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Review Article

Evaluation of the accuracy of FeNO in pediatric asthma diagnosis: a meta-analysis

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Abstract: Objective: FeNO measurement has frequently been used in asthma diagnosis. Thus, the present study aimed to evaluate the diagnostic accuracy of FeNO in children with asthma. Methods: Articles from PubMed, Embase, Web of Science, and ProQuest databases, up through January 30, 2018, were extracted for this systematic review and diagnostic meta-analysis. Quality of studies was evaluated by the QUADAS method. Sensitivity and specificity were estimated using a bivariate model. Moreover, summary receiver-operating characteristic (SROC) curves were calculated and publication bias was estimated with Deeks' funnel plot asymmetry test. Results: A total of 20 studies were selected for the present meta-analysis. No publication bias was found in selected studies. Overall sensitivity in the meta-analysis was 0.57 (95% CI: 0.47-0.67), overall specificity was 0.61 (95% CI: 0.46-0.75), and area under the SROC curve was 0.62 (95% CI: 0.57-0.66). Significant heterogeneity was found from Asian countries, cutoff values, study cases, and the model of control (P=0.0015). Conclusion: There appears to be dissatisfactory accuracy of FeNO concerning diagnosis of pediatric asthma. The results suggest that FeNO cannot be used as an independent biomarker for the diagnosis of asthma in children.

Keywords: FeNO, pediatric asthma, meta-analysis, diagnosis value

Introduction

Asthma is one of the most common breathing disorders affecting people, worldwide. It is characterized by airway inflammation and recurrent episodes of breathing difficulties [1, 2]. Of these clinical characteristics of asthma attacks, eosinophilic airway inflammation is one of the most prevalent symptoms [3, 4]. Overwhelming studies have shown that biomarkers, such as exhaled nitric oxide (FeNO), are effective indictors in monitoring eosinophilic airway inflammation [5, 6].

Several studies have reported that FeNO levels were elevated in asthma patients [5, 7]. Moreover, FeNO levels were found to be associated with eosinophilic cell counts of plasma and sputum, as well as the levels of total immunoglobulin E. Additionally, an increase in FeNO was found not only in asthma, but in other inflammation diseases, including upper respiratory infections, chronic obstructive pulmonary disease, pulmonary artery hypertension, and cystic fibrosis [8-11]. FeNO measurement has been considered as a simple, convenient, and non-invasive method for evaluating airway inflammation and a useful approach for asthma diagnosis. However, it was reported that FeNO levels might be influenced by a variety of factors, such as age, gender, height, diet, smoking habits, and corticosteroids [12, 13].

With multiple published articles, inconsistent diagnostic outcomes of FeNO, concerning asthma, have made its clinical application a source of confusion. Evaluating the accuracy of FeNO in diagnosis of asthma, Guo et al. conducted a systematic review. Results showed that FeNO could be used as an accurate biomarker for diagnosis of asthma in steroid-naïve or non-smoking patients [14]. Although FeNO measurement has been more frequently adopted for asthma diagnosis, the diagnostic value of FeNO in children with asthma has not been as satisfactory as in adult patients. The meta-analysis by Lu et al. suggested that FeNO had little clinical benefit in guiding treatment for pediatric

