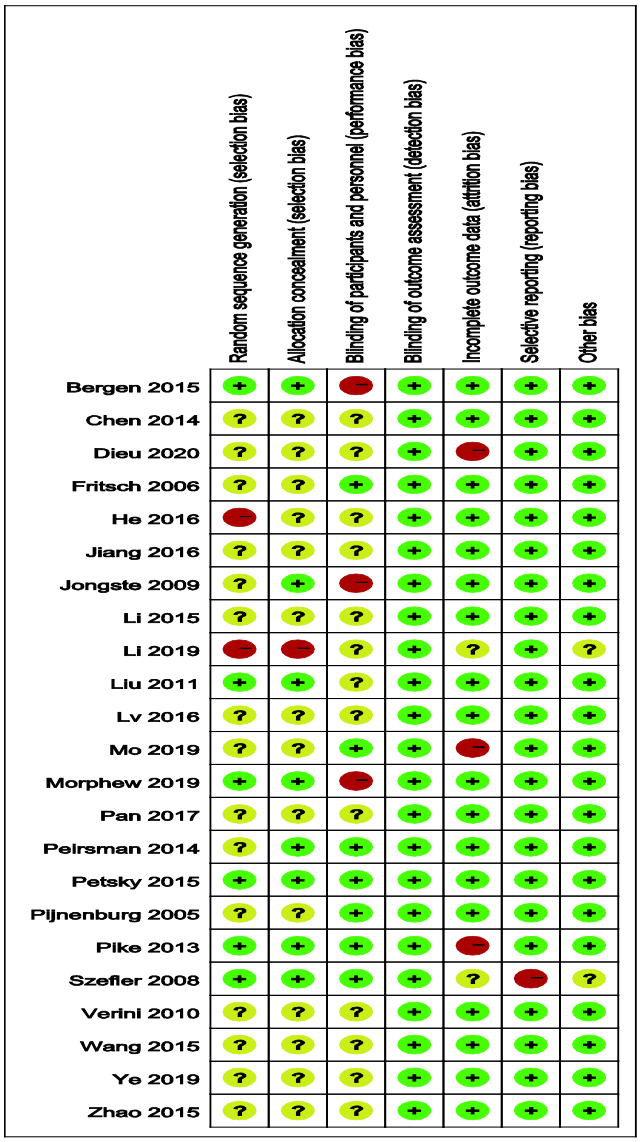

Fig.2: Forest plot comparing the effect of FENO versus control on the numbers of children with ≥1 asthma exacerbation. FENO: fractional exhaled nitric oxide.

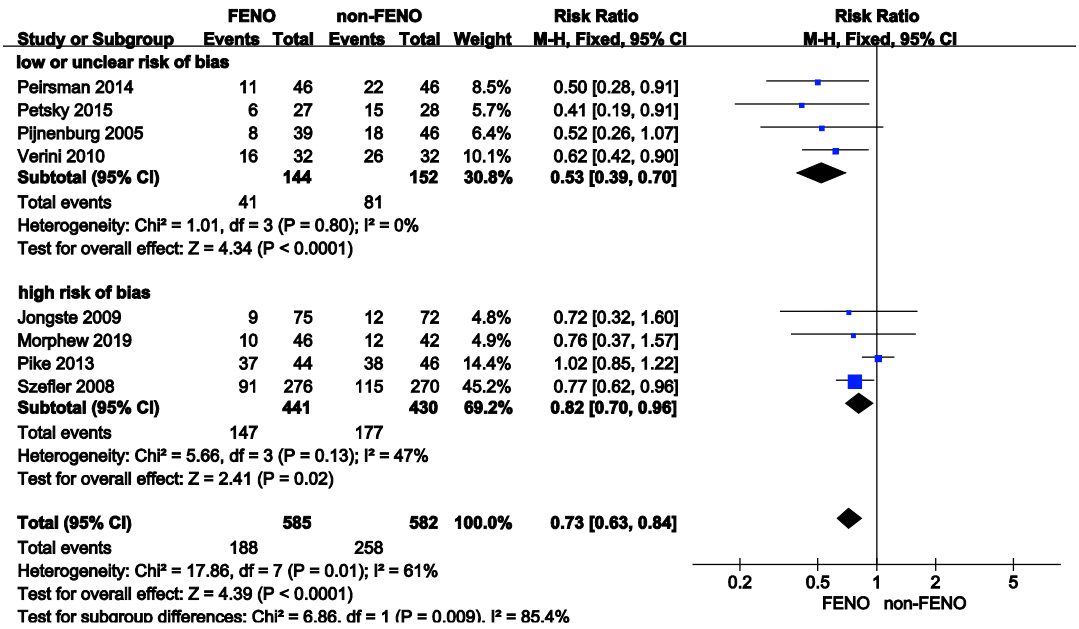

Fig.3: Forest plot comparing the effect of FENO versus control on exacerbation frequency (per person-year). FENO: fractional exhaled nitric oxide.

