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Role of Exhaled Nitric Oxide in Management of Asthma in Pediatric Patients: A Systematic Review

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Abstract

***Background*:** Fractional exhaled nitric oxide (FeNO) has emerged as a potential tool for managing asthma in children, but its precise role remains under investigation. ***Objectives*:** This systematic review aims to comprehensively evaluate the current research on FeNO's utility in managing pediatric asthma. ***Methods*:** We conducted a systematic search of electronic databases like PubMed, MEDLINE, Science Direct, and Scopus. Two independent reviewers screened and extracted data from eligible studies. ***Results*:** Sixteen studies including 4612 participants in total and more than half of them 2558 (55.5%) were males—were included in our data. Intermediate FeNO levels had a higher yearly hospitalization rate than those with low or high FeNO levels. FeNO can be a predictive marker as one study found that FeNO levels of more than 35 ppb have the highest risk of developing respiratory disease in the future. Regarding the benefits of FeNO-guided therapy, the use of FENO in conjunction with GINA guidelines for ICS titration can help reduce daily ICS doses and treatment costs. FeNO was found reliable as an asthma biomarker only in children with concomitant aeroallergen sensitivity. ***Conclusion*:** The evidence for the effectiveness of FeNO-guided asthma care in children is critical. The effect of FeNO-guided treatment on pharmaceutical use is unclear. Any benefits in illness control must be balanced against the risk of increased drug use, particularly ICS, as higher rates were frequently observed in children with FeNO-guided monitoring. There is an obvious need for larger, longer-term research to address these problems before making firm recommendations for routine therapeutic use.

Keywords: Asthma, Pediatric, Children, Exhaled Nitric Oxide, FeNO, Diagnosis, Management.

INTRODUCTION

Asthma is one of the most common chronic respiratory diseases affecting pediatric patients worldwide. It is characterized by inflammation of the airways, which leads to breathing difficulties, wheezing, coughing, and chest tightness [1]. The management of asthma in pediatric patients is crucial to controlling symptoms, preventing exacerbations, and improving quality of life. One important tool in the management of asthma is the measurement of exhaled nitric oxide (eNO) [2].

Exhaled nitric oxide is a marker of airway inflammation in asthma. It is produced by inflammatory cells in the airways, such as eosinophils, and is elevated in patients with allergic asthma. Measuring eNO levels can provide valuable information about the degree of airway inflammation in pediatric patients with asthma. It can help identify patients who may benefit from anti-inflammatory treatment, such as inhaled corticosteroids, and monitor the response to treatment over time [3].

Several studies have shown that measuring eNO levels can help guide asthma management in pediatric patients. For example, a study published in the Journal of Pediatrics found that monitoring eNO levels in children with asthma helped reduce the need for oral corticosteroids and emergency department visits. Another study published in the European Respiratory Journal showed that adding eNO measurement to standard clinical care improved asthma control in children [4].

In addition to guiding treatment decisions, measuring eNO levels can also help identify patients at risk of asthma exacerbations. A study published in the Journal of Allergy and Clinical Immunology found that elevated eNO levels were associated with an increased risk of asthma exacerbations in children. Monitoring eNO levels in pediatric patients with asthma can help identify those at risk of exacerbations and initiate preventive measures, such as adjusting medication doses or providing education on asthma management [5].

Overall, the role of exhaled nitric oxide in the management of asthma in pediatric patients is becoming increasingly recognized. Measuring eNO levels can provide valuable information about airway inflammation, guide treatment decisions, and identify patients at risk of exacerbations. Incorporating eNO measurement into routine asthma care for pediatric patients can help improve outcomes and quality of life [6].

Asthma is a chronic condition affecting millions of children worldwide. Optimizing asthma management is crucial for improving quality of life and preventing complications. FeNO measurement offers a non-invasive way to assess airway inflammation, potentially aiding in asthma management. Despite growing interest, the role of FeNO in managing pediatric asthma remains unclear. This systematic review aims to synthesize existing research and provide a comprehensive picture of FeNO's utility. There is a lack of clear consensus on how best to utilize FeNO measurements for managing asthma in pediatric patients. To systematically evaluate the current body of research on the role of FeNO in managing asthma in pediatric patients.

