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Number 197

The Clinical Utility of Fractional Exhaled Nitric Oxide (FeNO) in Asthma Management

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www.ahrq.gov

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Prepared by:
Mayo Clinic Evidence-based Practice Center
Rochester, MN

Investigators:
Zhen Wang, Ph.D.
Paolo Pianosi, M.D.
Karina Keogh, M.D.
Feras Zaiem, M.D.
Mouaz Alsawas, M.D., M.Sc.
Fares Alahdab, M.D
Jehad Almasri, M.D.
Khaled Mohammed, M.B.C.H
Laura Larrea-Mantilla, M.D.
Wigdan Farah, M.B.B.S
Lubna Daraz, Ph.D.
Patricia Barrionuevo, M.D.
Shalak Gunjal, M.S.
Larry J. Prokop, M.L.S
M. Hassan Murad, M.D., M.P.H.

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Key Messages

Purpose of Review
To assess the role of measuring the fractional concentration of exhaled nitric oxide (FeNO) in the diagnosis, treatment and monitoring of asthma.

Key Messages

- Depending on the FeNO cutoff, the likelihood of having asthma in people ages 5 years and older increases by 2.8 to 7.0 times given a positive FeNO test result.
- FeNO is modestly more accurate in diagnosing steroid-naïve asthmatics, children (ages 5-18), and nonsmokers than other patients suspected to have asthma.
- FeNO results can predict which patients will respond to inhaled corticosteroid therapy.
- Using FeNO to manage long-term control medications including dose titration, weaning, and monitoring of adherence, reduces the frequency of exacerbations.
- There is insufficient evidence supporting the use of FeNO in children (ages 0-4) for predicting a future diagnosis of asthma.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fisher Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

Gopal Khanna, M.B.A.
Director
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Arlene Bierman, M.D., M.S.
Director Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Aysegul Gozu, M.D., M.P.H.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

David W. Niebuhr, M.D., M.P.H., M.Sc.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

Technical Experts who provided input to this report

Anas Daghestani, M.D.
Austin Regional Clinic
Austin, TX

Serpil C. Erzurum, M.D.
Cleveland Clinic Foundation
Cleveland, OH

Rohit Katial, M.D.
University of Colorado
Denver, CO

Todd A. Mahr, M.D.
Gundersen Lutheran Medical Center
La Crosse, WI

John G. Mastronarde, M.D., M.S.c.*
Providence Portland Medical Center and
The Oregon Clinic
Portland, OR

Wayne J. Morgan, MD
College of Medicine Tucson, University of Arizona
Tucson, AZ

Shahzeb Munir, M.D.*
University of Wisconsin School of Medicine and Public Health
Madison, WI

Sally Wenzel, M.D.*
University of Pittsburgh
Pittsburgh, PA

* Technical Experts who also reviewed the report.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers:

Benjamin Gaston, M.D.
Rainbow Babies and Children's Hospital and
Case Western Reserve University
Cleveland, OH

Elliot Israel, M.D.
Brigham and Women's Hospital,
Harvard Medical School
Boston, MA

Nicholas Kenyon, M.D.
University of California, Davis
Sacramento, CA

Augusto Litonjua, M.D., M.P.H.
Harvard Medical School
Boston, MA

John Sundy, M.D., P.h.D.
Duke University School of Medicine
Durham, NC

The Clinical Utility of Fractional Exhaled Nitric Oxide in Asthma Management

Structured Abstract

Objectives. To evaluate the clinical utility and diagnostic accuracy of fractional exhaled nitric oxide (FeNO) in people age 5 years and older with asthma; and the ability of FeNO measured at age 4 years or younger to predict a future diagnosis of asthma.

Data sources. MEDLINE, EMBASE, Cochrane Central Databases, and SciVerse Scopus, references lists, trials registries, and grey literature sources.

Review methods. We searched from databases' inception to April 2017 for studies enrolling patients with or suspected to have asthma that evaluated the diagnosis or clinical utility of FeNO. We included randomized and nonrandomized comparative studies.

Results. We included 175 studies. In adults (>18) and children (ages 5-18), 43 studies showed that FeNO results increased the odds of correctly diagnosing asthma between 5.85 and16.95 fold. Using FeNO cutoffs of <20, 20-30, 30-40, ≥40 part per billion (ppb); respectively, FeNO testing had sensitivities of 0.79, 0.64, 0.53 and 0.41; and specificities of 0.72, 0.81, 0.84, 0.94 (Strength of Evidence (SOE): Moderate). Depending on the FeNO cutoff, the posttest odds of having asthma given a positive FeNO test result increased by 2.80 to 7.00 fold. Diagnostic accuracy was modestly better in steroid-naïve asthmatics, children and nonsmokers than the overall population. Data from 58 studies showed that in adults and children (age 5-18), FeNO levels had a weak association with asthma control and the risk of subsequent and prior exacerbations (SOE: Low). Elevated FeNO levels were likely more predictive of exacerbation risk in those with atopy. In adults and children with acute asthma exacerbations, FeNO levels did not correlate with exacerbation severity and were poorly reproducible. In children and adolescents (ages 5-18), FeNO levels were inversely associated with adherence to inhaled corticosteroids (SOE: Low). Data from 14 randomized controlled trials showed that asthma management following algorithms that included FeNO monitoring, compared to no FeNO, reduced the risk of exacerbations (SOE: High) but did not affect other outcomes such as hospitalization, or quality of life. FeNO testing may identify patients who were more likely to respond to inhaled corticosteroids (SOE: Low). FeNO testing predicted exacerbations in patients undergoing ICS reduction or withdrawal. Data from 9 studies showed that althoughFeNO levels in children at age 0-4 years correlated with the Asthma Predictive Index and wheezing (SOE: Low), there was insufficient evidence to determine if FeNO results at age 0-4 years can reliably predict a future asthma diagnosis.

Conclusions. This systematic review provides the diagnostic accuracy measures of FeNO in people ages 5 years and older. Test performance is modestly better in steroid-naïve asthmatics, children, and nonsmokers than the general population with suspected asthma. Algorithms that include FeNO measurements can help in monitoring response to anti-inflammatory, or long-term control medications, including dose titration, weaning, and treatment adherence. At this time, evidence is insufficient to support the measurement of FeNO in children under the age of 5 as a means for predicting a future diagnosis of asthma.

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Executive Summary

Objectives and Rationale for the Review

This report summarizes a systematic review on “The Clinical Utility of Fractional Exhaled Nitric Oxide in Asthma Management”. This was one of the 6 high priority topics within asthma identified by an NHLBI Advisory Council Asthma Expert Working group. [1]

Background

The diagnosis of asthma is a clinical diagnosis and is challenging without a criterion standard test. Fractional exhaled nitric oxide (FeNO) testing has been suggested as a diagnostic test for asthma. It has also been studied as a tool that aids in selecting asthma treatments, predicting response to therapy (e.g., inhaled corticosteroids) and for monitoring the response to therapy. In young children with recurrent wheezing, FeNO may predict the ones who are likely to be diagnosed with asthma later in childhood.

Data Sources

We conducted a comprehensive literature search of six databases from the inception of the databases to April 4, 2017: MEDLINE® In-Process & Other Non-Indexed Citations, MEDLINE®, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and SciVerse Scopus. The systematic review protocol is available in the full report.

Results

We found 175 studies that met the eligibility criteria for inclusion in this review.

KQ 1.a: What is the diagnostic accuracy of FeNO measurement(s) for making the diagnosis of asthma in individuals ages 5 and older?

Key Points

- The diagnostic accuracy of FeNO for the diagnosis of asthma varies with the FeNO level used for diagnosis. Sensitivity and specificity per cutoff were: <20 ppb (0.79, 0.72), 20-30 ppb (0.64, 0.81), 30-40 ppb (0.53, 0.84), ≥40 ppb (0.41, 0.94). (SOE: Moderate).
- Depending on the FeNO cutoff, the posttest odds of having asthma given a positive FeNO test result increased by 2.80 to 7.00 fold. (SOE: Moderate).
- Diagnostic accuracy is likely higher in nonsmokers, in children and in steroid-naïve asthmatics.

KQ 1.b: What is the clinical utility of FeNO measurements in monitoring disease activity and asthma outcomes in individuals with asthma ages 5 and older?

Key Points

- In adults (ages >18) and children (ages 5 -18), FeNO level is weakly associated with asthma control (as measured by the ACQ and ACT).This association can be further attenuated in those who smoke, pregnant or are on ICS. (SOE: Low)
- In adults (ages >18) and children (ages 5 -18), FeNO levels have a weak association with the risk of subsequent and prior exacerbations. (SOE: Low) The association between FeNO levels and exacerbation risk is likely stronger in individuals (ages>5 years) with atopy. (SOE: Low)
- In adults (ages >18) and children (ages 5 -18) with acute asthma exacerbations, FeNO levels do not correlate with exacerbation severity and were poorly reproducible. (SOE: Low)
- In children (ages 5 - 12) and adolescents (ages 13 - 18), FeNO levels were inversely associated with adherence to asthma medications (mainly ICS). (SOE: Low)

KQ 1.c: What is the clinical utility of FeNO measurements to select medication options (including steroids) for individuals ages 5 and older?

Key Points

- In adults (ages of >18 years) and children (ages of 5-18 years), using asthma management algorithms that incorporate FeNO testing reduced the risk of exacerbations (SOE: High), and possibly the risk of exacerbations requiring oral steroids (SOE: Moderate), but did not affect other outcomes such as hospitalization, quality of life, asthma control, or FEV1% predicted.
- FeNO testing can identify patients who are more likely to respond to inhaled corticosteroids (SOE: Low).

KQ 1.d: What is the clinical utility of FeNO measurements to monitor response to treatment in individuals ages 5 and older?

Key Points

- FeNO levels are reduced when patients with asthma take inhaled corticosteroids, leukotriene receptor antagonists or omalizumab. FeNO levels are not reduced when patients with asthma take long acting beta agonists.
- FeNO predicts exacerbations in patients undergoing ICS reduction or withdrawal, but FeNO alone is likely insufficient and its ability to predict exacerbations can be substantially enhanced by clinical measures (e.g. ACT).

KQ 1.e. In children ages 0-4 years with recurrent wheezing, how accurate is FeNO testing in predicting the future development of asthma at age 5 and above?

Key Points

- It is unclear whether FeNO testing in children at ages 0-4 years with symptoms suggestive of asthma can predict a future asthma diagnosis (SOE: insufficient).

Limitations

For several of the key questions (KQ 1.b-e), studies were quite heterogeneous in terms of design, population, control tests, control strategies, and outcome measures. For the diagnostic accuracy question (KQ 1.a), the main challenge relates to the lack of true gold standard for diagnosis.

Applicability

The current literature reports on patients and settings similar to contemporary clinical practice. Clinicians considering FeNO as an adjunct to diagnose asthma should expect a fair number of false negatives and an even a larger number of false positives and should be aware of pretest odds (prevalence).

Suggestions for Future Research

- Studies with explicit asthma diagnostic criteria and better stratification according to asthma phenotype are needed to identify populations who may benefit from serial FeNO measurement.
- Studies of FeNO-based medication titration are needed and should focus on symptomatic patients with previously documented elevated FeNO. Studies evaluating disease activity and outcomes should use validated measures of activity and well defined outcomes.
- The role of serial FeNO measurements in children ages 0-5 year who develop illness associated with wheezing remains unclear. Cohort studies of such infants with follow up into later years of childhood and adolescence are needed to establish if persistently elevated levels correlate with increased risk of ultimate asthma diagnosis.

Conclusions

FeNO has moderate accuracy to diagnose asthma in people ages 5 years and older. Test performance is modestly better in steroid-naïve asthmatics, children, and nonsmokers than the general population with suspected asthma. Algorithms that include FeNO measurements can help in monitoring response to anti-inflammatory or long-term control medications, including dose titration, weaning, or treatment adherence. At this time, there is insufficient evidence supporting the measurement of FeNO in children under the age of 5 as a means for predicting a future diagnosis of asthma.

References

1. National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group. Needs Assessment Report for Potential Update of the Expert Panel Report-3 (2007): Guidelines for the Diagnosis and Management of Asthma. 2015. https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/Asthma-Needs-Assessment-Report.pdf. Accessed July 18, 2016.

Introduction

Background

Asthma is a chronic inflammatory disorder of the airways, characterized by varying degrees of airflow obstruction. Bronchoconstriction, inflammatory cell infiltration, and airway edema reduce airflow intermittently, often in response to specific exposures, resulting in respiratory symptoms.[1] In the United States (U.S.), the current prevalence of asthma has increased over the past decade, from an estimated 22.2 million Americans in 2005 to 24.0 million Americans in 2014.[2, 3] Asthma can significantly affect patients' and families' quality-of-life and ability to pursue activities such as school, work, and exercise. Globally, asthma ranks 14th based on the burden of disease, as measured by disability adjusted life years.[4] In US, asthma contributes significantly to health care resource utilization and associated costs. For example, in 2012, asthma was one of the top 20 leading diagnosis groups for primary care visits and was the main reason for 1.8 million emergency department visits and 439,000 hospitalizations. Although the severity of disease varies among patients and over time in the same patient, asthma can be fatal, accounting for approximately one death per 100,000 Americans.[5]

Diagnosing asthma is challenging. The common symptoms, such as shortness of breath, wheezing, and cough, are relatively non-specific. Various tests, including spirometry pre and post bronchodilator, and bronchoprovocation challenge, may be used by clinicians to aide in the diagnosis of asthma in the appropriate clinical context. However, the diagnosis remains clinical, based on compatible symptoms and evidence of reversible airway obstruction; no single criterion standard diagnostic test exists. More recently, fractional exhaled nitric oxide (FeNO) concentration has been added to the list of tests that clinicians may use to diagnose asthma, select treatment options, and monitor the response to therapy.