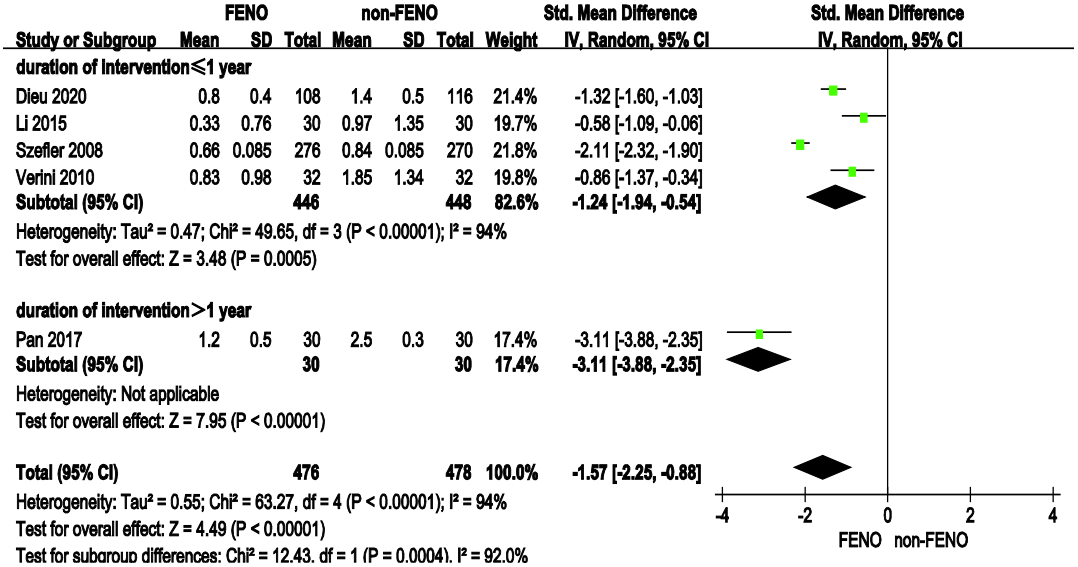

Fig.4: Forest plot comparing the effect of FENO versus control on daily ICS dose. FENO: fractional exhaled nitric oxide; ICS: inhaled corticosteroids.

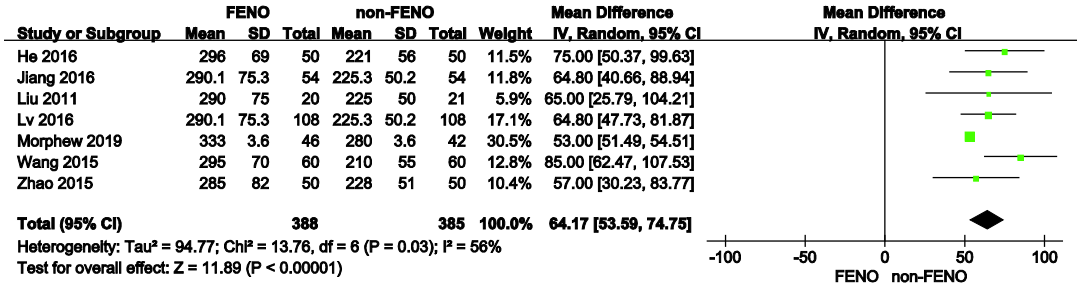

Fig.5: Forest plot comparing the effect of FENO versus control on the rate of symptom control. FENO: fractional exhaled nitric oxide.