Study Objectives:

- To assess the diagnostic accuracy of FeNO for childhood asthma.
- To evaluate the effectiveness of FeNO in monitoring asthma control in children.
- To analyze the impact of FeNO-guided therapy on asthma outcomes in pediatric patients.
- To investigate the potential of FeNO in predicting response to asthma medications in children.
- To identify limitations and areas for further research regarding FeNO and pediatric asthma management.

METHODS

Study Design and Duration: This was a systematic review conducted in July 2024.

Search Strategy

In carrying out this systematic review we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7]. We conducted a systematic search of electronic databases like PubMed, MEDLINE, Science Direct, and Scopus. A detailed search strategy was formulated using a combination of Medical Subject Headings (MeSH) terms and relevant keywords tailored to capture studies on childhood asthma, FeNO, and its application in management. For instance, the search might include terms like "asthma" or "wheezing" alongside "child" or "pediatric" and "exhaled nitric oxide" or "FeNO" combined with keywords like "management," "diagnosis," or "treatment." We also considered including grey literature sources like conference proceedings and theses to capture a broader range of potential studies.

Eligibility Criteria:

Inclusion Criteria:

1. Studies focusing on pediatric patients with asthma.
2. Studies assessing the role of exhaled nitric oxide in the management of asthma.
3. Randomized controlled trials, observational studies, and systematic reviews.
4. Studies published in the English language.
5. Studies conducted within the last 5 years (2020-2024)
6. Studies involving participants aged 18 years and below.
7. Studies reporting quantitative outcomes related to the use of exhaled nitric oxide in asthma management.

Exclusion Criteria:

1. Studies not focusing on pediatric patients with asthma.
2. Studies not evaluating the role of exhaled nitric oxide in asthma management.
3. Case reports, case series, editorials, and letters to the editor.
4. Studies published in languages other than English.
5. Studies involving adult participants only.
6. Studies not reporting quantitative outcomes related to the use of exhaled nitric oxide in asthma management.

Data Extraction

Rayyan (QCRI) [8] was used to confirm the accuracy of the search results. Using the inclusion and exclusion criteria, the titles and abstracts that were found during the search were assessed for relevancy. The study team carefully reviewed all papers that satisfied the inclusion criteria. Consensus was used to settle any disputes. A predetermined data extraction form was used to record important study details, such as titles, authors, publication year, study location, participant demographics, gender distribution, FeNO quantification, and role of FeNO in the diagnosis and management of asthma. To evaluate the risk of bias, a third-party assessment method was created.

Data Synthesis Strategy

The findings from the included studies were synthesized using a narrative synthesis approach. This involves grouping studies by research question and summarizing the key findings for each group. We also explored potential sources of variation across studies, such as differences in participant characteristics, FeNO measurement methods, and intervention protocols employed.

Risk of Bias Assessment

The study's quality was assessed using the critical assessment criteria for studies reporting prevalence data developed by the Joanna Briggs Institute (JBI) [9]. There were nine questions in this instrument, and a score of 1 was given for a positive response and a score of 0 for a negative, ambiguous, or irrelevant response. Low, moderate, and high quality will be assigned to scores that fall between four and seven, and eight and above, accordingly. Disagreements were settled through conversation after researchers evaluated the studies' quality independently.

RESULTS

Search Results

After 989 duplicates were removed, a total of 1912 study papers were found through a systematic search. After 923 studies had their titles and abstracts evaluated, 806 papers were discarded. Eight articles were not located out of the 117 reports that were required to be retrieved. 109 papers were screened for full-text assessment; 63 were rejected because the study results were wrong, 26 because the population type was inaccurate, 2 articles were editor's letters, and 2 were abstracts. Sixteen research publications in this systematic review satisfied the requirements for eligibility. An overview of the procedure used to choose the research is illustrated in Figure 1.