Nitric oxide (NO) is a gas normally found in each exhaled breath in all humans. Patients with asthma often have increased levels of inducible nitric oxide synthase (iNOS2), the enzyme that produces NO in their airway epithelium. Patterns of airway inflammation in asthma are heterogenous. Atopic asthma appears to be associated with a Th2 cytokine pattern of inflammation, with increased levels of IL4 ,IL5 , and IL13. Th2 inflammation is also associated with elevated IgE levels and eosinophilia. IL13 production leads to an influx of eosinophils to inflamed tissue and their continued presence there. IL5 leads to eosinophil differentiation, maturation and activation. Sampling airway tissue, or even evaluating sputum for eosinophilia, can be technically difficult, and labor intensive. FeNO measurement has been evaluated as a surrogate biomarker for eosinophilia/Th2 inflammation. Studies evaluating specific therapies targeting the cytokines involved in Th2 inflammation individually suggest that blocking IL13 leads to a reduction in FeNO levels, whereas reductions in IL-5 do not cause reduction in FeNO levels.[6]

FeNO can be measured by exhalation into an analyzer. It has been found to be elevated in patients with atopic asthma (i.e., asthma associated with either positive skin test or specific IgE to aeroallergens) and was shown to correlate modestly with eosinophilia in sputum and endobronchial biopsy in steroid-naïve patients.[7-11] It has also been found to be elevated in both children and adults with atopy without a diagnosis of asthma, (eg atopic rhinitis).[12, 13]

FeNO levels in atopic patients appear to correlate with number of positive skin prick tests and tests of bronchial hyperresponsiveness.[13] There is a significant overlap in patients with atopic upper and lower respiratory tract disease, and other studies have found occult obstruction on pulmonary function testing in patients with chronic rhinosinusitis.[14]

In young children, the diagnosis of asthma is particularly challenging, given their inability to perform some of the diagnostic tests used in older individuals and the high prevalence of wheezing in children with respiratory infections. One potential use of FeNO is to predict which children who have repeated episodes of wheezing are likely to be diagnosed with asthma later in childhood. There are some data to suggest that FeNO compares favorably to other predictive tests to address the challenges in such children.[15-17]

In individuals who have been diagnosed with asthma, FeNO may be useful to predict which treatments are likely to be most helpful to a given patient, to follow the response to treatment, or to aid in the assessment of adherence to certain therapies (e.g., inhaled corticosteroids).[18] Ascertaining whether a patient has ‘responded" to a given therapy can be difficult, given the inherent variability in the disease, the non-specific nature of many measures of response, and the time required to demonstrate an effect of treatment. In addition, as an inflammatory marker, FeNO may also identify patients in whom non-compliance with anti-inflammatory medications (such as inhaled corticosteroids) may be an issue.

Multiple factors may confound the interpretation of FeNO data. These include asthma phenotype, atopy, use of inhaled or oral corticosteroids, patient's weight, and age. In addition, FeNO measurements can be affected by acute changes proximal to the time of testing, such as exposure to tobacco smoke, use of bronchodilators, fasting state or food intake, or use of mouthwash. Moreover, the criteria for the "normal" range of FeNO (and the level considered diagnostic of a disease state, such as asthma) and the level of change in FeNO that is clinically significant remain uncertain.

Purpose and Scope of the Systematic Review

In 1989, the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health initiated the National Asthma Education and Prevention Program (NAEPP) to address growing concern about asthma in the US. One of the first accomplishments of the NAEPP was to convene a panel of experts who produced a report, National Asthma Education and Prevention Program Expert Panel Report (EPR): Guidelines for the Diagnosis and Management of Asthma, in 1991. The guidelines address the diagnosis, evaluation, and treatment of asthma. Given the most recent report, EPR-3, was published in 2007,[1] NHLBI assessed the need for an update by requesting information from the public, NAEPP Coordinating Committee Members and its affiliates, and members of the 2007 Expert Panel. Collected information was provided to the NHLBI Advisory Council Asthma Expert Working Group, which produced a report to summarize the process and recommendations from their needs assessment.[19] The Working Group identified six high priority topics that should be updated. For each topic, key questions meriting a systematic literature review were formulated. NHLBI engaged AHRQ to perform the systematic reviews through its Evidence-based Practice Centers (EPC). This document represents the systematic review of "The Role of FeNO in the diagnosis and treatment of asthma". The review also will highlight areas of controversy and identify needs for future research on this priority area.

We address the following Key Questions (KQs) as they pertain to the PICOTS (population, interventions, comparisons, outcomes, timing, and setting) (Table 1). Figure 1 shows the analytic framework that we developed for this systematic review.

Key Questions (KQs)

KQ 1: What is the clinical utility of FeNO measurements in the management of asthma in addition to, or instead of, other tests that might be performed? Specifically,

- a: What is the diagnostic accuracy of FeNO measurement(s) for making the diagnosis of asthma in individuals ages 5 and older?
- b: What is the clinical utility of FeNO measurements in monitoring disease activity and asthma outcomes in individuals with asthma ages 5 and older?
- c: What is the clinical utility of FeNO measurements to select medication options (including steroids) for individuals ages 5 and older?
- d: What is the clinical utility of FeNO measurements to monitor response to treatment in individuals ages 5 and older?
- e: In children ages 0-4 years with recurrent wheezing, how accurate is FeNO testing in predicting the future development of asthma at age 5 and above?

Table 1. PICOTS (population, interventions, comparisons, outcomes, timing, and setting)

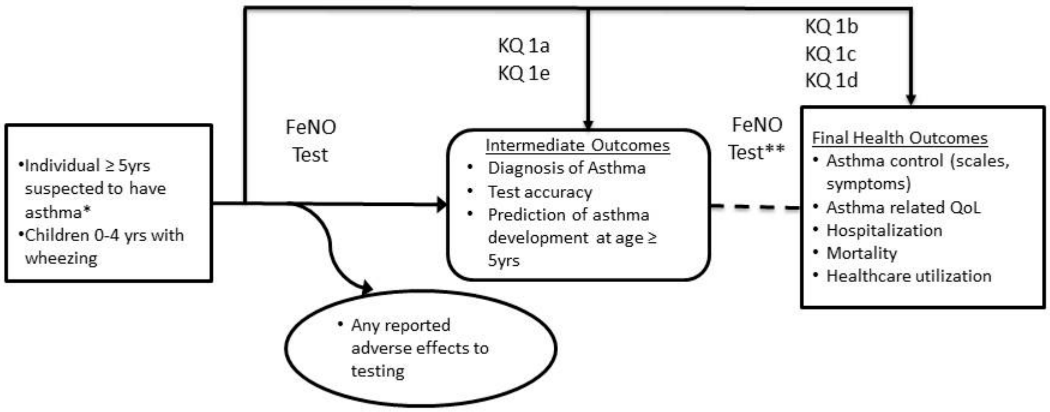
Key Question	Population	Interventions	Comparisons	Outcomes	Timing	Setting
KQ 1.a	Ages 5 years and older suspected to have asthma, especially those who experience wheezing with respiratory tract infections.	FeNO measurement (single or multiple measurements done one-time or as longitudinal measurements over time).	Standard diagnostic testing of asthma made by health care providers based on history, clinical course and the available tests (spirometry, bronchodilator responsiveness, bronchoprovocation challenge, sputum eosinophils; peripheral blood eosinophils; peak flow variability)	Diagnostic accuracy measures (sensitivity and specificity, positive and negative predictive values, likelihood ratios of a positive and negative test)	Studies with any duration of followup	Outpatient and hospital
KQ 1.b	Ages 5 years and older with asthma (all levels of severity)		Standard monitoring methods of asthma made by health care providers based on history, clinical course and the available tests (spirometry, peak flow, assessment of symptoms using questionnaires (ACQ, ACT)	1) Asthma control composite scores (ACT, ACQ) 2) Exacerbations (systemic corticosteroids use, hospitalizations, ED visits, ICU admission/intubations, death) 3) Health care utilization and costs (inpatient and outpatient visits,		
KQ 1.c			Selection of medications by health care providers based on history, clinical course and the available			

Key Question	Population	Interventions	Comparisons	Outcomes	Timing	Setting
			tests (blood eosinophils, induced sputum, bronchalveolar lavage, allergy tests (skin testing, serum allergen specific IgE))	medication use, resource use) 4) Spirometry 5) Asthma specific quality of life (AQLQ, PAQLQ, PACQLQ) 6) Adherence to treatment 7) Adverse events to FeNO testing		
KQ 1.d			Response to treatment as determined by health care providers based on history, clinical course and the available tests (spirometry, peak flow, assessment of symptoms using questionnaires (ACQ, ACT)			
KQ 1.e	Ages 0-4 years with recurrent wheezing episodes at the time of testing but outcome ascertained at age 5 or older		Diagnosis of asthma and Asthma Predictive Index	Incidence, positive and negative predictive values for asthma diagnosis in children ages 5 and above		

ACQ: Asthma Control Questionnaire; ACT:Asthma Control Test; AQLQ: Asthma Quality of Life Questionnaire; ED: emergency department; FeNO:Fractional exhaled nitric oxide; ICU:intensive care unit; IgE:immunoglobulim E; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; PACQLQ:Pediatric Asthma Caregivers Asthma Quality of Life Questionnaire

Figure 1. Analytic framework

Analytic framework. Fractional Exhaled Nitric Oxide Clinical Utility in Asthma Management.



*Primarily individuals with wheezing & respiratory tract infection although some may not have wheezing
**The purpose of a FeNO Test performed after a diagnosis is established would be to monitor disease activity, choose treatment & assess response to treatment

Methods

To conduct this systematic review, we followed the established methodologies outlined in the EPC *Methods Guide for Comparative Effectiveness Reviews*.[20] We established an 8-member technical expert panel to provide input in the research process, including literature search strategy, additional relevant literature, analysis plan, and reporting findings. The study protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO #: CRD42016047887).

Criteria for Inclusion/Exclusion of Studies in the Review

We included FeNO studies that enrolled patients with suspected asthma (KQ 1.a and KQ 1.e) or confirmed asthma (KQ 1.b-d) who were 5 years of age or older (except KQ 1.e; in which patients were 4 years or younger at the time of FeNO testing). Studies had to evaluate FeNO diagnostic accuracy or clinical utility according to PICOTS (Table 1) and Key Questions (KQs). Both randomized and nonrandomized studies were included for all KQs. We included longitudinal, cross sectional, and case control studies. Uncontrolled case series were included only if they reported adverse effects of FeNO testing.

We excluded studies that did not fit the PICOTS or those with mixed population (e.g. asthma and chronic obstructive lung disease) without reporting separate results for individuals with asthma. We also excluded surveys, narrative reviews, editorials, letters, or erratum, qualitative research, *in vitro* studies, and animal studies.

Literature Search Strategies

We conducted a comprehensive literature search of six databases. Specifically, they were Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Ovid MEDLINE®, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and SciVerse Scopus from the inception of the databases inception to April 4, 2017. A medical librarian developed and executed the search strategy (Appendix A). We used a web-based systematic review software, DistillerSR (Evidence Partners Incorporated, Ottawa, Canada), to facilitate study selection.

We searched relevant systematic reviews and conducted reference mining of relevant publications to identify additional literature. We searched gray literature through all of the following: U.S. Food and Drug Administration (FDA) device registration studies, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ's Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites.

Independent reviewers, working in pairs, screened the titles and abstracts of all citations using pre-specified inclusion and exclusion criteria. Studies included by either reviewer were retrieved for full-text screening. Independent reviewers in pairs screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus. If they did not reach consensus, a third reviewer resolved the difference.

Data Abstraction and Data Management

We developed a standardized data extraction form to extract study characteristics: author, study design, inclusion and exclusion criteria, patient characteristics, interventions, comparisons, outcomes, and related items for assessing study quality and applicability. All study team members pilot-tested the standardized form using 10 randomly selected studies and iteratively modified it as needed. Single reviewers extracted data with a second reviewer verifying all entries. We noted whether FeNO measurement was done online (i.e., real-time gas analysis) or offline (exhaled gas is collected during tidal breathing into impermeable bag for subsequent analysis).

Assessment of Methodological Risk of Bias of Individual Studies

We evaluated the risk of bias of each included study using predefined criteria. For RCTs we used the Cochrane Risk of Bias tool to assess sequence generation; allocation concealment; participant, personnel, and outcome assessor blinding; attrition bias; incomplete outcome data; selective outcome reporting; and other sources of bias.[21] For observational studies, we used items derived from the New Castle Ottawa scale.[22] For diagnostic studies, we used the QUADAS-2 instrument.[23]

Data Synthesis

We narratively summarized the key features and characteristics (e.g., study populations, design, intervention, outcomes, and conclusions) of the included studies and present in evidence tables for each KQs.

For diagnostic questions, we used the symmetric hierarchical summary receiver operating characteristic (HSROC) models to jointly estimate sensitivity and specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic odds ratio (DOR).[24] DOR is a single indicator of diagnostic performance that facilitates comparison across tests. It was defined as the ratio of the odds of positivity in subjects with disease relative to the odds in subjects without disease and is calculated as (true positives × true negatives) / (false positives × false negatives).[25] We also drew the HSROC curves based on the estimates. For clinical utility and harm questions, we used the DerSimonian-Laird random effects model with the Knapp and Hartung adjustment of the variance.[26] We evaluated heterogeneity between studies using the I^2 indicator; we examined potential publication bias by evaluating funnel plots symmetry and Deeks' funnel plot asymmetry tests if the number of studies was large (n>20).

To explore heterogeneity, we conducted subgroup analyses based on factors defined a priori:

- Robustness of "reference test" used in the literature
- Test cutoff values
- Risk of bias
- Control group description
- Tobacco use
- Asthma phenotype (eosinophilic, neutrophilic, paucicellular) or atopy status
- Use of inhaled/oral corticosteroids prior to FeNO testing
- Whether appropriate testing protocol was followed (alcohol consumption, fasting state or food intake, prior use of mouthwash)
- Body mass index (BMI) or weight
- Manufacturer and device model (chemiluminescence, electrochemical methods)
- Exhalation flow rate
- Age (ages 0-4, 5-11, 12 and above).

Grading the Strength of Evidence for Major Comparisons and Outcomes

We graded the body of evidence as per the EPC *Methods Guide on Comparative Effectiveness Reviews* on assessing the strength of evidence (SOE). We focused on the diagnostic accuracy measures, asthma control composite scores, exacerbations, and asthma-specific quality of life.[20] These outcomes are chosen because they are either clinically important from a patient or other stakeholder perspective or highly relevant for decision making (diagnostic accuracy measures).[27] Grading the SOE was done for each comparison and for each outcome.

For outcomes of efficacy and clinical utility, randomized trials start as high strength of evidence and observational studies start as low strength of evidence. The domains considered were: the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs. surrogate outcomes); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of publication bias. When imprecision was associated with a very small sample size (less than an arbitrarily chosen cutoff of 400) or with a wide confidence interval that includes no effect and a relative risk reduction that exceeds 25 percent, we rated down SOE two levels and labeled this as severe imprecision.

In diagnostic studies, observational studies can start as high SOE for diagnostic accuracy outcomes. SOE rating can be rated down primarily because of methodological limitations of the studies, lack of precision, and likelihood of publication bias. We did not rate down for statistical heterogeneity (which is always high in diagnostic meta-analyses) or consider diagnostic accuracy measures as surrogate outcomes.[28, 29]

When studies were heterogeneous in population, intervention and methods; and not appropriate for meta-analysis, we have narratively provided a summary statement about the findings and conveyed our certainty in such findings as a SOE rating.[30-32] In this case and in the absecnce of a single pooled estimate of the effect size, we narratively rated the SOE considering the meaning and connotation of SOE domains (methodological limitations of the studies, precision, directness, consistency and the likelihood of publication bias).[30, 32]

Based on this assessment and the initial study design, we assigned SOE rating as high, moderate, low, or ‘insufficient evidence to estimate an effect’.