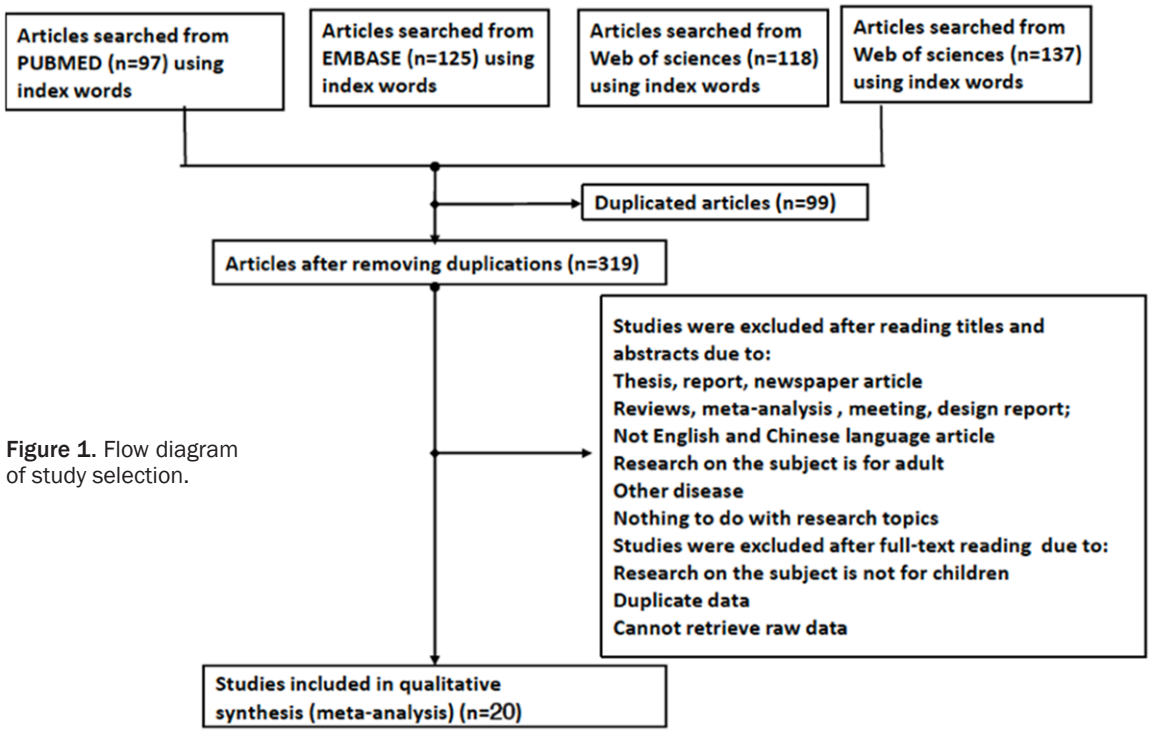

Figure 1. Flow diagram of study selection.

asthma [15]. Due to conflicting findings in previous studies, the present study attempted to collect new published articles and conduct a meta-analysis, aiming to assess the diagnostic accuracy of FeNO for pediatric asthma.

Material and methods

Search strategy

PubMed, Embase, Web of Science, and ProQuest databases were searched until January 30, 2018. Search terms used for identifying studies were as follows: (pediatric OR children OR infant OR kid OR "minority teens") AND (asthma OR wheeze OR dyspnea OR "suffocative catarrh") AND ("fractional exhaled nitric oxide" OR FENO) AND (specificity AND sensitivity or ROC or "diagnosis value"). Language of published articles was limited to English and Chinese. Appropriate studies were then selected for systematic analysis. The search process was conducted by two independent individuals. Studies satisfying the following criteria were included in this analysis: (1) Study population younger than 18 years old; (2) Studies focused on evaluating the diagnostic accuracy of FeNO; (3) Contained enough data to establish 2×2 contingency table (true positive, false negative, false positive, and true negative) for systematic analysis; and (4) Identified asthma patients from controls. Articles with the following criteria were excluded: (1) Case reports, editorials, academic dissertation, published letters, and reviews; (2) Study population included adults; (3) Not only focused on diagnosing asthma but also other diseases; (4) Non-English and non-Chinese publications; (5) Replicated data; and (6) Without enough data to build a 2×2 contingency table. Two investigators screened studies, independently, based on the above criteria. A third investigator was used to resolve discrepancies.

Data extraction and quality assessment

Information, including first author, country, year of publication, sample size, age, gender, single or double-blind study, FeNO level detection criteria, and sensitivity and specificity of diagnosis, was extracted from the studies. If crucial information was not presented in articles, corresponding authors were contacted by e-mail.

Each included study was evaluated according to Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews (QUADAS). This has often been used as an assessment tool for systematic reviews. A total of 14 items was included in this QUADAS. Study qual-