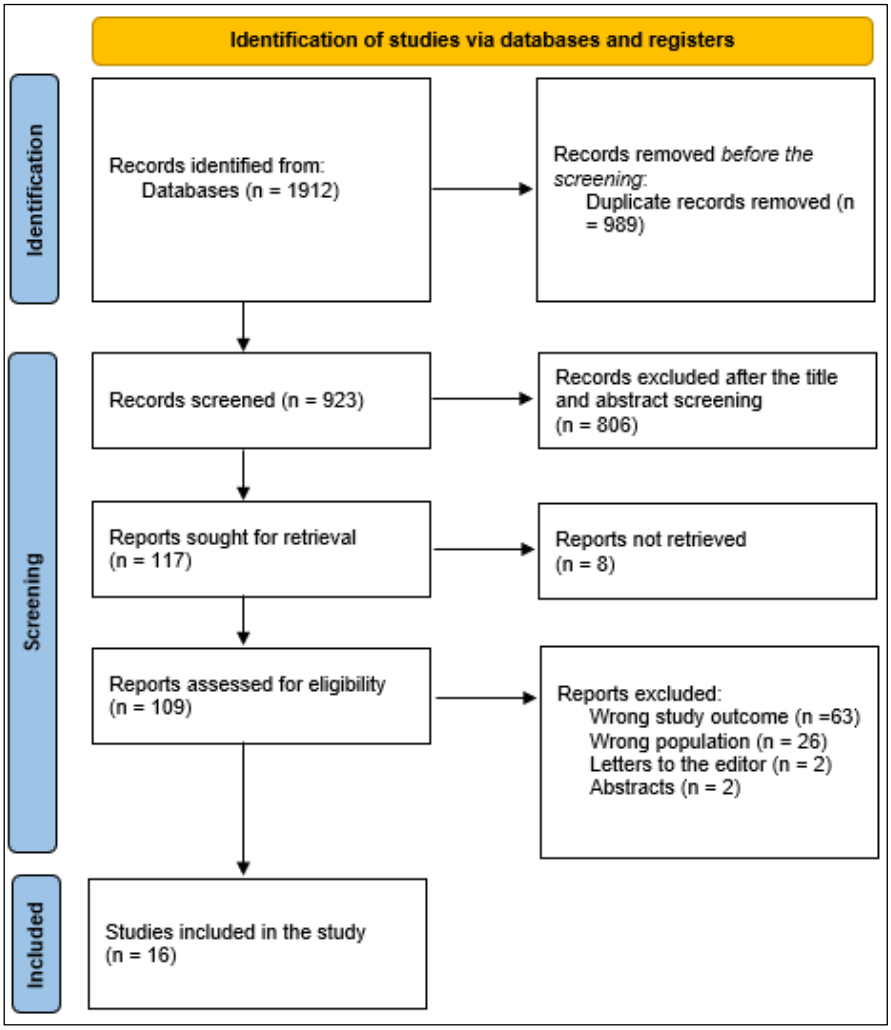

Figure 1: Study decision is summed up in a PRISMA diagram

Sociodemographic Features of the Comprised Studies

The research publications' sociodemographic information is displayed in Table 1. Sixteen studies including 4612 participants in total and more than half of them 2558 (55.5%) were males—were included in our data. Eight studies were prospective cohorts [11, 13, 14, 16, 17, 21, 23, 24], three were cross-sectional studies [12,

22, 25], three were case-controls [15, 18, 19], and two were retrospective cohorts [10, 20]. Six studies were conducted in China [11, 16, 18, 19, 20, 24], three in Poland [12, 22, 25], two in the USA [10, 21], one in Switzerland [13], one in Vietnam [14], one in Slovak Republic [15], one in Denmark [17], and one in Taiwan [23].