Assessing Applicability

We followed the procedures outlined in the EPC *Methods Guide for Comparative Effectiveness Reviews* to assess the applicability of the findings within and across studies.[20] We determined the applicability for each outcome qualitatively using the PICOTS framework. We focused on whether the populations, interventions, and comparisons in existing studies are representative of current practice.

Peer Review and Public Commentary

A draft version of the draft report was posted for peer review and for public comments in April , 2017, and revised in response to comments. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

Search Results

The electronic searches identified 3,884 citations. Additional 61 citations were identified through gray literature search and cross referencing. After title and abstract screening, 955 required full text review and 175 studies met eligibility criteria for inclusion in this review (Figure 2). Studies addressed the key questions as follows:

- 43 studies addressed KQ 1.a about diagnostic accuracy of FeNO measurement.
- 58 studies addressed KQ 1.b about clinical utility of FeNO measurements in monitoring disease activity.
- 24 studies addressed KQ 1.c about clinical utility of FeNO measurements to select medication options, including 14 RCTs, that tested algorithms based on FeNO to guide drug therapy and monitoring.
- 41 studies addressed KQ 1.d about clinical utility of FeNO measurements to monitor response to treatment.
- 9 studies addressed KQ 1.e about the predictive ability of FeNO measures in children less than 5 years of age on the development of asthma in children older than 5 years.

Table 2 summarizes the number of studies included per KQ by study design and age group. A list of the studies excluded at the full-text review stage is in Appendix B. We did not include three studies that were not published in English (one in Spanish, one in Turkish, and one in Japanese). A search of ClinicalTrials.gov identified 93 ongoing studies.

Figure 2. Literature flow diagram

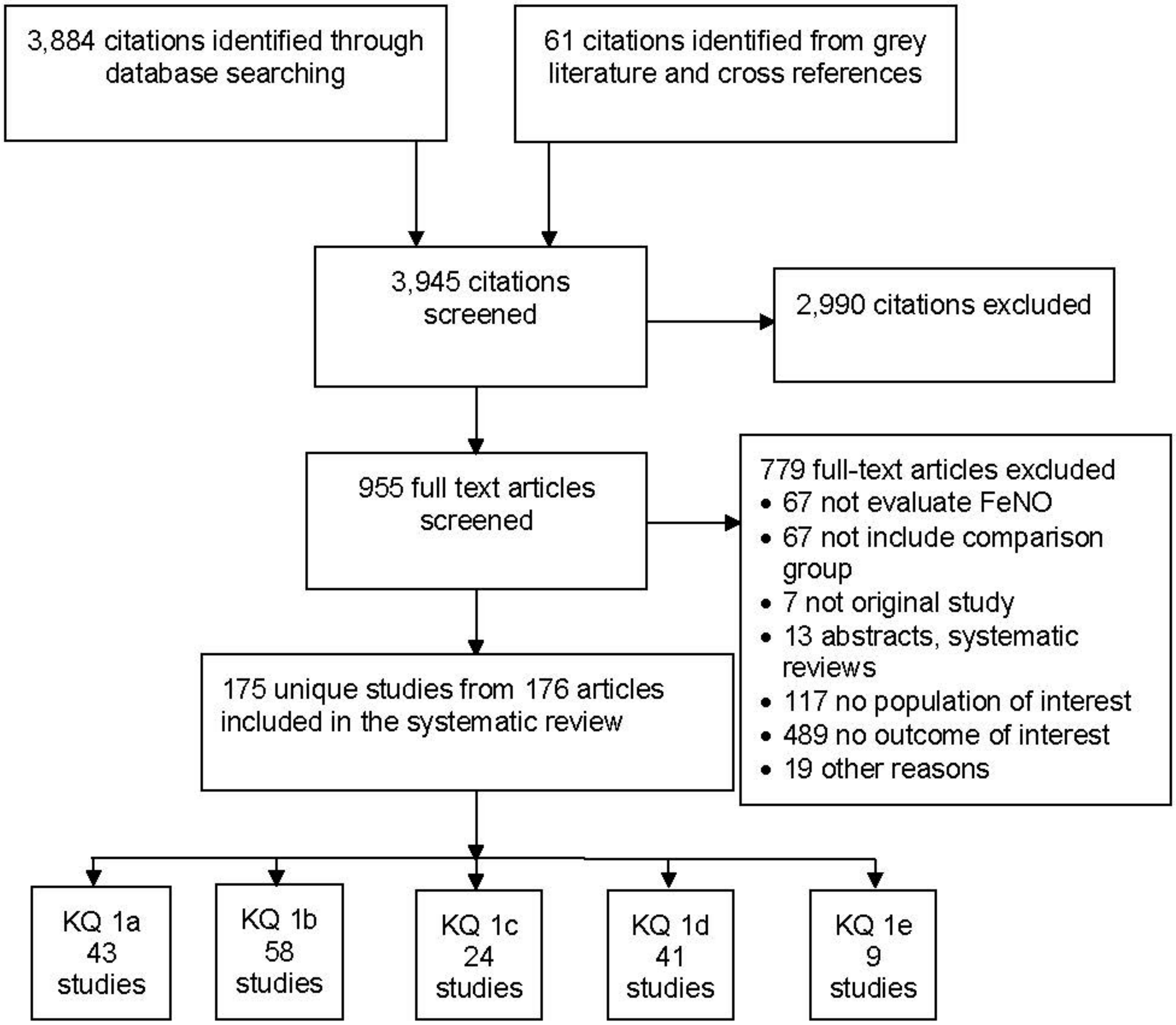


Table 2. Number of studies included per Key Questions, study design, and age group

		KQ1a	KQ1b	KQ1c (RCT/Non RCT)	KQ1d	KQ1e
Study Design	**RCTs**	-	7	14	20	-
	Non RCTs	43	51	10	21	9
Age Group	**≥18 years**	33	30	15	23	-
	13-18 years	4	4	1	2	-
	5-12 years	6	24	8	16	-
	0-4 years	-	-	-	-	9
TOTAL		43	58	24	41	9

KQ: key question; NA: not applicable; RCT: randomized controlled trial

Analysis Results

KQ 1.a: What is the diagnostic accuracy of FeNO measurement(s) for making the diagnosis of asthma in individuals ages 5 and older?

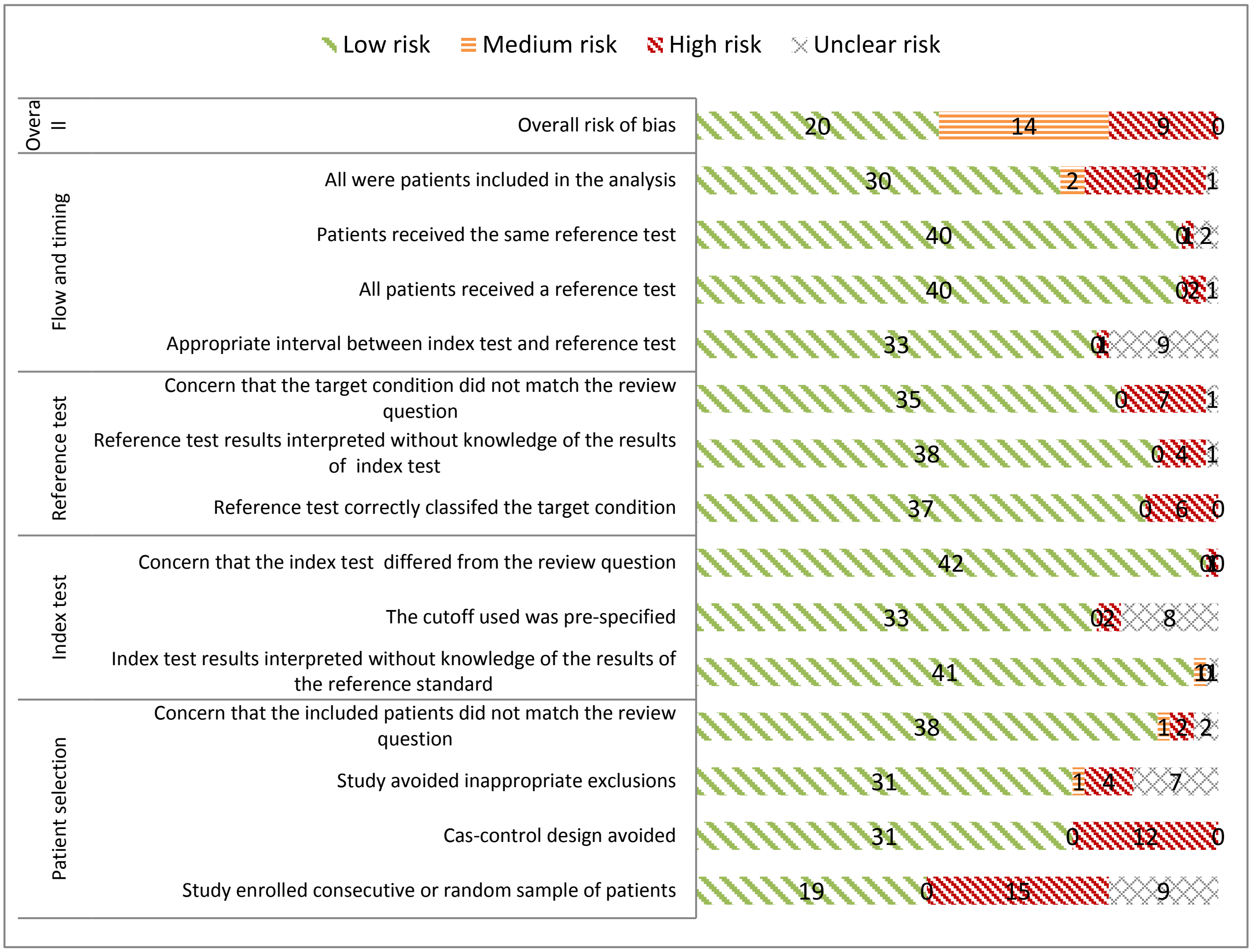
Key Points

- **The diagnostic accuracy of FeNO for the diagnosis of asthma varies with the FeNO level used for diagnosis. Sensitivity and specificity per cutoff were: <20 ppb (0.79, 0.72), 20-30 ppb (0.64, 0.81), 30-40 ppb (0.53, 0.84), ≥40 ppb (0.41, 0.94). (SOE: Moderate).**
- **Depending on the FeNO cutoff, the posttest odds of having asthma given a positive FeNO test result increased by 2.80 to 7.00 fold. (SOE: Moderate).**
- **In steroid-naïve asthmatics, FeNO had the highest accuracy at cutoffs of <20 ppb compared to all patients included in the main analysis (sensitivity 0.79, specificity 0.77 and diagnostic odds ratio (DOR) 12.25).**
- **Diagnostic accuracy is higher in nonsmokers (compared to smokers) and in children (compared to adults).**

Forty-three studies with a total of 13,747 patients were included for analysis. The characteristics of these studies are in Appendix Table C.1. The majority of the studies (33 studies) included only adults >18 years old; 6 studies had children with average age 4-12 years and 4 included patients with average age 13-18 years. 19 studies were nonrandomized longitudinal studies, 23 cross sectional studies, and 1 case-control study. The studies were conducted in the United States (n=2), Canada (n=2), Europe (n=26), and other countries (n=13).

FeNO was measured online in 10 studies, offline in 3, and 1 used both methods. In terms of reference test used to compare with FeNO, 12 studies used clinical diagnosis, 13 used positive bronchial challenge test, and 20 combined tests (clinical diagnosis, positive bronchial challenge, and/or bronchodilator response). The majority of the studies had low or medium risk of bias. High risk of bias was noted primarily in the areas of cohort selection, including representativeness of the study population (whether patients were consecutive and represented the total eligible patients in a particular institution) and whether studies enrolled patients with diagnostic uncertainty (i.e., with symptoms suggestive of asthma). The details of risk of bias assessment are presented in Appendix Table G.1 and summarized in Figure 3. The overall risk of bias was low in 47% of the studies. Since the risk of bias was unclear or high in about half of the studies, the SOE was rated down to moderate.

Figure 3. Risk of bias assessment for diagnostic accuracy studies using QUADAS-2 (n= 43, KQ 1.a)



Using Deeks' funnel plot asymmetry tests and visual inspection of funnel plots, we found potential publication bias for cutoffs<20, and no indication of publication bias for cutoffs 20-30 (Appendix Figures D.10-11). We were not able to evaluate potential publication bias for other cutoffs. Overall there was no strong evidence of publication bias.

For cutoffs of <20, 20-30, 30-40, and ≥40 parts per billion (ppb); respectively, FeNO testing has sensitivities of 0.79, 0.64, 0.53, and 0.41; and specificities of 0.72, 0.81, 0.84, and 0.94. Overall DORs ranged from approximately 5.85 to 16.95 (Appendix Figure D.1-4). The strength of evidence assessment is summarized in Table 3. Detailed assessment of SOE is available in Appendix Table H.1.