Table 1. Summary of eligible articles

Study	Study location	Standardized Guidelines for Asthma	Standardized Guidelines for FeNO	Age Range	Patients with/ without Asthma	Source of control	ROC	Cutoff values (ppb)	Sensitivity	Specificity	PPV	NPV
An (2015)	China	DTBAC diagnostic criteria	ATS and ERS	1-3 years old	58/30	Population based	0.712	22.75	0.993	0.388	-	-
Sachs-Olsen (2010)	Norway	Physician-diagnosed	ATS and ERS	10-11 years old	31/196	Population based	0.8	15.6	0.35	0.94	0.5	0.9
Glowacka (2013)	Poland	GINA diagnostic criteria	ATS and ERS	8-16 years old	33/25	Population based	0.8366	-	0.75	0.80		
Singer (2013)	Switzerland	Physician-diagnosed	ATS and ERS	1-4 years old	68/98	Hospital based	-	10	0.75	0.623	0.58	0.782
Liu (2011)	Chinese	Physician-diagnosed	ATS and ERS	8-12 years old	52/35	Hospital based	0.818	34.5	0.712	0.686	0.755	0.605
Woo (2013)	Korea	ISAAC questionnaire	ATS and ERS	8-16 years old	167/78	Hospital based	0.76	22	0.569	0.872	0.905	0.486
Yao (2011)	China	ISAAC questionnaire	ATS and ERS	7-13 years old	70/1548	Hospital based	0.67	28	0.643	0.699	0.88	0.977
Wang (2015)	China	DTBAC diagnostic criteria	ATS and ERS	6-9 years old	150/150	Population based	0.902	19.5	0.833	0.867		
Sivan (2009)	Israel	Physician-diagnosed	ATS and ERS	5-18 years old	69/44	Hospital based	0.906	19	0.86	0.89	0.92	0.8
Zhu (2015)	China	DTBAC diagnostic criteria	ATS and ERS	6-12 years old	38/71	Hospital based	0.94	25.5	0.84	0.943	0.915	0.814
Inoue (2016)	Japan	GINA diagnostic criteria	Niox Mino device	6-16 years old	28/27	Hospital based	0.72	11.7	0.75	0.70		
Jerzynska (2014)	Poland	GINA diagnostic criteria	ATS and ERS	6-18 years old	329/60	Hospital based	-	23	0.9	0.52	0.25	0.97
Grzelewski (2014)	Poland	GINA diagnostic criteria	ATS and ERS	6-18 years old	1065/709	Hospital based	0.553	15.8	0.63	0.44	0.59	0.49
Zetterquis (2008)	Sweden	Physician-diagnosed	ATS and ERS	6-17 years old	27/21	Population based	-	20	1.00	0.68	0.63	1.00
Boon (2014)	Austria	GINA diagnostic criteria	ATS and ERS	8-18 years old	45/38	Hospital based	-	10	0.780	0.640		
Mahut (2009)	France	GINA diagnostic criteria	ATS and ERS	8-14 years old	118/81	Hospital based	-	23	0.47	0.95		
Raj (2016)	India	GINA diagnostic criteria	ATS and ERS	5-15 years old	156/51	Hospital based	0.448	20	0.46	0.41	0.71	0.20
Seo (2018)	Korea	GINA diagnostic criteria	ATS and ERS	0-18 years old	79/53	Hospital based	0.856	30	0.81	0.84	0.89	0.75
Biju (2016)	Singapore	GINA diagnostic criteria	ATS and ERS	6-18 years old	27/30	Hospital based	0.564	25	0.44	0.30	0.36	0.38
Nualanong (2016)	Thailand	GINA diagnostic criteria	ATS and ERS	7-18 years old	13/57	Population based	0.704	31	0.85	0.81	0.50	0.96

ISAAC: International Study of Asthma and Allergies in Childhood.

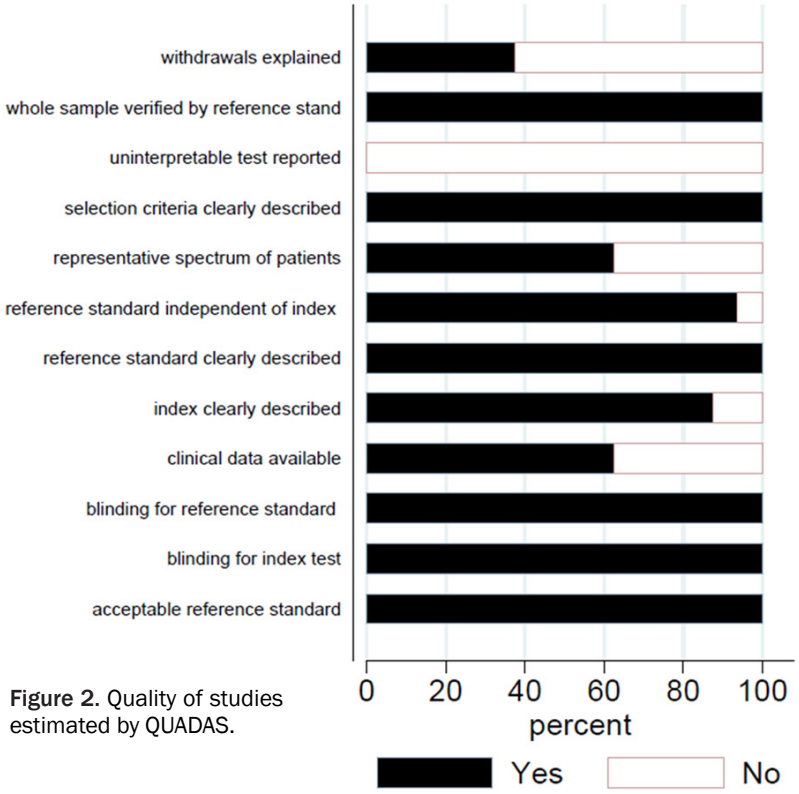

Figure 2. Quality of studies estimated by QUADAS.

ity was ranked as: yes, no, or unclear. Quality assessment was conducted by two independent investigators.