Clinical Outcomes

Role of FeNO in the Management of Pediatric Asthma

The clinical features are displayed in Table (2). Seven studies have investigated the role of FeNO in the management of pediatric asthma [10-16]. Intermediate FeNO levels had a higher yearly hospitalization rate (2.8 ± 6.2) than those with low or high FeNO levels [10]. FeNO can be a predictive marker as one study found that FeNO levels of more than 35 ppb have the highest risk of developing respiratory disease in the future [12]. Regarding the benefits of FeNO-guided therapy, the use of FENO in conjunction with GINA guidelines for ICS titration can help reduce daily ICS doses and treatment costs [14]. The normal range of FeNO in children plays a limited function in assessing standardized asthma therapy efficacy [11], is not linked with either control or attack [13], and has no relationship with cough reflex sensitivity [15].

Role of FeNO in the Diagnosis and Prognosis of Pediatric Asthma

Nine studies have explored the use of FeNO as a diagnostic and/ or prognostic tool for pediatric asthma [17-25]. FeNO was found reliable as an asthma biomarker only in children with concomitant aeroallergen sensitivity and those with IgE-mediated symptoms [17, 21, 24]. FeNO can be used as an additional diagnostic technique for chest tightness-variant asthma, with 18.5 ppb being the ideal cutoff threshold [18], and provides the highest diagnostic accuracy for asthma at 35 ppb as a cutoff point [25]. Dynamic monitoring of FeNO and exhaled carbon monoxide is a good indicator of airway inflammation, making it a valuable clinical tool for determining the severity of asthma in children [20].

Table 1: The sociodemographic attributes of the participating populations

Study	Study design	Country	Participants	Mean age	Males (%)
Chen *et al.*, 2023 [10]	Retrospective cohort	USA	323	11.8 ± 3.4	162 (50.2%)
Yang *et al.*, 2023 [11]	Prospective cohort	China	115	7 to 9	83 (72.2%)
Barański, 2024 [12]	Cross-sectional	Poland	128	6 - 9	58 (45%)
Ardura-Garcia *et al.*, 2023 [13]	Prospective cohort	Switzerland	516	6 - 12	293 (56.8%)
Dinh-Thi-Dieu *et al.*, 2020 [14]	Prospective cohort	Vietnam	224	6 - 16	141 (62.9%)
Peter *et al.*, 2020 [15]	Case-control	Slovak Republic	25	9±1	11 (44%)
Wu *et al.*, 2022 [16]	Prospective cohort	China	57	5 - 14	43 (75.4%)
Sunde *et al.*, 2023 [17]	Prospective cohort	Denmark	411	NM	263 (63.9%)
Zhang *et al.*, 2023 [18]	Case-control	China	95	6 - 14	52 (54.7%)
Zhang *et al.*, 2022 [19]	Case-control	China	140	8.7 ± 1.9	99 (70.7%)
Xie *et al.*, 2020 [20]	Retrospective cohort	China	100	6.5 ± 2.5	64 (64%)
Flashner *et al.*, 2021 [21]	Prospective cohort	USA	929	13 ± 1	466 (50%)
Barański & Zejda, 2022 [22]	Cross-sectional	Poland	449	7.5 ± 0.8	224 (49.9%)
Lin *et al.*, 2022 [23]	Prospective cohort	Taiwan	560	9	314 (56.1%)
Ngo-Minh *et al.*, 2020 [24]	Prospective cohort	China	93	9 ± 3	58 (62.4%)
Barański & Schlünssen, 2022 [25]	Cross-sectional	Poland	447	6 - 9	227 (50.8%)

Table 2: Clinical features and results of the included research

Study	Population type	Main outcomes	JBI
Role of FeNO in the management of pediatric asthma			
Chen *et al.*, 2023 [10]	PFT laboratory technician	Children with intermediate FeNO levels had a higher yearly hospitalization rate (2.8 ± 6.2) than those with low or high FeNO levels (1.3 ± 2.8 and 1.3 ± 2.5, respectively).	Moderate
Yang *et al.*, 2023 [11]	According to the guidelines by the ATS/ERS	The normal range of FeNO in children plays a limited function in assessing standardized asthma therapy efficacy in children.	Moderate
Barański, 2024 [12]	According to ERS/ATS recommendations	Children with asthma-like symptoms and FeNO levels of more than 35 ppb have the highest risk of developing respiratory disease in the future.	Moderate
Ardura-Garcia *et al.*, 2023 [13]	NM	FeNO levels at baseline were not linked with either control or attack.	Moderate