Table 3. Strength of evidence (SOE) for KQ 1.a

FeNO CutOff [a]	Reference Test	Study Design and Sample Size	Conclusion	SOE (Rationale)
<20 ppb	Clinical diagnosis	8 observational studies[33-40] (1,199 Patients)	Sensitivity 0.79; 95% CI (0.58 to 0.91) Specificity 0.82; 95% CI (0.67 to 0.91) DOR 16.95; 95% CI (6.65 to 43.19) LR+ 4.40; 95% CI (2.40 to 8.06) LR- 0.26; 95% CI (0.13 to 0.53)	Moderate (risk of bias)
	Positive bronchial challenge	5 observational studies [38, 41-44] (320 Patients)	Sensitivity 0.83; 95% CI (0.72 to 0.91) Specificity 0.64; 95% CI (0.46 to 0.79) DOR 8.68; 95% CI (2.94 to 25.65) LR+ 2.30; 95% CI (1.38 to 3.82) LR- 0.26; 95% CI (0.14 to 0.51)	Moderate (risk of bias)
	Combination of clinical diagnosis, bronchial challenge, and/or Bronchodilator response	9 observational studies [45-53] (2,683Patients)	Sensitivity 0.79; 95% CI (0.68 to 0.87) Specificity 0.65; 95% CI (0.44 to 0.81) DOR 6.88; 95% CI (3.15 to 15.01) LR+ 2.23; 95% CI (1.36 3.65) LR- 0.32; 95% CI (0.21 to 0.50)	Moderate (risk of bias)
	Overall (all available studies regardless of reference test)	21 observational studies [33-53] (4,129 Patients)	Sensitivity 0.79; 95% CI (0.71 to 0.86) Specificity 0.72; 95% CI (0.59 to 0.81) DOR 9.70; 95% CI (5.57 to 16.90) LR+ 2.80; 95% CI (1.94 to 4.03) LR- 0.29; 95% CI (0.21 to 0.40)	Moderate (risk of bias)
20-30 ppb	Clinical diagnosis	5 observational studies [37, 40, 46, 54, 55] (2,637 Patients)	Sensitivity 0.64; 95% CI (0.36 to 0.85) Specificity 0.85; 95% CI (0.70 to 0.93) DOR 10.35; 95% CI (2.58 to 41.61) LR+ 4.32; 95% CI (1.98 to 9.91) LR- 0.42; 95% CI (0.20 to 0.89)	Moderate (risk of bias)
	Combination of clinical diagnosis, bronchial challenge/ Bronchodilator response	15 observational studies [45-48, 51-53, 56-64] (2,327Patients)	Sensitivity 0.63; 95% CI (0.55 to 0.70) Specificity 0.79; 95% CI (0.69 to 0.87) DOR 6.53; 95% CI (4.06 to 10.52) LR+ 3.06; 95% CI (2.09 to 4.47) LR- 0.47; 95% CI (0.39 to 0.56)	Moderate (risk of bias)
	Overall (all available studies regardless of reference test)	22 observational studies [37, 39-41, 45-48, 51-65] (5,189 Patients)	Sensitivity 0.64; 95% CI (0.55 to 0.72) Specificity 0.81; 95% CI (0.74 to 0.87) DOR 7.62; 95% CI (4.72 to 12.30) LR+ 3.39; 95% CI (2.43 to 4.73) LR- 0.44; 95% CI (0.35 to 0.56)	Moderate (risk of bias)
30-40 ppb	Overall (all available studies regardless of reference test)	10 observational studies [42, 44-47, 51, 57, 66-68] (1,753 Patients)	Sensitivity 0.53; 95% CI (0.37 to 0.68) Specificity 0.84; 95% CI (0.77 to 0.89) DOR 5.85; 95% CI (3.64 to 9.41) LR+ 3.29; 95% CI (2.52 to 4.31) LR- 0.56; 95% CI (0.42 to 0.76)	Moderate (risk of bias)

FeNO CutOff [a]	Reference Test	Study Design and Sample Size	Conclusion	SOE (Rationale)
>=40 ppb	Combination of clinical diagnosis, bronchial challenge/ bronchodilator response	8 observational studies [45, 46, 52, 58, 60, 63, 69, 70] (1,142 Patients)	Sensitivity 0.40; 95% CI (0.24 to 0.58) Specificity 0.95; 95% CI (0.92 to 0.97) DOR 13.16; 95% CI (7.21 to 24.02) LR+ 8.36; 95% CI (5.20 to 13.44) LR- 0.64; 95% CI (0.48 to 0.83)	Moderate (risk of bias)
	Overall (all available studies regardless of reference test)	10 observational studies [42, 45, 52, 58, 60, 63, 69-72] (1,368 Patients)	Sensitivity 0.41; 95% CI (0.27 to 0.57) Specificity 0.94; 95% CI (0.89 to 0.97) DOR 11.17; 95% CI (6.67 to 18.71) LR+ 7.00; 95% CI (4.43 to 11.07) LR- 0.63; 95% CI (0.49 to 0.80)	Moderate (risk of bias)

CI:Confidence interval; DOR:diagnostic odds ratio; FeNO:Fractional exhaled nitric oxide; LR+ : likelihood ratio for a positive test; LR- : likelihood ratio for a negative test; SOE:Strength of evidence

[a] Only rows with available data are presented. Subgroups without data are omitted.

Subgroup and Sensitivity Analyses

Data on the diagnostic accuracy of FeNO for asthma were insufficient to assess the impact of several factors as planned in the protocol. The feasible subgroup analyses had been based on FeNO cutoffs, the type of reference test (clinical diagnosis, positive bronchial challenge, and a combined test (clinical diagnosis, positive bronchial challenge, and/or bronchodilator response), risk of bias, tobacco use, age group (age<=18 years vs. age >18 years), and whether the control group consisted of healthy controls (vs. symptomatic individuals without a diagnosis of asthma). The findings of the subgroup analyses were summarized as follows:

- Analysis of the impact of the FeNO levels used for diagnosis of asthma showed that cutoff levels affect sensitivity and specificity, with increasing specificity and decreasing sensitivity as cutoffs increased above 20 ppb (Table 3). Cutoffs of ≥ 40 ppb had the highest accuracy but were not as sensitive.
- Assessment of the impact of the reference test (Table 3) showed that the reference test may partially explain heterogeneity in the diagnostic accuracy of FeNO (comparative data were available mostly for cutoffs < 20 ppb).
- Control group characteristics impacted the diagnostic accuracy of FeNO; the diagnostic accuracy of FeNO may be overestimated in studies that used healthy controls compared to symptomatic controls (for cutoffs <20 ppb, DOR was 16.45 for healthy controls compared to 4.42 for symptomatic controls) (Appendix Table E.1).
- Subgroup analysis based on the risk of bias showed that the risk of bias may partially explain heterogeneity in the diagnostic accuracy of FeNO with greater reported diagnostic accuracy as the risk of bias increases (DORs across cutoffs of 10.97, 8.15 and 7.29 for high, medium and low risk; respectively) (Appendix Table E.2).
- Subgroup analysis based on tobacco use showed that the diagnostic accuracy was markedly higher in studies of nonsmokers comparing to smokers. (Appendix Table E.3).
- Subgroup analysis based on age showed that diagnostic accuracy was overall higher in children (age <= 18 years) than adults (age > 18 years) (Appendix Table E.4).

In a sensitivity analysis, we were only able to analyze studies that evaluated the diagnostic accuracy of FeNO in steroid-naïve asthmatics (the remaining studies had a mix of population, steroid naïve, and steroid users). At cutoffs of <20 ppb, FeNO had the highest accuracy in this group of patients compared to patients in the main results (sensitivity 0.79, specificity 0.77 and DOR 12.25). Results in other cutoffs were different and inconsistent. In another sensitivity analysis, we analyzed only studies that evaluated the diagnostic accuracy of FeNO in asthmatic patients with atopy. The results, which included a small number of studies (n=4), showed accuracy measures that were similar to those from the main analysis (sensitivity 0.63; specificity 0.79; DOR 6.67) (Appendix Table F.1).

KQ 1.b: What is the clinical utility of FeNO measurements in monitoring disease activity and asthma outcomes in individuals with asthma ages 5 and older?

Key Points

- **In adults (ages >18) and children (ages 5 -18), FeNO levels are weakly associated with asthma control (as measured by the ACQ and ACT).This associateion can be further attenuated in those who smoke, pregnant or are on ICS. (SOE: Low)**
- **In adults (ages >18) and children (ages 5 -18), FeNO levels have a weak association with the risk of subsequent and prior exacerbations. (SOE: Low) The association between FeNO levels and exacerbation risk is likely increased in individuals (ages>5 years) with atopy. (SOE: Low)**
- **In adults (ages >18) and children (ages 5 -18)with acute asthma exacerbations, FeNO levels do not correlate with exacerbation severity and were poorly reproducible. (SOE: Low)**
- **In children (ages 5 - 12) and adolescents (ages 13 - 18), FeNO levels were inversely associated with adherence to asthma medications (mainly ICS). (SOE: Low)**

58 studies with a total of 8,999patients were included in KQ 1.b. The characteristics of these studies are in Appendix Table C.2 and C.3. 30 studies included only adults >18 years old; 24 studies had children with average age of 5-12 years and 4 included patients with average age of 13-18 years. 34 studies were nonrandomized longitudinal studies, 7 RCTs, and 17 cross sectional studies. The studies were conducted in the United States (n=9), in Canada (n=1), in Europe (n=33), and in other countries (n=15).

FeNO was measured online in 20 studies, offline in 3, and 1 used both methods. Heterogeneity in study populations, designs, and outcome types precluded meta-analysis; therefore, we presented these data in narrative form only. The detailed risk of bias assessment is presented in Appendix Table G.2 and Table G.3 and summarized in Figures 4 and 5 for randomized controlled trials and observational studies; respectively. The risk of bias was low or medium overall in most of the RCTs and observational studies.

Figure 4. Risk of bias assessment of randomized controlled trials using the Cochrane Risk of Bias tool (n=7, KQ 1.b)

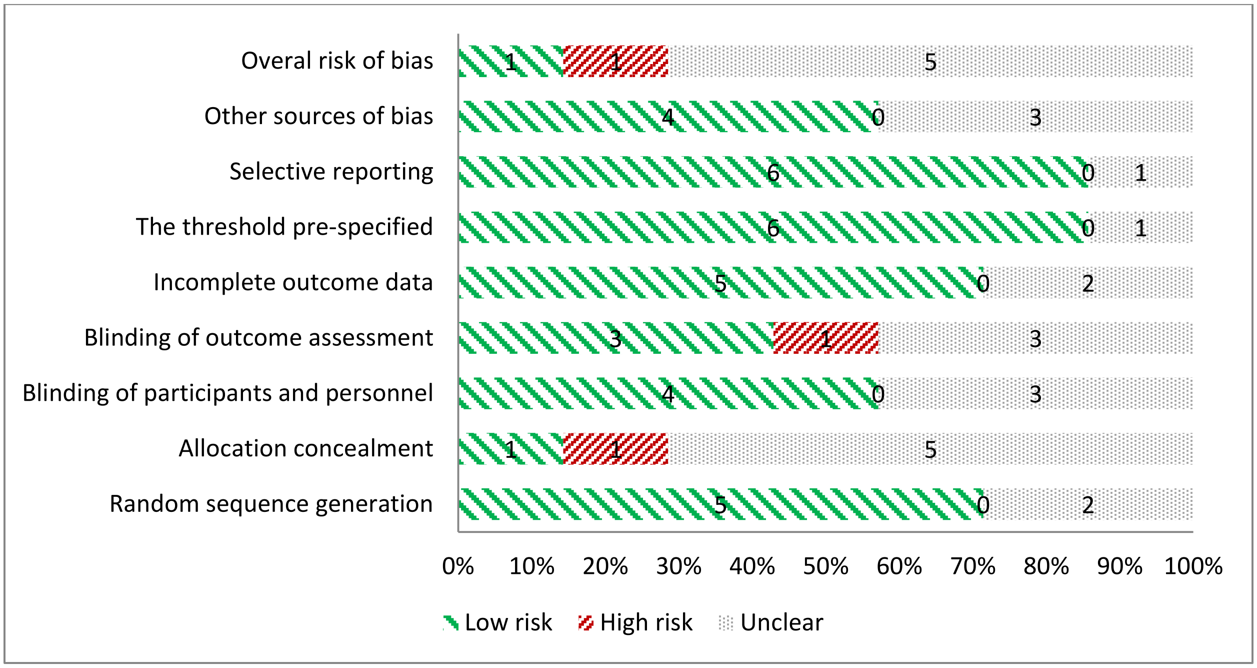
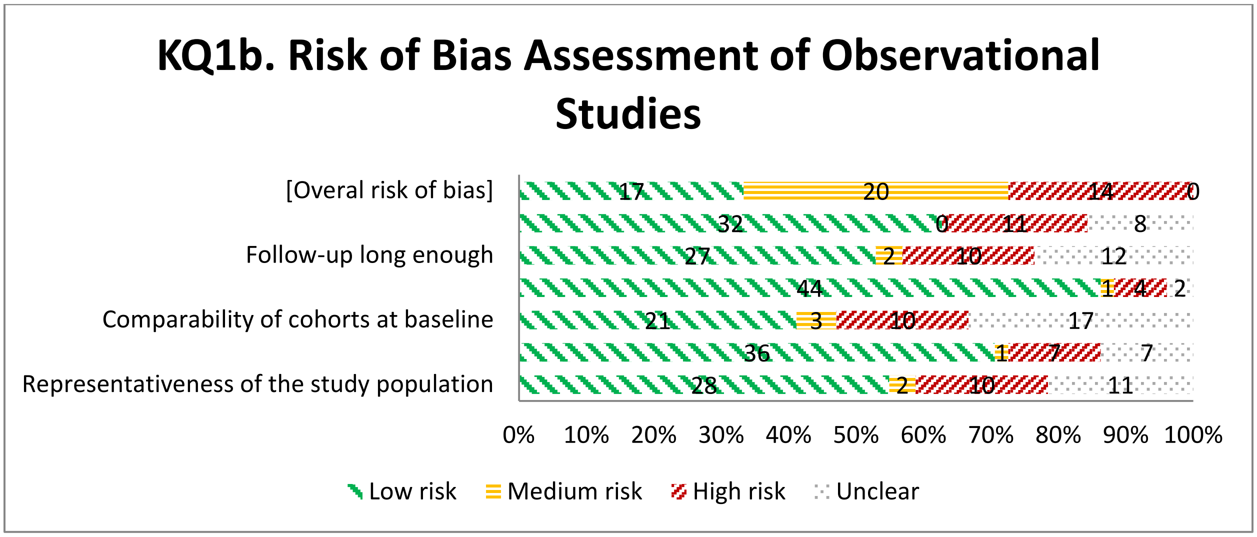


Figure 5. Risk of bias assessment of observational studies using the New-Castle Ottawa Scale (n=51, KQ 1.b)



Using FeNO To Monitor Asthma Control and Predict Exacerbations

Adults (ages >18 years)

Five studies assessed the correlation between FeNO measurements and ACQ scores, a measure of asthma control. Overall, the correlation was weak, and FeNO did not reliably differentiate patients who were well-controlled versus borderline controlled versus not well-controlled.[73-77] In a cross sectional study, a single measurement of FeNO had lower area under the curve (AUC) (0.59) for identifying uncontrolled asthmatics (defined using ACQ-7) than sputum eosinophils (0.72) or methacholine responsiveness (0.72)[73]. In a prospective study, adults with not well controlled persistent asthma and a positive bronchodilator test had maintenance treatment adjusted at the beginning of the study and were reevaluated after 4 weeks using ACQ-7 versus ACQ-7+ FeNO. The combination of FeNO and ACQ-7 demosntrated 14.8% higher proportion of patients with not well controlled asthma.[77]

An inverse correlation between ACT scores and FeNO was noted across numerous studies with various ACT and FeNO cutoffs.[78-86] The correlation (r) between FeNO and ACT in patients on ICS for 3 months was -0.31 in one study.[85] In another study, mean FeNO values were significantly higher in patients with an ACT score <20 compared to those patients with an ACT score ≥20 (65.5 vs 27.4 ppb, p<0.001).[78] FeNO level of >47 ppb was used to indicate inflammation and uncontrolled asthma. The best pair of sensitivity and specificity and AUC were observed at ACT cutoff of 19 (0.91, 0.81 and 0.91; respectively) whereas at ACT cutoff of 20 the sensitivity was 95.2, and the specificity was 68.8.[78] In a study of steroid naïve nonsmoking asthmatics, FeNO level strongly correlated with ACT at baseline and after 6-8 weeks of ICS treatment (r= - 0.74 and -0.68; respectively).[87]