Statistical analysis

Meta-analyses of included studies was carried out with software Stata 12.0 (StataCorp LP, College Station, TX, USA). This study tabulated 2*2 contingency tables, including true positives, false negatives, false positives, and true negatives. Pooled sensitivity, specificity, positive likelihood ratios (LR+), negative likelihood ratios (LR-), and diagnostic odds ratios (DOR) with 95% CI were obtained using a random-effects model (I^2>50% with heterogeneity) or a fixed-effects model (I^2<50% with no heterogeneity). Summary receiver operating characteristic (SROC) curves were derived to calculate the area under the curve and Q index. Spearman's model was applied to assess heterogeneity caused by different cut-off values. Meta-regression was used to analyze heterogeneity sources. Forest plots, Cochran's Q, and Chi-squared tests were used to determine heterogeneity caused by other factors. P<0.05 indicates statistical significance. Deeks' funnel plot asymmetry assay was performed to investigate publication bias, with P<0.05 indicating remarkable heterogeneity.

Results

After removing 99 duplicated articles, 319 studies remained for further investigation. Titles, abstracts, and full-texts of studies were read for exclusion. A total of 20 studies were included in qualitative synthesis [16-35]. A screen flow diagram is presented in **Figure 1** and details of included studies are listed in **Table 1**. Moreover, included articles were evaluated by QUADAS, with no uninterpretable tests reported. Studies prepared for systematic review contained clear and acceptable reference standards, though nearly 60 percent of articles did not explain withdrawals (**Figure 2**).

Meta-analysis was then conducted to evaluate the diagnostic value of FeNO on pediatric asthma. As presented in **Figure 3**, overall sensitivity was 0.57 (95% CI: 0.47-0.67, *P*<0.05) and overall specificity was 0.61 (95% CI: 0.46-0.75, *P*<0.05). Moreover, the overall odds ratio of diagnostic scores for FeNO in diagnosing children with asthma was 2.02 (95% CI: 1.11-3.68, *P*<0.05) (**Figure 4**), indicating that FeNO was inefficient for diagnosis of pediatric asthma. Furthermore, the AUC area under SROC curve was 0.49 (95% CI: 0.45-0.54, *P*<0.05) (**Figure 5**). With a PLR of 1.5 (95% CI: 1.0-2.3) and an NLR of 0.7 (95% CI: 0.49-0.98), post-test probability was similar with pre-test probability (66%). PPV was 0.50 (95% CI: 0.43-0.57) and NPV was 0.50 (95% CI: 0.42-0.57).

Heterogeneity source and subgroup analysis

As the forest plot shows, statistical heterogeneity was found for diagnostic accuracy of FeNO in asthma (I^2=99%, *P*<0.05). The value (0.29, *P*=0.08) in Spearman's model suggests that heterogeneity was not caused by threshold effects. Thus, regression analysis was conducted to find the source of heterogeneity: Asian countries, population age, cutoff values, case sizes, and the model of control. Results revealed that countries, cutoff values, study cases, and the model of control were the main sources of heterogeneity (*P*=0.0015) (**Figure 6**). Sub-