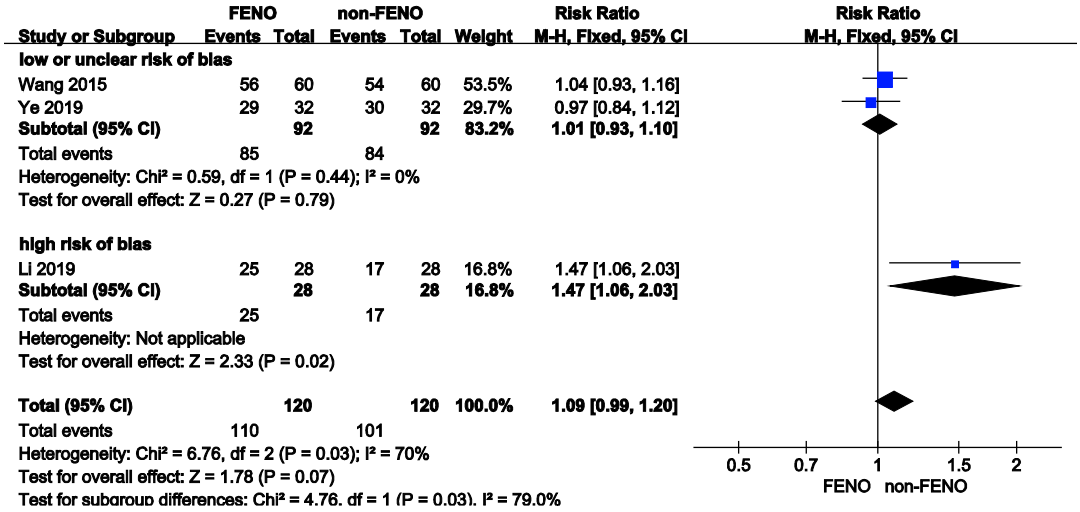

Fig.6: Forest plot comparing the effect of FENO versus control on Asthma Severity Score. FENO: fractional exhaled nitric oxide.

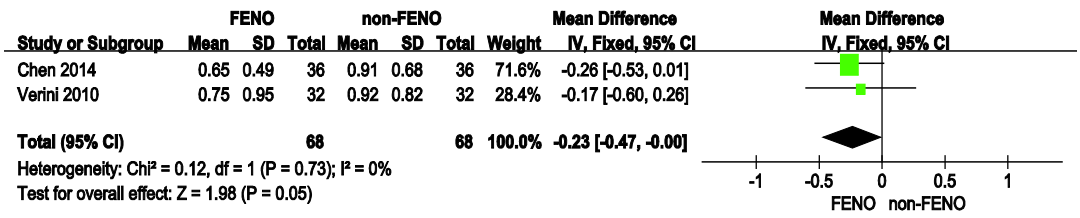

Fig.7: Forest plot comparing the effect of FENO versus control on end-point FEV1%pred. FENO: fractional exhaled nitric oxide; FEV1%pred: the percent predicted forced expiratory volume in the first second.

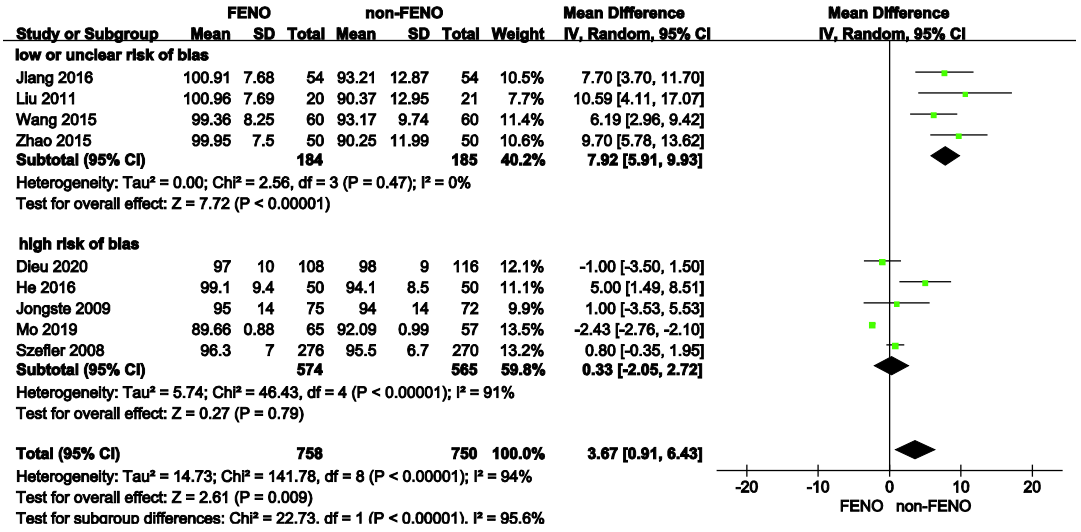

Fig.8: Forest plot comparing the effect of FENO versus control on time to SABA use. FENO: fractional exhaled nitric oxide; SABA: short-acting beta2-agonists.