In a study of patients with established stable asthma without recent exacerbations, FeNO had AUC of 0.79 for the identification of not well-controlled asthma (determined by ACT following GINA cutoffs).[79] AUC was, however, lower in those who smoked (smokers on ICS with FeNO cutoff of > 23 ppb had AUC of 0.60; and smokers not on ICS with FeNO cutoff of > 19 pbb had AUC of 0.68).[79] FeNO values >30 ppb were associated with positive predictive values > 0.85, indicating a status of not well-controlled asthma (except in smokers).[79] In a study with older population (ages>65 years), FeNO values were statistically significantly higher in those with uncontrolled asthma than those with controlled/partly controlled (regardless of whether asthma control was determined using GINA control criteria or using ACT with a cutoff of 19).[80]

The association between asthma control and FeNO was weakened in patients on ICS as observed in four studies.[79, 81-83] In addition, pregnant women who had monthly FeNO measurements showed a weak correlation between FeNO and ACT and wide variation in FeNO values. Results were the same in atopic and non atopic women. FeNO levels did not significantly differ in women before and after they lost asthma control.[84] In a prospective study that followed patients who were mostly on ICS (age 10 and over) for 12 weeks, FeNO did not correlate with ACQ or with shortened ACQ (without FEV_1).[86]

In terms of the use of FeNO to predict asthma exacerbations, several studies showed higher FeNO values in patients who had had exacerbations prior to the test (retrospective analysis) or had developed exacerbations after the test (prospective analysis).[88-90] However; in one study of 267 adult asthmatics recruited from primary care clinics, FeNO values measured 12 months before and 3 months after exacerbations were significantly *lower* in frequently exacerbating patients receiving higher doses of maintenance ICS (compared to patients with mild disease who were corticosteroid naïve).[88] In that study, measurement of FeNO was an insensitive method for identifying patients who subsequently exacerbated (sensitivity, 66.7%; specificity, 51.9% at a cutoff value of 20 ppb) suggesting that intensive ICS treatment can confound the clinical utility of FeNO.[88] In another study, baseline FeNO values did not predict urgent care visits or exacerbations over the subsequent 6 months.[76] In asthmatic patients on ICS, FeNO >40 ppb yielded 0.75 sensitivity and 0.90 specificity for identifying subjects with high variability in peak expiratory flow (which may suggest increased variation in airway caliber among patients with stable asthma).[89] In atopic 12 to 56-year-old persistent asthmatic patients on ICS, higher FeNO levels were significantly correlated with more short-acting beta agonists dispensing and oral steroids courses in the past year, and lower FEV_1 percent predicted levels.[83] In another small study, 22 adults with moderate and severe persistent asthma who had an exacerbation in the previous 2 weeks had a higher mean FeNO value compared to those who did not (29.7 ppb vs. 12.9 ppb).[90] In a multivariable regression, FeNo was the only significant predictor of exacerbations (whereas patients' assessment of their own disease, peak flow, ICS dose, and FEV_1 were not).[90]

Summary

In adults with asthma, numerous observational studies showed that FeNO levels have weak associations both with asthma control (as measured by ACQ and ACT) and that FeNO can modestly predict exacerbations. The magnitude of association between FeNO and control tests is likely reduced in patients on ICS, smoke, or pregnant. The overall strength of this evidence is low because of the observational nature of the majority of evidence.

Children (ages 5 to 18)

Thirty studies evaluated the association of FeNO levels with asthma control. The definition of asthma control, however, varied among studies although commonly depended on history, clinical symptoms, and lung function. Asthmatic children (n=133, aged 5 to 14 years) who had recent symptoms (within the preceeding month of the test) compared to those without recent symptoms had higher FeNO levels (14.6 ppb vs. 6.0 ppb, p=0.004). FeNO levels also differed significantly between the controlled and uncontrolled subgroups (8.5 ppb vs. 26.4 ppb, p-0.03).[91]Another cross sectional study recruited children with stable asthma (majority were on ICS, majority were allergic defined by a radio-allergosorbent test class 2 or higher or a positive skin test).[92] Children with insufficient, acceptable, or good control of asthma had FeNO levels of 28 ppb, 15 ppb, 11ppb; respectively ($p<0.01$).[93] Conversely in another study, children with allergic rhinitis and stable non severe asthma, FeNO was elevated but did not correlate with nasal or asthma symptoms.[92] A prospective study also showed that FeNO values did not correlate with current disease severity in children (determined using history, clinical symptoms, and lung function). Values above normal (defined in this study as > 13 ppb) had a sensitivity of 0.67 and a specificity of 0.65 to predict a step up in therapy by providers.[94] In another study, FeNO at a cutoff point of 22.9 ppb had moderate accuracy (sensitivity of 80% and specificity of 60%) to predict exacerbations in children with mild to moderate asthma who were managed using symptoms, b-agonist use, lung function, and FeNO (measured during 5 visits in 6 weeks intervals).[95] In a prospective study of patients with atopic asthma (mean age 12.6, range 7-20), FeNO of 31 ppb provided optimal sensitivity (92.3%) and specificity (75.4%) to predict subsequent exacerbations.[96]

In a cross sectional study of children with asthma (mostly mild persistent), FeNO levels differentiated controlled, partly controlled, and uncontrolled in those not on ICS (but the trend was not statistically significant in patients on ICS).[97] In another study in children on ICS, FeNO measured every 2 months did not predict exacerbations even when combined with inflammatory markers and clinical characteristics.[98] In high risk children (minorities in urban areas with persistent asthma and atopy) on controller medication, FeNO measurement every 3 months was not a significant predictor of acute visits, emergency department visits, unscheduled doctor visits, or hospitalization in adjusted analysis.[99] Four other studies also suggested no or weak association of FeNO and ACT in ICS users.[100-103]

In children with atopic asthma, FeNO was significantly elevated in those with exercise induced reduction of FEV_1 (> 15%) with a negative predictive value (NPV) of 100% and a positive predictive value (PPV) of 28%. NPV and PPV for reported asthma symptoms within 2 weeks preceding the study were 96% and 26%. Thus, FeNO had good utility to exclude exercise-induced bronchoconstriction in atopic children.[104] In another study in which 33 percent of the asthmatic children age 4-7 had atopic dermatitis, FeNO values correlated with asthma severity, atopic dermatitis and steroids use; and marginally with allergic rhinitis (p=0.06).[105] And in a third study in patients aged 8-16 years with atopic asthma not receiving daily controller therapy and monitored bi-monthly over 2 years, loss of asthma control was predicted by the highest FeNO value of serial measurements and the percentage of sampling time points when FeNO > 21 ppb.[106] Lastly, one RCT enrolled 280 children with atopic asthma and compared three management approaches: web-based monthly monitoring of ACT, versus FeNO and ACT every 4 months, versus standard care. There was no difference in terms of ACT or asthma free days. Lower ICS use was noted in the web based approach. Quality-adjusted life years (QALYs) and costs were not statistically significantly different.[107, 108]

Summary

In children with asthma, evidence from numerous studies suggests that FeNO levels have weak association with ACT, and risk of exacerbation. There is some evidence to suggest that the association may be attenuated in patients on ICS but increased in those with atopy. The overall strength of this evidence is low because of the observational nature of the majority of evidence.

Utility of FeNO Testing in the Acute Setting (during exacerbations)

In children with acute exacerbation of asthma, FeNO during exacerbation was not higher than median values during followup (mean followup: 434 days) but was significantly higher than personal best. FeNO during acute exacerbation did not correlate with the severity of acute exacerbation (measured using the Pulmonary Score) and could not diagnose or predict exacerbation.[109]

In adults seen in the ED, an increase in FeNO was observed in almost all patients with acute asthma. However; FeNO and its initial variation, within 2 hours, were not related to the severity of the attack (measured at presentation using a French instrument developed by Salmeron et al[110]) or the effectiveness of bronchodilator treatment.[111] In a study of patients age 2–18 years seen in an urban ED for acute asthma exacerbation, measurement of FeNO was difficult for a large proportion of children and did not correlate with other measures of acute severity.[112] Similar results were shown in a fourth study that combined adults and children presenting to ED.[113] In this study, There was no association between FeNO values at presentation and NIH class of asthma severity, the risk of hospitalization, or relapse. Triplicate measurements of FeNO had a poor coefficient of variation suggesting poor reproducibility (12%, interquartile range: 5-15%).[113]

Summary

The strength of evidence supporting the utility of FeNO testing in adults and children presenting to the ED or during acute exacerbations is low. FeNO results did not correlate well with asthma severity or symptoms.

Using FeNO to Monitor Adherence to Therapy

3 studies explicitly described using FeNO to ascertain adherence to asthma medications (mainly ICS). In one RCT, FeNO concentrations in adolescents with adherence of more than 50 percent of assigned doses of mostly ICS (measured using a built-in dose counter and a structured questionnaire) was 24 ppb compared to 31ppb in those with <50 percent adherence.[114] A second study in children demonstrated that FeNO values were associated with adherence to inhaled budesonide (r^2 =0.59) as assessed using dose counters[115]. A third study also in children showed that high FeNO level (>25 ppb) was associated with lower adherence rates to any asthma medication using the parental reported Medication Adherence Report Scale (OR: 0.4; 95% CI: 0.3–0.6).[100]

Summary

The strength of evidence supporting the association between FeNO values and medication adherence (mainly ICS) is low. Evidence supporting a FeNO-based adherence monitoring program are unavailable (in terms of cost effectiveness, acceptability, feasibility and outcomes, of such program). The strength of evidence assessment is summarized in Table 4. Detailed assessment of SOE is available in Appendix Table H.2.

Table 4. Strength of evidence (SOE) for KQ 1.b

Question	Study Design and Sample Size	Conclusion	SOE (Rationale)
Can FeNO levels predict the current control of asthma or the risk of future exacerbations?	19 observational studies in adults [73-85, 88-90, 116-118] (4,146 Patients) 22 observational in children [91, 93-95, 97-101, 104-108, 119-126] (3,926 Patients)	In adults and children: -FeNO levels have a weak association with predicting current control, as based on asthma control tests (ACQ and ACT). -FeNO levels have a weak association with the risk of subsequent and prior exacerbations. -These associations may be attenuated in those on ICS, smoke or pregnant, and may be increased in those with atopy.	Low (Observational studies)
Can FeNO be used to monitor asthma status during acute exacerbations?	4 observational studies [109, 111-113] (1,013 patients)	In adults and children: FeNO levels do not correlate with exacerbation severity and were poorly reproducible.	Low (Observational studies)
Can FeNO be used to monitor adherence to asthma medications?	3 observational studies [100, 114, 115] (1,035 patients)	In children and adolescents: FeNO levels were associated with adherence to asthma medications (primarily ICS).	Low (Observational studies)

ACT:Asthma Control Test, ACQ:Asthma Control Questionnaire, FeNO:Fractional Exhaled Nitric Oxide, ICS: inhaled corticosteroids; SOE:Strength of evidence

KQ 1.c: What is the clinical utility of FeNO measurements to select medication options (including steroids) for individuals ages 5 and older?

Key Points

- **In adults (ages of >18 years) and children (ages of 5-18 years), using asthma management algorithms that incorporate FeNO testing reduced the risk of exacerbations (SOE: High), and possibly the risk of exacerbations requiring oral**

steroids (SOE: Moderate), but did not affect other outcomes such as hospitalization, quality of life, asthma control, or FEV_1% predicted.

- **Management algorithms that incorporate FeNO testing may be associated with a modest reduction in medical expenses, compared to management approaches that do not include FeNO testing.**
- **FeNO testing can identify patients who are more likely to respond to inhaled corticosteroids (SOE: Low).**

24 studies with a total of 2,820 patients were included in KQ 1.c. The characteristics of these studies are in Appendix Tables C.4-6. The majority of the studies (15 studies) included only adults >18 years old; 8 studies had children with average age of 5-12 years and 1 included patients with average age of 13-18 years. 8 studies were nonrandomized longitudinal studies, 14 RCTs, and 2 cross sectional studies. The studies were conducted in the United States (n=3), in Europe (n=16), and in other countries (n=5). FeNO was measured online in 14 studies.

The detailed risk of bias assessment is presented in Appendix Tables G.4 and G.5 and summarized in Figures 6 and 7 for RCTs and observational studies; respectively. The overall risk of bias was low in 36% of the RCTs and 50% of the observational studies.