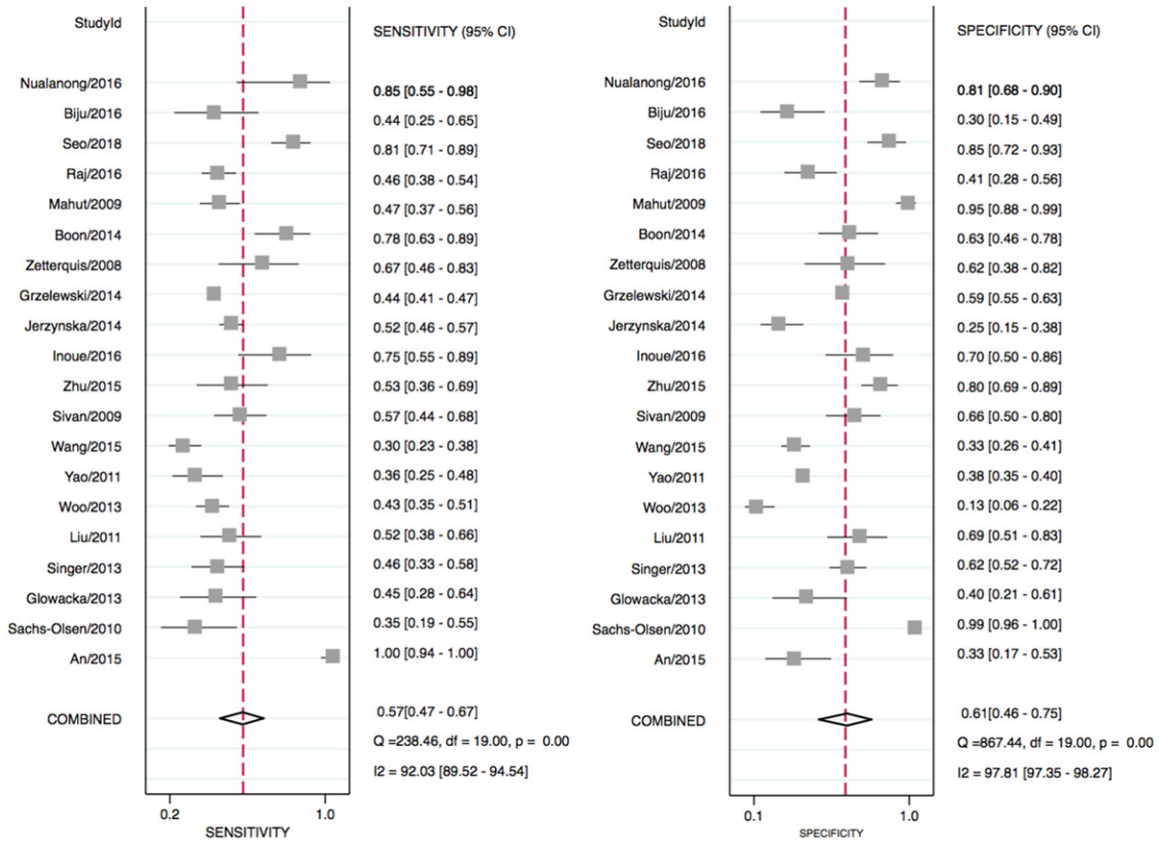

Figure 3. Forest plot of sensitivity and specificity of FeNO in diagnosis of children with asthma in included studies.

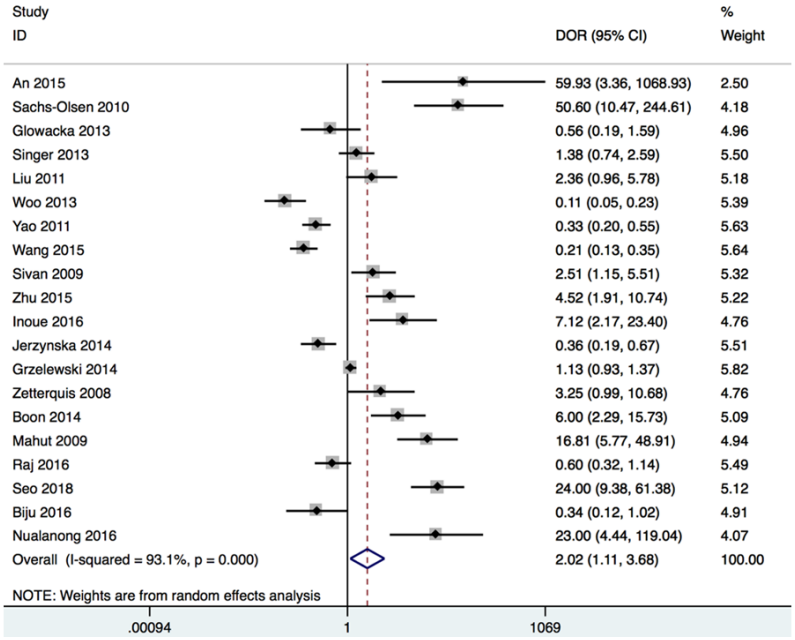

Figure 4. Forest plot of DOR for the diagnostic accuracy of FeNO in children with asthma.

group analysis on Asian countries, cutoff values, study cases, and the model of control was performed, indicating that the DOR in each group ranged from 0 to 1. The pooled diagnostic accuracy of FeNO is collected in **Table 2**.