Study	Population type	Main outcomes	JBI
Dinh-Thi-Dieu *et al.*, 2020 [14]	The NIOX MINO	The use of FENO in conjunction with GINA guidelines for ICS titration can help reduce daily ICS doses and treatment costs.	High
Peter *et al.*, 2020 [15]	Niox Vero®	There is no relationship between cough reflex sensitivity and FeNO in children with asthma or in the control group.	High
Wu *et al.*, 2022 [16]	Medi-Softhyp	Dynamic fluctuations in FeNO levels throughout the bronchodilator response test. Using a bronchodilator causes a substantial difference in FeNO levels between BDR+ and BDR− children with asthma.	Moderate
Role of FeNO in the diagnosis and prognosis of pediatric asthma			
Sunde *et al.*, 2023 [17]	NM	Asthma was linked to higher FeNO levels in children with aeroallergen sensitization (1.44 (1.23-1.69), $p < .0001$), but lower FeNO levels in nonsensitized children (0.80 (0.65-0.99), $p = .05$. These results demonstrate that FeNO is only a reliable asthma biomarker in children with concomitant aeroallergen sensitivity.	Moderate
Zhang *et al.*, 2023 [18]	The NIOX VERO FeNO analyzer	FeNO can be used as an additional diagnostic technique for chest tightness-variant asthma, with 18.5 ppb being the ideal cutoff threshold.	Moderate
Zhang *et al.*, 2022 [19]	According to the ATS/ERS guidelines	Combining Angle β with FeNO and FEV1/FVC% improves diagnosis accuracy for asthma in children who are in school.	Moderate
Xie *et al.*, 2020 [20]	Nanocoulomb exhalation analyzer	Dynamic monitoring of FeNO and exhaled carbon monoxide is a good indicator of airway inflammation, making it a valuable clinical tool for determining the severity of asthma in children.	Moderate
Flashner *et al.*, 2021 [21]	NM	The association between asthma and FeNO is limited to those with IgE-mediated symptoms. Even in the absence of asthma, persons with allergic sensitization may have increased FeNO levels.	Moderate
Barański & Zejda, 2022 [22]	The NIOX MINO	FeNO had the highest diagnosis accuracy for isolated asthma without atopy against children who did not have any other respiratory or allergy diseases.	Moderate
Lin *et al.*, 2022 [23]	The NIOX MINO	Low childhood asthma control test scores were associated with elevated FeNO levels ($r = -0.394$). A combination of FeNO and Impulse oscillometry measures accurately predicts childhood asthma, with or without control.	Moderate
Ngo-Minh *et al.*, 2020 [24]	Medisoft	Exhaled NO is an asthma biomarker that may be useful in predicting asthma management in short-term follow-up in asthmatic children.	High
Barański & Schlünssen, 2022 [25]	NM	The FeNO cut-off has the highest accuracy for epidemiological asthma screening at 35 ppb. For isolated asthma, FeNO had the highest accuracy at 92.9%.	Moderate

*NM=Not-mentioned

DISCUSSION

Noninvasive inflammatory measurements are becoming increasingly popular as a reference for asthma management. Prognostic studies analyzed in this review assess the accuracy of FeNO in predicting clinical outcomes rather than the usefulness in patient management directly. This review found that intermediate FeNO levels had a higher yearly hospitalization rate than those with low or high FeNO levels [10]. FeNO can be a predictive marker as one study found that FeNO levels of more than 35 ppb have the highest risk of developing respiratory disease in the future [12].