Figure 6. Risk of bias assessment of randomized controlled trials using the Cochrane Risk of Bias tool (n=14, KQ 1.c)

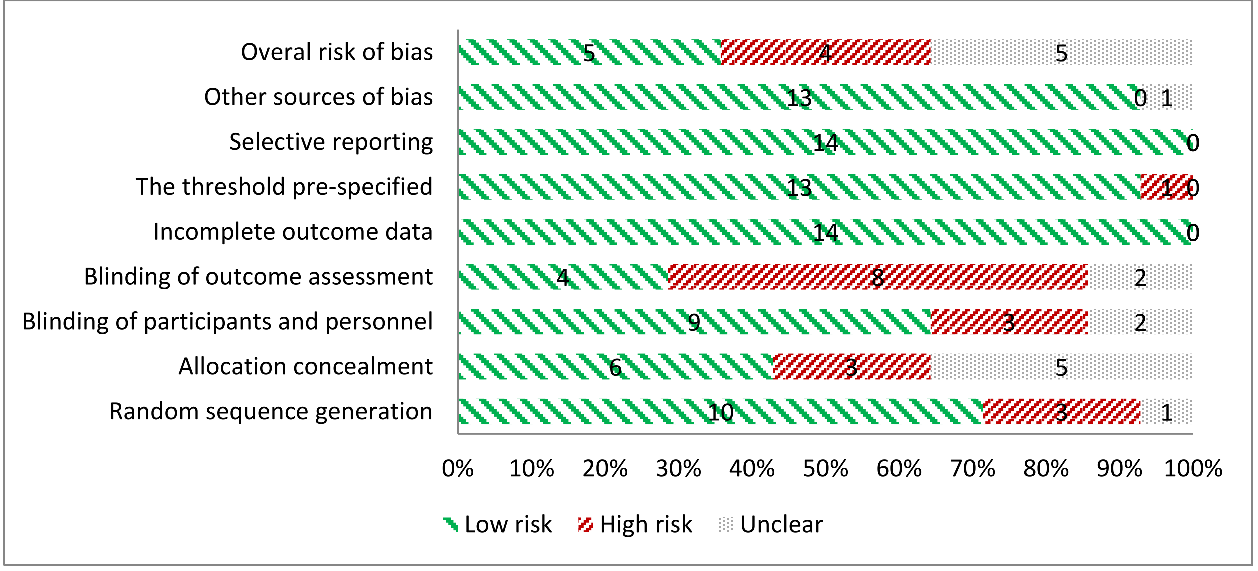
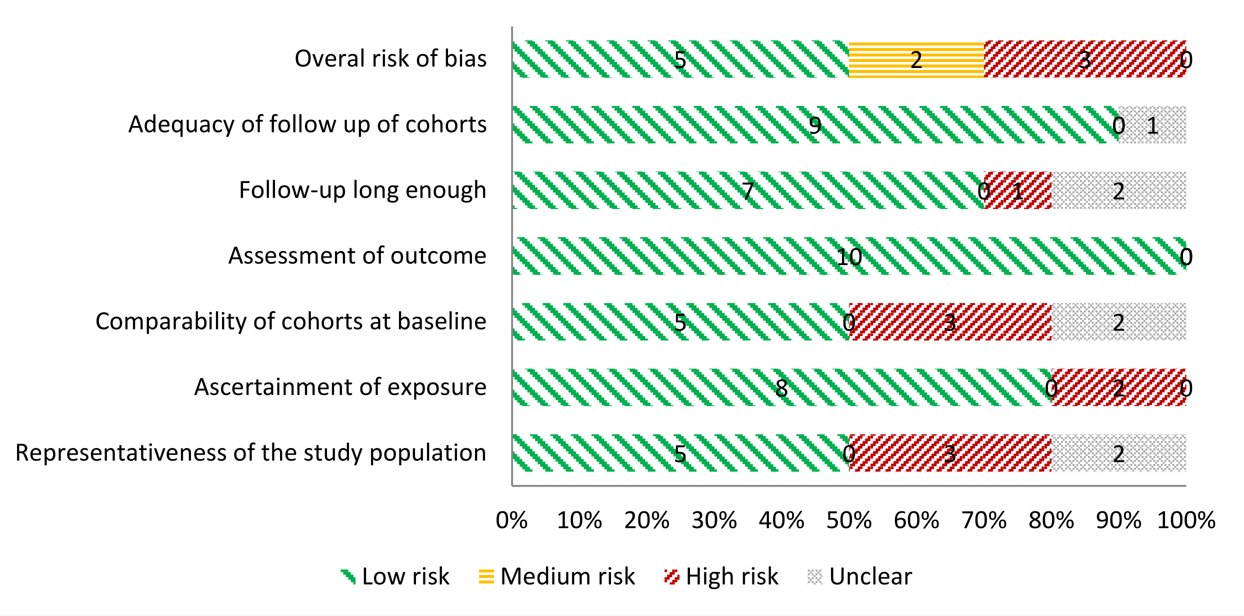


Figure 7. Risk of bias assessment of observational studies using the New-Castle Ottawa Scale (n=10, KQ 1.c)



Using FeNO to Guide Asthma Medication Selection, Monitoring and Management

Randomized Controlled Trials

14 RCTs evaluated various strategies in which FeNO was used to monitor disease activity and to change therapy (stepping up therapy vs. stepping down therapy). These trials aimed to evaluate the incremental value of adding an algorithm in which FeNO was maintained below a certain level (variable across studies) compared to standard monitoring that included spirometry and clinical parameters (which was the control intervention that varied across studies).

Trials were conducted in adults[114, 127-133] (FeNO cutoffs between 15 and 35 ppb, followup 4 to 12 months), children[95, 108, 134-138] (FeNO cutoffs between 20 and 30 ppb, or between 10 and 15 ppb with symptoms, followup 6-12 months), and in pregnant women[139].

In adults (ages of >18 years) and children (ages of 5 to 18 years), FeNO based strategies were associated with reduction in the risk of exacerbations (Figures 8 and 9). Other outcomes did not differ signficantly in children or adults, including hospitalization from asthma, exacerbations requiring oral steroids, FEV_1 % predicted, ACT, or quality of life questionnaires (Appendix Figures D.5-9). For the outcome of exacerbations requiring oral steroids, exploratory analysis that combines data from adults and children, demonstrated that the reduction was statistically significant (I^2=0%), suggesting that this analysis in each subgroup analysis (adults or children) was underpowered because of small sample sizes. The strength of evidence is summarized in Table 5. The number of patients needed to treat using FeNO-based algorithms to prevent one person with exacerbation is 9 (for both, adults and children).

Figure 8. Risk of exacerbations in adults (ages>18 years)

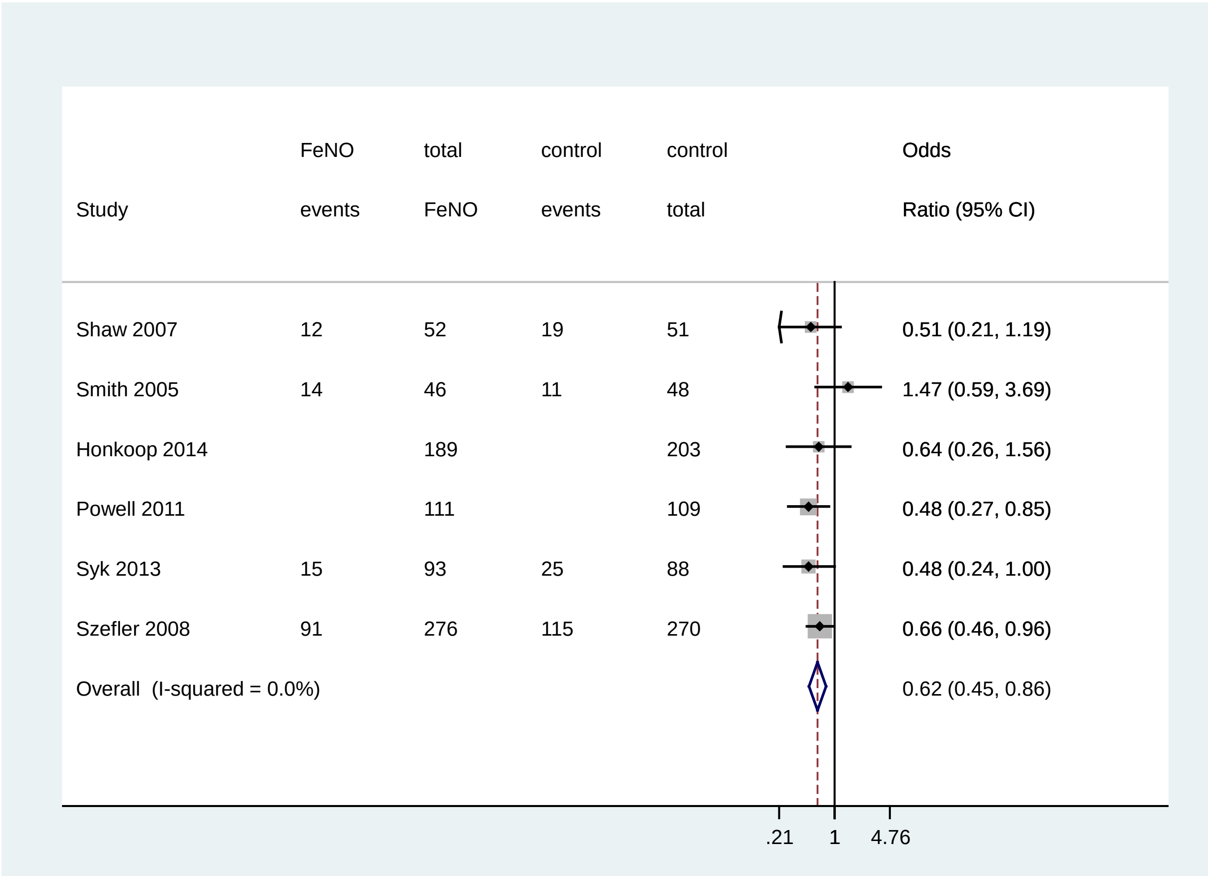


Figure 8 legend: Meta-analysis of the outcome of asthma exacerbations in adults. Columns show the number of exacerbations and sample size for each study (when available) and the odds ratio of every study represented as a square. The diamond reflects the pooled odds ratio. Odds ratio under 1.0 suggests reduction in the risk of exacerbations in those using a FeNO based algorithm compared to standard monitoring without FeNO.

Figure 9. Risk of exacerbations in children (ages between 5 and 18)

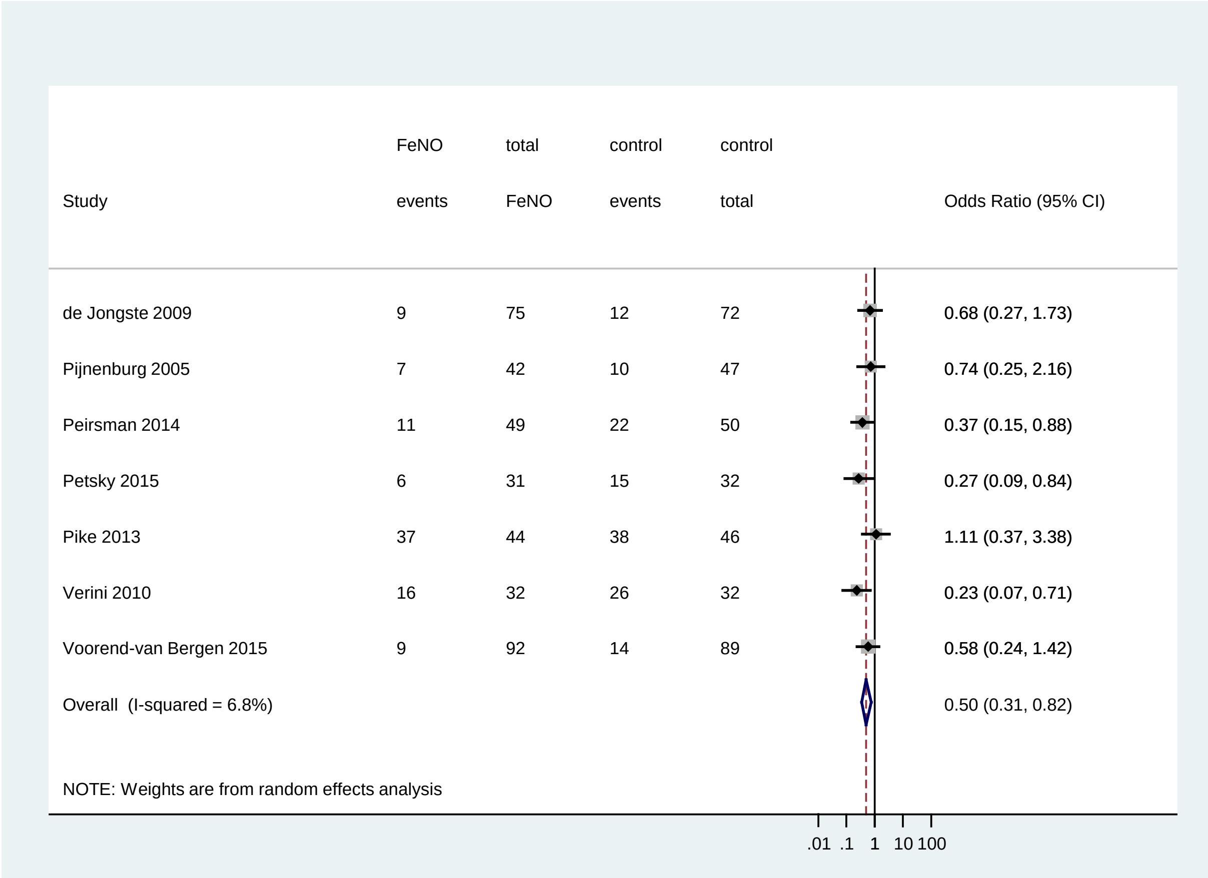


Figure 9 legend: Meta-analysis of the outcome of asthma exacerbations in children. Columns show the number of exacerbations and sample size for each study (when available) and the odds ratio of every study represented as a square. The diamond reflects the pooled odds ratio. Odds ratio under 1.0 suggests reduction in the risk of exacerbations in those using a FeNO based algorithm compared to standard monitoring without FeNO.

FeNO-based algorithms varied across trials in terms of FeNO cutoffs for changing therapy and frequency of testing; the details of these algorithms are described in Appendix Table I.2. Data were insufficient to determine whether a certain approach was the most effective; however, analyses consistently suggested that the effect might be similar across these algorithms. There was no statistically significant difference on any outcome between studies at increased risk of bias and studies at decreased risk of bias. We did not identify any studies that reported on adverse effects of FeNO testing per se, or of the strategy that used FeNO testing.

Other Randomized Trials Not Included in Meta-Analysis

Three trials were not included in meta-analysis because of being a cluster trial[128], focusing on oral corticosteroid tapering strategies[130] and for evaluating a combination of FeNO and sputum eosinophils to guide management[129].

Honkoop et al. allocated 611 adults with asthma from primary care clinics to three treatment strategies: (1) aiming at ACQ score <1.50; (2) ACQ score <0.75; and (3) aiming at ACQ score <0.75 and FeNO value <25 ppb. During the 12-month followup, treatment was adjusted every 3 months by using an online decision support tool. The strategy that included FeNO improved asthma control compared with the ACQ <1.50 strategy (P < 0.02). There were no differences in quality of life.[128]

Hashimoto et al. enrolled 95 adults (ages of 18-75 years) with prednisone-dependent asthma and compared two tapering strategies over 6 months: internet-based monitoring system (home monitoring of symptoms, lung function, and FeNO weekly titrated below 10 ppb) versus conventional treatment based on GINA guidelines (conventional strategy, no FeNO testing). Changes in prednisone dose from baseline averaged -4.79 mg/day versus +1.59 mg/day, in the internet strategy group compared with the conventional treatment group, respectively ($p < 0.001$). Asthma control, asthma-related quality of life, FEV_1, exacerbations, hospitalizations, and satisfaction with the strategy were not statistically different between groups.[130]

Malerba et al. enrolled 28 adults with asthma (mean age of 46 years) and compared treatment based on the combination of FeNO and sputum eosinophils to treatment based on clinical score. At 24 months, exacerbation rate and mean symptom scores were lower in the intervention than in the control group.[129]

Observational Studies

Observational studies also evaluated the effect of using FeNO to guide therapy. In adults, two studies showed that titration of ICS based on FeNO and sputum eosinophils in those with mild-to-moderate persistent asthma (compared with conventional management) was associated with reduction in symptom scores and ICS dosage, and fewer exacerbations.[140, 141] One study in children showed that FeNO values above 13 ppb weakly correlated with the changes in asthma therapy and had a modest sensitivity of 0.67 and a specificity of 0.65 to predict a step up in therapy.[94] In a mixed age population, treatment decisions made in an office visit based on a single FeNO test in 50 asthmatic patients led to change in therapy in a small proportion of patients (augmentation in 20% and reduction in 16%).[142] These studies were overall at moderate to high risk of bias.