Publication bias

Deeks' funnel plot asymmetry test was performed to investigate whether publication bias exited in this meta-analysis. Since the slope was not significantly different in **Figure 7**, no publication bias existed in this meta-analysis.

Discussion

Asthma is a heterogeneous disease. Asthma patients with different clinical characteristics have various responses to asthma medicines. Although lung function testing has been the gold standard for

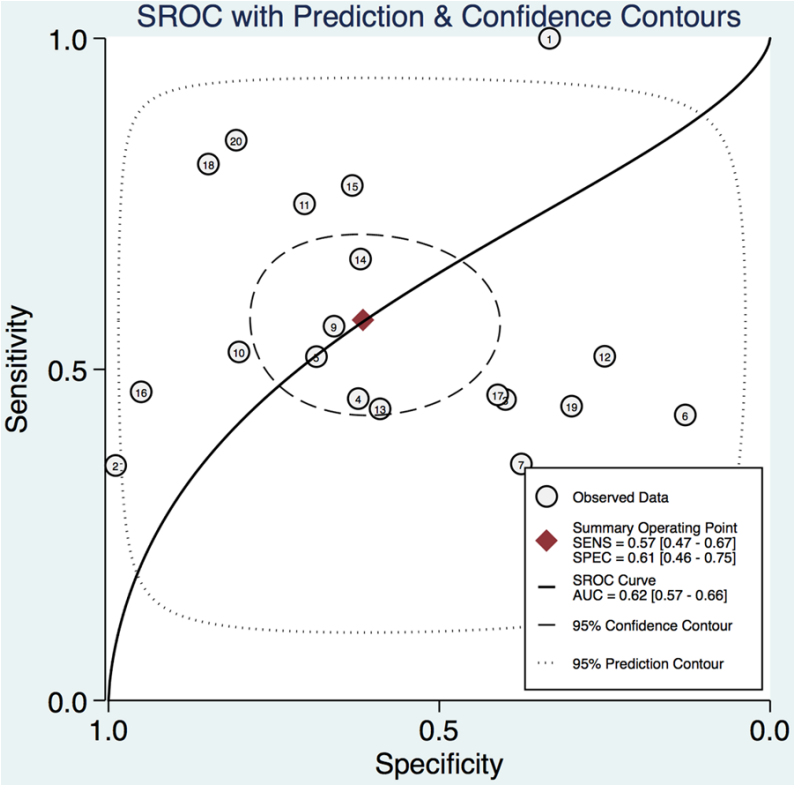

Figure 5. SROC diagram assessing the sensitivity and specificity for diagnostic accuracy of FeNO in pediatric asthma.

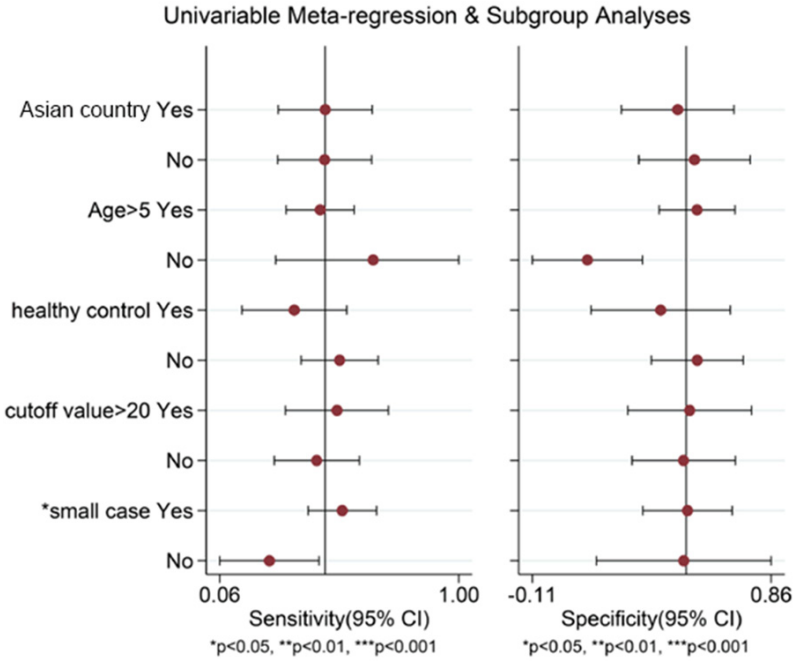

Figure 6. Subgroup analyses to evaluate heterogeneity from FeNO diagnostic accuracy across studies.