When the initial observations of elevated FeNO in asthmatic people were published over 20 years ago [26, 27], our understanding of asthma was not as wide as it is today. Asthma was primarily classified as intrinsic or extrinsic, with both being predominantly eosinophilic [28]. It is widely recognized that FeNO levels rise most

significantly in T-helper type 2 lymphocyte-driven eosinophilic inflammation of the airways [29] and that this increase can be easily decreased with ICS. As a result, FeNO was investigated as a potential "inflammometer" in asthma as a whole, rather than specific subtypes. However, a wide range of asthma phenotypes have been identified [30], some of which are distinguished by neutrophilic instead of eosinophilic inflammation, whereas others may lack mucosal inflammation altogether. These non-eosinophilic forms of asthma are most likely unrelated to FeNO levels.

In the current systematic review, only a few studies investigated inflammatory activity and phenotype, and a quarter of the studies analyzed the proportion of participants with eosinophilic asthma in their sample. Furthermore, only one study investigated the capacity of FeNO to forecast ICS responsiveness in eosinophilic and noneosinophilic asthma [14].

Regarding the benefits of FeNO-guided therapy in this review, the use of FENO in conjunction with GINA guidelines for ICS titration can help reduce daily ICS doses and treatment costs [14]. Fielding *et al.*, reported that in comparison to normal practice, FENO-guided asthma medication may be more effective in improving asthma outcomes for individuals who are not treated with leukotriene receptor antagonists and are not obese [31]. Gomersal *et al.*, the potential usefulness of FeNO monitoring is unclear. Trends toward lower exacerbation and greater medication use were observed, but they seldom reached statistical significance [32].

This review found that FeNO was reliable as an asthma biomarker only in children with concomitant aeroallergen sensitivity and those with IgE-mediated symptoms [17, 21, 24]. The strongest support for FENO as a diagnostic tool arises from a small number of trials in which children with nonspecific respiratory symptoms had their FeNO levels evaluated and then classified as having asthma or not having asthma. A newly formed European Respiratory Society (ERS) task force [33] recognized five studies using this design and discovered a link between increasing FeNO concentrations and an increased likelihood of asthma; additionally, reducing FeNO concentrations was linked with a lower likelihood of asthma.

We also found that FeNO can be used as an additional diagnostic technique for chest tightness-variant asthma, with 18.5 ppb being the ideal cutoff threshold [18], and provides the highest diagnostic accuracy for asthma at 35 ppb as a cutoff point [25]. There is no consensus on which cut-off should be used for diagnosing asthma in youngsters. The values of <20 ppb as "normal" and >35 ppb as "elevated" [34] are based on normative data from a cross-sectional whole-population research [35]. Both the UK asthma guidelines [36, 37] and the National Asthma Education and Prevention Program (United States of America) [38] stipulate a positive cut-off of more than 35 ppb. According to the American Thoracic Society (ATS), readings more than 35 ppb indicate that a child's symptoms are responsive to steroids [39].

Limitations

The number of studies included in each study topic in this evaluation was minimal, making it difficult to draw definite conclusions. Furthermore, despite the inclusion of prospective, retrospective, and observational designs, the material was mostly of poor quality, with small sample sizes and moderate or high overall risk of bias. Furthermore, the studies used a variety of designs, treatment regimes, FeNO cut-off values, FeNO quantification methods, follow-up periods, and patient inclusion criteria.

CONCLUSION

The evidence for the effectiveness of FeNO-guided asthma care in children is mixed. The effect of FeNO-guided treatment on pharmaceutical use is unclear. Any benefits in illness control must be balanced against the risk for increased drug use, particularly ICS, as higher rates were frequently observed in children with FeNO-guided monitoring. There is an obvious need for larger, longer-term research to address these problems before making firm recommendations for routine therapeutic use. Further research should look into the effect of baseline asthma severity and various therapeutic algorithms on the effectiveness of FeNO-guided therapy. Larger, longer-term studies are needed to have a better understanding of the effect of FeNO monitoring over the course of time.

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