Cost and Utilization Data

Only a few studies addressed cost-effectiveness and economic evaluation of FeNO-based treatment strategies. Honkoop et al., in a cluster RCT, showed that medication costs over a year was lower for a treatment strategy that kept ACQ score <1.50, followed by keeping ACQ score <0.75 and FeNO value <25 ppb, followed by keeping ACQ score <0.75 ($452, $456, $551; $P \leq 0.04$).[128]

Beerthuizen et al. assessed the cost-effectiveness of web-based monthly monitoring and of 4-monthly monitoring of FeNO compared with standard care (followup evaluation of RCT in 272 children with asthma, aged 4-18 years, followed for 1 year). No statistically significant differences were found in QALYs and costs between the three strategies. The web-based strategy had 77 percent chance of being most cost-effective from a health care perspective at a willingness to pay a generally accepted €40 000/QALY. The FeNO-based strategy had 83 percent chance of being most cost-effective at €40 000/QALY from a societal perspective.[107]

Berg et al. evaluated cost effectiveness from a German payer perspective comparing FeNO based approaches for diagnosis and management to standard guidelines in a mixed-age population with asthma. Asthma diagnosis based on FeNO measurement resulted in a cost of €38 per patient comparing to €26 for standard diagnostics. In patients with mild to severe asthma, asthma management with FeNO measurement instead of standard guidelines results in cost-savings of €30 per patient year (up to savings of €160 in a more severe population).[143]

In a mixed-age population, treatment decisions made in a single office visit based on a single FeNO test were estimated to reduce cost by $629 per patient per year. [142] Lastly, a cost-effectiveness analysis model evaluated adding FeNO monitoring to asthma management over a 1-year period. The results showed that adding FeNO to standard asthma care saved €62.53 per patient-year in the adult population and improved quality-adjusted life years by 0.026 per patient-year. The budget impact analysis revealed a potential net yearly saving of €129 million if FeNO monitoring had been applied across primary care settings in Spain.[144]

Using FeNO To Aid in Drug Type Selection

Several studies used FeNO to determine whether patients would respond to ICS. In adults, FeNO > 47 ppb predicted a positive response to ICS (defined as change in symptoms, peak flows, spirometry, or airway hyperresponsiveness to adenosine based on established guidelines and recommendations) in patients with undiagnosed respiratory symptoms.[145] In another study, FeNO reliably predicted those who responded to ICS (AUC 0.89 and 0.86 at 4 and 12 weeks; respectively); FeNO levels <27ppb predicted non-response in adults with undifferentiated chronic respiratory symptoms.[146] In steroid-naive adults with asthma, FeNO predicted clinical responsiveness to ICS but the combination of FeNO values and urinary bromotyrosine levels had the best prediction power.[147] In children, FeNO identified ICS dependent asthma phenotype[148] but this study used complex orthogonal varimax rotation to phenotype patients rather than more traditional classification. FeNO >20 ppb predicted exacerbations in another study in children with mild asthma on low-dose ICS who were switched to montelukast.[149] SOE summary is available in Table 5. Detailed assessment of SOE is available in Appendix Table H.3.

Table 5.Strength of evidence (SOE) for KQ 1.c

Comparison	Outcome	Study Design and Sample Size	Conclusion	SOE (Rationale)
Adults. (Mean age range 30-52 years)[2] Tailoring asthma interventions based on FeNO measurements Management based on clinical symptoms and/or spirometry. FeNO cutoff (15 to 35 ppb) Followup (4 to 12 months)	Exacerbations[1]	6 RCTs[114, 127, 128, 132, 133, 139] (1,536 patients)	Reduced with FeNO monitoring (OR: 0.62; 95% CI 0.45 to 0.86; I^2=0%; 111 events fewer per 1,000)	High
	Exacerbations requiring systemic steroids	4 RCTs[114, 127, 133, 139] (1,041 patients)	Reduced with FeNO monitoring (OR 0.71; 95% CI 0.44 to 1.15; I^2=0%)	Moderate (Imprecision)
	Hospitalizations	4 RCTs[114, 127, 132, 139] (1,034 patients)	No difference (OR: 0.59; 95% CI 0.16 to 2.19; I^2=19%)	Low (Severe imprecision)
	Quality of life	2 RCTs[128, 131] (621 patients)	No difference in AQLQ between groups (MD: 0.00; 95% CI, -0.64 to 0.64; I^2=0%)	Low (Severe imprecision)
	FEV_1 % predicted	5 RCTs[114, 127, 128, 133, 139] (1,348 patients)	MD between groups: 0.45; 95% CI, -0.81 to 1.72; I^2=0%	Insufficient (Severe imprecision and indirectness)
	Asthma control test	5 RCTs[114, 127, 131, 132, 139] (1,523 patients)	No difference (MD between groups: -0.08; 95% CI, -0.21 to 0.06; I^2=0%)	Low (Severe imprecision)
Children. Age (age range 6-18 years)[3]	Exacerbations[1]	7 RCTs[95, 108, 134-138] (733	Reduced with FeNO monitoring	High

Comparison	Outcome	Study Design and Sample Size	Conclusion	SOE (Rationale)
Tailoring asthma interventions based on FeNO measurements		patients)	(OR: 0.50; 95% CI 0.31 to 0.82; I^2=7%; 116 events fewer per 1,000)	
Management based on clinical symptoms and/or spirometry. FeNO cutoff (20 to 30 ppb) Followup (6 to 12 months)	Exacerbations requiring systemic steroids	6 RCTs[95, 108, 134, 136-138] (733 patients)	reduced with FeNO monitoring (OR 0.58; 95% CI 0.31 to 1.07; I^2=0%)	Moderate (Imprecision)
	Hospitalizations	(623 patients) 5 RCTs[108, 134-137] (564 patients)	No difference (OR: 0.78; 95% CI 0.14 to 4.29; I^2=0%)	Low (Severe imprecision)
	Quality of life	3 RCTs[108, 136, 137] (380 patients)	No difference in PACQLQ between groups (MD: 0.09; 95% CI, -0.28 to 0.47; I^2=0%)	Low (Severe imprecision)
	FEV_1 % predicted	5 RCTs[108, 134-138] (635 patients)	MD between groups: 1.50; 95% CI, -2.63 to 6.62; I^2=60%	Insufficient (Severe imprecision, indirectness and inconsistency)
	Asthma control test	1 RCT[108] (178 patients)	No difference between groups (MD: 1.00; 95% CI, -0.09 to 2.09)	Low (Severe imprecision)

CI: Confidence interval, FeNO:Fractional Exhaled Nitric Oxide, FEV:Forced expiratory volume in 1 second, MD:Mean difference, OR:Odds ratio, RCT:Randomized clinical trial; SOE:Strength of evidence

[1] This analysis was done using a unit of analysis of (number of patients with at least 1 event). Analysis can also be done using "the number of exacerbations" as a unit of analysis (therefore, the same patient can have multiple exacerbations). The results remain the same (i.e. FeNO based approach is associated with statistically significant reduction in exacerbations).

[2] One study enrolled 12-20 years old and a second study in pregnancy enrolled women with mean age of 29 years.

[3] The mean age ranged across studies 11-12 years.

KQ 1.d: What is the clinical utility of FeNO measurements to monitor response to treatment in individuals ages 5 and older?

Key Points

- **FeNO levels are reduced when patients with asthma take inhaled corticosteroids, leukotriene receptor antagonists or omalizumab.**
- **FeNO levels are not reduced when patients with asthma take long acting beta agonists.**
- **FeNO predicts exacerbations in patients undergoing ICS reduction or withdrawal, but FeNO alone is likely insufficient and its ability to predict exacerbations can be substantially enhanced by clinical measures (e.g. ACT).**

41 studies with a total of 1,728 patients were included in KQ 1.d. The characteristics of these studies are in Appendix Table C.7-11. The majority of the studies (23 studies) included only adults aged >18 years; 16 studies had children with the average age of 5-12 years and 2 included patients with the average age of 13-18 years. 16 studies were nonrandomized longitudinal studies, 20 RCTs, and 5 cross sectional studies. The studies were conducted in the United States (n=6), in Canada (n=3), in Europe (n=16), and in other countries (n=16). FeNO was measured online in 17 studies and offline in 1 study. The details of the risk of bias assessment is presented in Appendix Tables G.6 and G.7 and summarized in Figures 10 and 11 for RCTs and observational studies respectively. The risk of bias was overall low in 35% of RCTs and 32% in observational studies.

Of the 41 included studies, 31 studies reported a change in FeNO levels after administration of an asthma drug. These 33 studies provided evidence only regarding which drugs could affect FeNO level (and thus may be theoretically monitored using FeNO). These studies had a different objective than evaluating the effectiveness of using FeNO for monitoring response to therapy. They did not test an established monitoring program that could provide evidence regarding patient important outcomes. Such evidence about the effectiveness of monitoring is better derived from the randomized trials described in KQ 1.c that evaluated FeNO-based algorithms for medication management. Eight other studies used FeNO to monitor the response to ICS when those medications were tapered or discontinued.

Figure 10. Risk of bias assessment of randomized controlled trials using the Cochrane Risk of Bias tool (n=20, KQ 1.d)

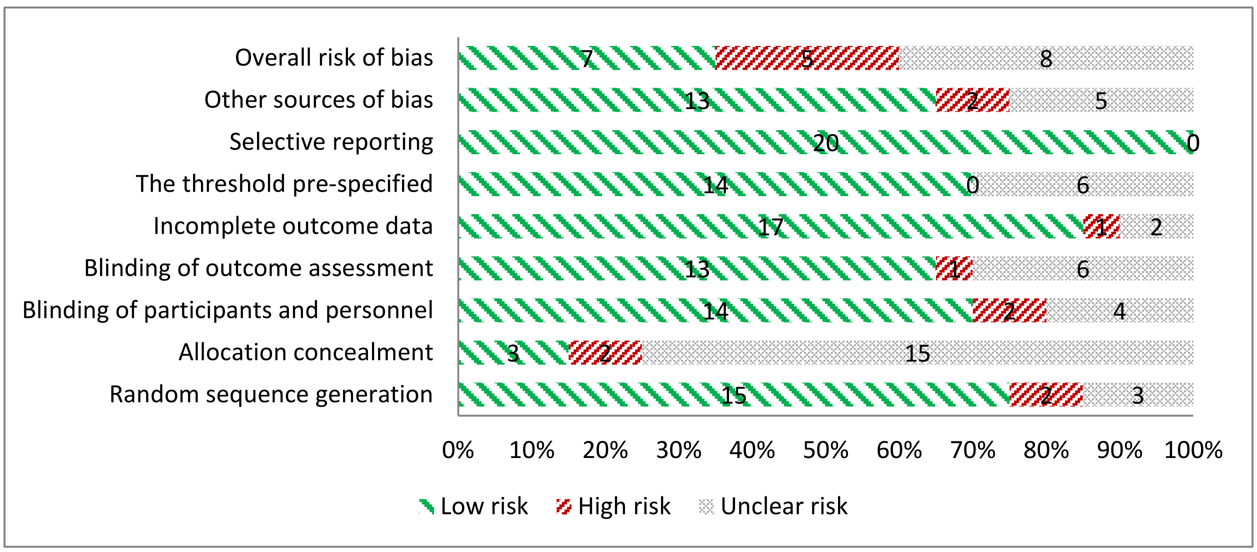
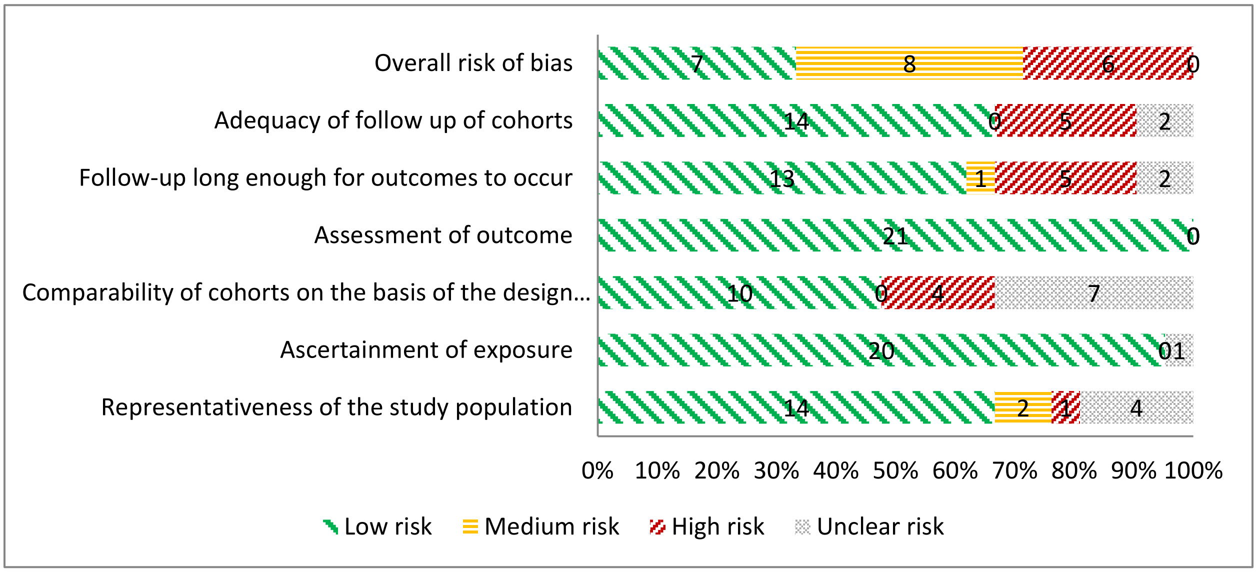


Figure 11. Risk of bias assessment of observational studies using the New-Castle Ottawa Scale (n=21, KQ 1.d)



Studies Documenting a Change in FeNO Associated With Certain Medications

Corticosteroids

Twenty-two studies demonstrated that FeNO levels declined after the administration of ICS. Response was seen after 4 to 8 weeks of treatment, though one study[150] showed reduction after 10 days without further reduction observed at 40 days. The decline in FeNO was dose-dependent and observed in both adults and children; in one study, it varied according to ICS type beyond the dose equivalents.[151] FeNO correlated with airway hyperresponsiveness in steroid-naïve mild asthmatics but not in steroid using asthmatics.[152] In a study of children with atopic persistent asthma, FeNO decreased significantly after 12 weeks of using either 80 or 160 mcg of inhaled ciclesonide (no difference between the two doses).[153] FeNO values decreased significantly after 5 days of oral prednisone given for acute exacerbation of asthma.[154]

Leukotriene Receptor Antagonists

Six studies showed that leukotriene receptor antagonists (LTRA) also reduced FeNO in adults (ages >18 years) and children (ages between 5 and 18 years). Montelukast reduced FeNO in adults with mild asthma in an RCT as early as day 1 with a maximum effect on reduction noted for day 7.[155] Pranlukast added to ICS plus inhaled long acting beta agonist (LABA) also reduced FeNO.[156] Montelukast reduced FeNO concentrations in children with asthma, and withdrawal of this medication increased FeNO values and was associated with worsening lung function and clinical deterioration in 4 of 14 children.[157] Withdrawal of montelukast led to rising FeNO in another study.[158]

Omalizumab

Omalizumab reduced exacerbations, and symptoms, and FeNO levels in both adults[159] and in children with asthma.[160]

Bronchodilators

Concerns regarding potential masking of inflammation by long acting beta-agonists were examined in 4 studies. Regular use of salmeterol did not increase FeNO levels in adults or children with asthma, regardless of whether they were taking ICS or not.[161-164] In a fifth study, adults (mean age 57) with symptomatic asthma on ICS and LABA were randomized to tiotropium vs continued same management. There was no difference in feNO between the two groups.[165]

Studies Reporting on FeNO use for ICS Reduction or Withdrawal

Eight studies described monitoring FeNO in patients undergoing ICS reduction or withdrawal (6 in adults and 2 in children).