diagnosis of asthma in children, it is instantaneous and could be affected by mental factors of the children. Hence, researchers have attempted to investigate appropriate biomarkers to guide medication for asthma patients. With accumulating studies illustrating the utility of biomarkers in asthma therapies, the application of airway biomarkers in clinic require cheap and convenient techniques, as well as standardized methods recognized by experts [36, 37]. Clinically, researchers have realized that combining the mannitol test and FeNO could help in differentiating eosinophilic and non-eosinophilic asthma in patients [38]. A real-life study with 217 unselected patients with asthma symptoms suggested a significant association between FeNO and airway hyperresponsiveness [39]. With limited information, FeNO was found to be useful for the diagnosis of eosinophilic asthma, predicting response to inhaled corticosteroid treatments [40, 41]. Another study showed that tailoring asthma medications, based on FeNO levels, could decrease the frequency of asthma exacerbations, especially in adults with frequent exacerbations [42]. Guo et al. found that the pooled sensitivity, specificity, and diagnostic odds ratio (DOR) for the entire population was 72% (95% CI, 70-74%), 78% (95% CI, 76-80%), and 15.92 (95 % CI, 10.70-23.68), respectively, in a systematic analysis containing 25 studies. Results indicated a favorable diagnostic value of FeNO in asthma [14]. Moreover, another systematic review found fair accuracy of FeNO for diagnosis of asthma, with over-

Table 2. Pooled diagnostic accuracy of FeNO

Group	No. of studies	No. of patients	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio + (95% CI)	Likelihood ratio - (95% CI)	DOR (95% CI)	AUROC (95% CI)	PPV (95% CI)	NPV (95% CI)
The entire population	20	10142	0.57 [0.47, 0.67]	0.61 [0.46, 0.75]	1.5 [1.0, 2.3]	0.70 [0.49, 0.98]	2 [1, 5]	0.49 [0.45-0.54]	0.50 [0.42, 0.57]	0.50 [0.43, 0.57]
Allergic asthma	4	1980	0.35 [0.18, 0.57]	0.47 [0.07, 0.91]	0.7 [0.1, 3.2]	1.39 [0.31, 6.30]	0 [0, 10]	0.35 [0.31-0.39]	0.49 [0.26, 0.65]	0.43 [0.26, 0.60]
Healthy control	6	1126	0.28 [0.14, 0.49]	0.54 [0.19, 0.85]	0.6 [0.2, 2.1]	1.34 [0.56, 3.18]	0 [0, 4]	0.33 [0.29-0.37]	0.45 [0.30, 0.60]	0.42 [0.25, 0.58]
No asthma control	15	8642	0.53 [0.39, 0.67]	0.56 [0.40, 0.70]	1.2 [0.7, 2.1]	0.84 [0.51, 1.40]	1 [1, 4]	0.56 [0.51-0.60]	0.50 [0.42, 0.57]	0.50 [0.43, 0.57]
Asian country	11	4275	0.47 [0.32, 0.64]	0.49 [0.29, 0.69]	0.9 [0.5, 1.8]	1.08 [0.56, 2.05]	1 [0, 3]	0.47 [0.43-0.52]	0.49 [0.39, 0.59]	0.40 [0.40, 0.58]
Cutoff value >20	9	4575	0.52 [0.30, 0.74]	0.52 [0.22, 0.80]	1.1 [0.4, 2.6]	0.92 [0.38, 2.21]	1 [0, 7]	0.53 [0.48-0.57]	0.51 [0.38, 0.65]	0.51 [0.39, 0.63]

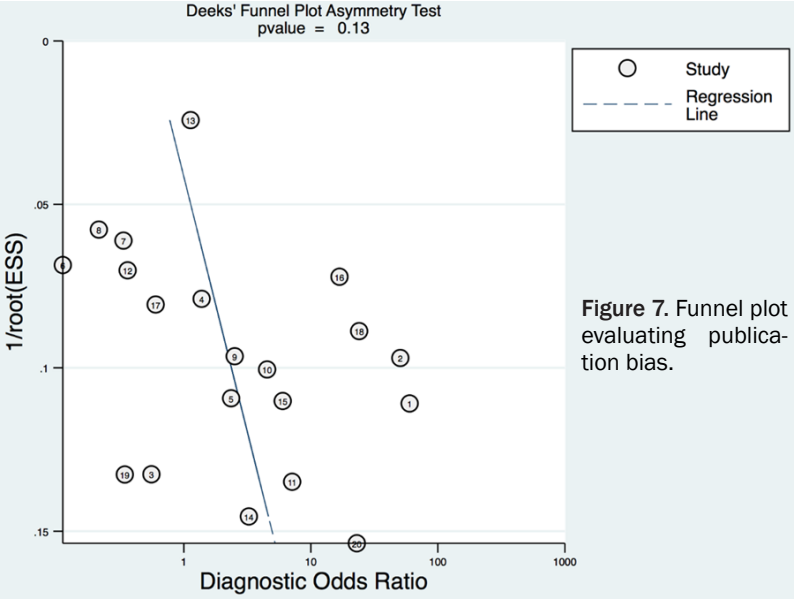

Figure 7. Funnel plot evaluating publication bias.

all specificity higher than sensitivity [43]. However, subgroup analysis among patients of various ages was not performed in this review.

Additionally, FeNO could be used as a noninvasive and objective indicator, assessing the severity of airway inflammation in children with asthma [44]. Multiple studies have performed FeNO testing for diagnosis, prediction, and treatment of asthma in children. Due to immune distortion in early childhood, the etiology of asthma may be different from adults [45]. A previous review showed that detection of FeNO levels might be beneficial to a subset of children, suggesting that FeNO was not appropriate for diagnosing all children with asthma [46].

In An's study, 58 children with asthma were recruited to evaluate the association between FeNO levels and asthma stages [30]. They found that FeNO levels in children with asthma, at different stages, were all significantly higher than that in healthy children. Asthmatic children at the acute exacerbation stage showed the highest FeNO levels, compared to children at the chronic persistent stage. It was recommended that FeNO measurements could be useful for diagnosis of asthma in young children. Wang et al. found that the optimal cut-off value of FeNO was 19.5 ppb for typical bronchial asthma diagnosis, suggesting that measurement of FeNO could be effective in determining typical bronchial asthma and cough variant asthma [29]. Other studies revealed that, except asthma, the highest FeNO levels in children may be caused by allergic sensitization, older age, rhinitis, and lower BMI [26].

The current systematic analysis indicates the poor diagnostic accuracy of FeNO in children with asthma (overall sensitivity of 0.48 and specificity of 0.52), in accordance with previous studies. In Jartti's meta-analysis, performed in 2012, they suggested using FeNO measurements to tailor the dose of inhaled corticosteroids in children should not be recommended in clinic. Excessive inhaled corticosteroid doses may occur in children without significant changes in FeNO levels [47]. Another meta-analysis conducted by Lu in 2015 revealed that FeNO levels were associated with a lower frequency of asthma exacerbation, while no significant differences between FeNO and conventional groups in FeNO value were found. This indicates that FeNO did not provide remarkable benefits in guiding treatment for asthma [15]. However, Tang suggested that FeNO could achieve a moderate diagnostic performance in children with asthma [48]. Despite the unsupportive results of FeNO on diagnosis of pediatric asthma, some intriguing findings were obtained in this meta-analysis. First, the study focused on evaluating the diagnostic accuracy of FeNO in pediatric asthma. Second, this study collected the latest research related to FeNO measurement on diagnosis of pediatric asthma. Third, subgroup analyses were performed to find the cause of heterogeneity in FeNO diagnostic accuracy. It was found that participants from Asian countries could influence the effects of FeNO, suggesting the diagnostic value of FeNO in Asian children may be higher than that in other countries. This could be explained by the fact that differences between population and genetic polymorphisms in children with asthma. Sample size also contributed to the inconsistent results in these studies. No publication bias was found in the current meta-analysis, but some limitations were present. Based on previous studies, a subset of children with asthma could still ben-

efit from the measurement of FeNO. More studies examining the mechanisms of FeNO in pediatric asthma are expected in the future.

Interestingly, another meta-analysis focusing on FeNO in asthma was found [49]. Compared to that study, the current study had obvious advantages. Korevaar's study [49] included 32 studies, investigating the diagnostic accuracy of FeNO in asthma. Only eight studies focused on children. The current analysis enrolled twenty studies, indicating that results were much more robust and reliable. However, the disadvantages compared to Korevaar's study are also obvious. Except for FeNO, they also investigated the prognostic accuracy of blood eosinophils and IgE in asthma. The current study only focused on FeNO. This may not be not comprehensive enough to summarize all potential invasive makers.

In conclusion, the present meta-analysis indicates that the diagnostic value of FeNO in children with asthma is not as favorable as that in adults. FeNO cannot be used as an independent indicator for diagnosis of pediatric asthma. Combining FeNO and other biomarkers may be an effective and noninvasive method for pediatric asthma diagnosis. However, more studies are required, investigating convenient methods of identifying the status of children with asthma.

Disclosure of conflict of interest

None.

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