In adults with asthma on high dose ICS that was reduced by 50 percent, FeNO values at baseline >15 ppb predicted reduction failure.[166] Both single measurements and changes of FeNO (10 ppb, 15 ppb, or an increase of > 60% over baseline) had positive predictive values that ranged from 80 to 90 percent for predicting and diagnosing loss of asthma control after ICS withdrawal.[167] In adult patients with moderate or severe asthma but no clinical symptoms of asthma for at least 6 months in whom ICS dose was reduced by half, FeNO was a statistically independent predictor of success.[168]

However, the response of FeNO in adults with moderate persistent asthma undergoing withdrawal of ICS was heterogeneous.[169] In one RCT, adults with newly diagnosed asthma received budesonide/formoterol for 8 weeks and were then randomized to continue or step-down group. In both groups, pulmonary function indicators and symptoms did not change. FeNO level decreased significantly in the dosage-continued group from 50.9 ppb to 45.0 ppb, and increased significantly in the step-down group from 51.0 ppb to 65.7 ppb.[170] Therefore, FeNO alone is likely insufficient to guide ICS withdrawal. In another study, adults with moderate asthma treated with either budesonide 400 μg plus salmeterol 100 μg or salmeterol/fluticasone 250 at 2 puffs, step down from medium to low dose was safely performed using a combined FeNO and ACT approach at 8 week intervals. [171]

Similarly, inconsistency is noted in studies in children. One study showed that FeNO measurements 2 and 4 weeks after discontinuation of ICS predicted those who relapsed (value of 49 ppb at 4 weeks after discontinuation had the best sensitivity (71%) and specificity (93%).[172] Conversely, another study showed that in children with moderate-to-severe asthma undergoing ICS reduction, FeNO measured biweekly and expressed either as a continuous variable or dichotomized, was not associated with future risk for exacerbations.[173] However, despite ICS dose held constant and all 32 children remaining in good control during the 2 month run-in period (before tapering ICS dose began), FeNO at start of dose reduction still averaged 38 ppb.

In conclusion, FeNO predicts exacerbation after ICS withdrawal or reduction, but its response is heterogeneous and its prediction can be substantially enhanced by clinical measures such as ACT. The SOE supporting the utility of FeNO in predicting exacerbations is low due to the observational nature of the studies.

KQ 1.e. In children ages 0-4 years with recurrent wheezing, how accurate is FeNO testing in predicting the future development of asthma at age 5 and above?

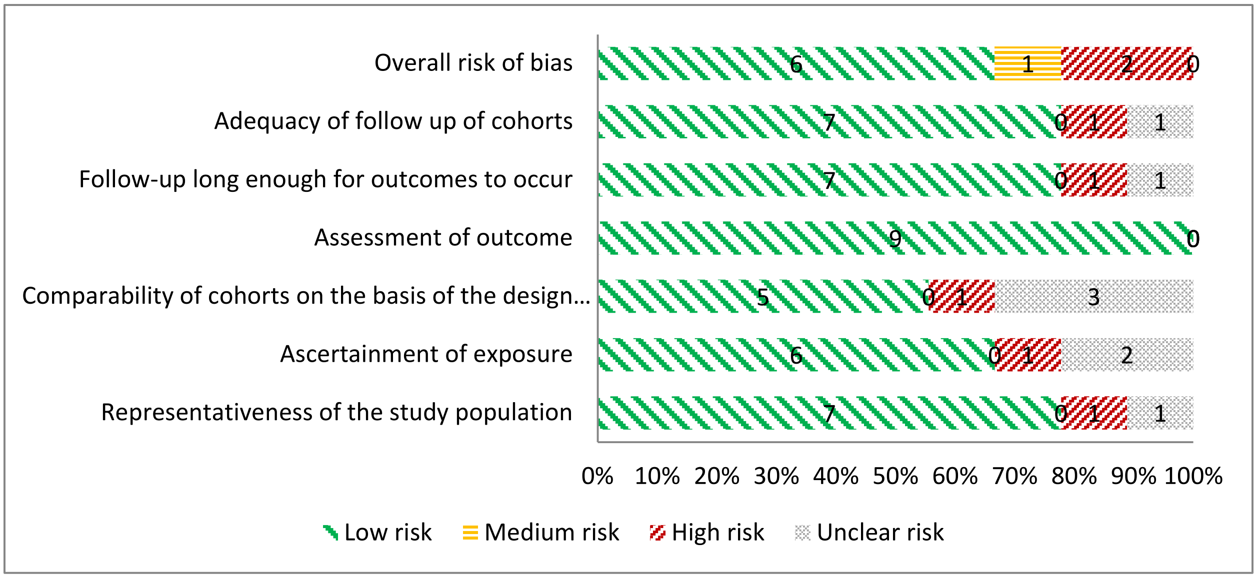
Key Points

- **It is unclear whether FeNO testing in children at ages 0-4 years with symptoms suggestive of asthma can predict a future asthma diagnosis (SOE: insufficient).**
- **The results of FeNO testing in children at ages 0-4 years correlate well with the Asthma Predictive Index and wheezing (SOE: Low).**
- **FeNO levels are higher in patients with current or persistent wheezing (compared to those with no or transient wheezing; respectively). This association is also observed in infants with atopy or eczema.**

Nine studies with a total of 1,735 patients were included in KQ I.e. The characteristics of these studies are in Appendix Table C.12. All studies included children less than 5 years old. 6 studies were nonrandomized longitudinal studies, and 3 cross sectional studies. The studies were conducted in the United States (n=2), in Europe (n=6), and in other countries (n=1).

FeNO was measured online in 5 studies and offline in 2 studies. The details of risk of bias assessment are provided in Appendix Table G.8 and summarized in Figure 12. The risk of bias was overall low in 67% of the observational studies. We also identified 7 additional studies that evaluated the correlation between FeNO measured in early childhood and current wheezing. These studies were excluded from the systematic review because they do not directly answer KQ 1.e; they are however summarized in Appendix Table I.1.

Figure 12. Risk of bias assessment of observational studies using the New-Castle Ottawa Scale (n=9, KQ 1.e)



We identified four studies in which FeNO was measured in early childhood and an outcome of asthma was subsequently diagnosed (after the age of 5). Two of the studies showed that higher FeNO predicted a diagnosis of asthma (one of them was specifically performed in infants with eczema).[15, 174] A third study showed contradictory results and a non-significant association with asthma diagnosis.[175] The fourth study is an ongoing prospective cohort that has reported only preliminary findings not relevant to this question; final results will be relevant because the study will attempt to develop a prediction rule based on data from demographics, history, specific IgE, FeNO and peak expiratory flow.[176] Another study was only published as an abstract. In a population-based birth cohort, FeNO was measured in 234 healthy term infants aged 5 weeks during quiet tidal breathing in unsedated sleep. At the follow-up with 6 years, FeNO at infancy was not associated with asthma, atopy or positive skin prick test at the age of 6 years. Associations were not modified by sex, parental atopy, parental asthma or smoking during pregnancy. [177, 178]

The four published studies overall had no major methodological limitations. This body of evidence was small (592 children in all), observational, and inconsistent; therefore, the strength of evidence supporting the outcome of asthma development is insufficient at the present time.

Five other studies examined the correlation between FeNO measured in early childhood and the Asthma Predictive Index (API).[179-183] Except for one study,[182] all showed good correlation between FeNO and API. In one study, FeNO was superior to API in predicting future exacerbations and persistence of wheezing at age 3 years. [180]

Lastly, seven studies evaluated the correlation between FeNO measured in early childhood and current wheezing.[16, 184-189] These studies were excluded from the systematic review, because they do not directly answer KQ 1.e; however, they showed that young children with wheezing had higher FeNO levels than non-wheezing children; particularly in those children with eczema, airway hyperresponsiveness, atopy, family history of atopy, and mothers who smoke.

Across these studies, the differences in FeNO values were small. It remains unclear whether FeNO values obtained in infants correlate with the FeNO levels measured with a standardized method at school age[190]. Therefore, though FeNO appears to reflect eosinophilic bronchial inflammation early in life, the current evidence is insufficient to state that FeNO performed in children at 0 to 4 years of age predicts a diagnosis of asthma at age 5 and above. However; future studies (one is ongoing[176]) may demonstrate otherwise. The strength of evidence assessment is summarized in Table 6. Detailed assessment of SOE is available in Appendix Table H.4.

Table 6. Strength of evidence (SOE) for KQ 1.e

Question	Study Design and Sample Size	Conclusion	SOE (Rationale)
FeNO testing done at age 0-4 years for the prediction of a future diagnosis of asthma.	3 observational studies[15, 174, 175] (346 patients)	- In children age 3-4 years with symptoms suggestive of asthma, FeNO predicted physician diagnosis of asthma at age 7 and wheezing at 8 years (OR in various models range 2.0 to 3.0). From the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort, the Netherlands. [15] - In children age 2-4 with recurrent wheeze, neither FeNO nor FeNO change after 8 weeks of ICS, predicted asthma diagnosis at age 6 years (diagnosis was verified by 2 pediatric pulmonologists. Odds ratios were 1.02 (0.98–1.05) and 1.01 (0.99–1.04); respectively. [175] - Infants with eczema (mean age 11 months) and high FeNO had greater risk of developing asthma at 5 years of age (for each 1 ppb, OR 1.13, 95% CI 1.01–1.26) [174]	Insufficient (observational study and inconsistency)
The association between FeNO testing done at age 0-4 years with the Asthma Predictive Index	5 observational studies[179-183] (959 patients)	In 4/5 studies, a significant correlation was observed between FeNO and the Asthma Predictive Index.	Low (observational studies)
The association between FeNO testing done at age 0-4 years with wheezing[a]	7 observational studies[16, 184-189] (1,126 patients)	-FeNO levels are higher in current wheezers and persistent wheezers (compared with non-wheezers and transient wheezers; respectively). -This association is particularly observed in infants with atopy or eczema.	Low (observational studies)

CI:Confidence interval; FeNO: Fractional Exhaled Nitric Oxide; ICS:Inhaled corticosteroids; PIAMA:Prevention and Incidence of Asthma and Mite Allergy; OR: Odds ratio; ppb: Parts per billion; SOE:Strength of evidence

[a]These studies did not fulfill the inclusion criteria of this systematic review because they did not have asthma diagnosis after the age of 5 years.

Discussion

We conducted a systematic review with meta-analyses to assess the diagnostic accuracy and clinical utility of FeNO testing in the management of asthma. We found that FeNO has moderate diagnostic accuracy for asthma with diagnostic odds ratios (DORs) that range from 5.85 to 16.95 across various cutoff points (in comparison, a test with 0.80 sensitivity and 0.80 specificity would have a DOR of 16). As expected, with increasing cutoff values, FeNO had gradual decrease in sensitivity and improved specificity (for cutoffs <20, 20-30, 30-40, ≥40 ppb; respectively, FeNO testing has sensitivities of 0.78, 0.63, 0.56 and 0.41; and specificities of 0.71, 0.81, 0.84, and 0.94). Therefore, knowing the cutoffs used for test interpretation is critical for interpretation by clinicians. Inferences from several preplanned subgroup analyses were limited due to limited number of studies and heterogeneity of population, intervention, and outcome; particularly regarding the impacts of reference test, the presence of atopy, and current use of ICS on FeNO diagnostic performance.

In terms of the role of FeNO in monitoring asthma activity, a large body of observational and heterogeneous literature suggests that FeNO has a weak association with the risk of subsequent and prior exacerbations and a weak association with asthma control tests (ACQ and ACT). Such associations may be higher among patients with atopy (i.e., asthma associated with either positive skin test or specific IgE to aeroallergens), consistent with these patients being more likely to have eosinophilic inflammation. Such findings underscore the need to consider atopic predisposition in patients with asthma, because FeNO may be elevated owing to atopy alone, even in absence of asthma symptoms or diagnosis. Levels of FeNO were significantly lower in frequently exacerbating patients receiving higher doses of maintenance ICS. This finding is potentially important, inasmuch as it suggests higher ICS dose may not help and direct clinician to seek co-morbidity, or choose alternative medications. In addition, in atopic adults with persistent asthma on ICS, higher FeNO levels were significantly correlated with more short acting beta agonists dispensing and oral steroids courses in the past year, and lower FEV_1 percent predicted levels; suggesting that perhaps treatment adherence should be scrutinized for such patients.

FeNO is unlikely to be helpful during acute exacerbations. This can be attributed to the presence of multiple factors that can cause or contribute to exacerbations, many of which are not associated with increased lower airway eosinophilic inflammation (even if this inflammation co-existed). We also found that FeNO has the potential to detect adherence to ICS, although the available data merely demonstrated an association of FeNO level with adherence assessed using dose counters or parent report. Studies did not describe a pragmatic adherence monitoring program with interventions to improve adherence; which would have provided more compelling evidence for the utility of using FeNO to evaluate adherence. Greater utility of FeNO as an aid in detecting adherence is expected in children (who can perform test satisfactorily) because most childhood asthma is atopic, unlike the situation in adults.

In terms of the clinical utility of FeNO to guide asthma management (select treatments, monitor response, step up and step down therapy, change therapies), we found moderate SOE from multiple RCTs suggesting that such an approach can lower the risk of exacerbations and the need for systemic steroids. The strength of evidence on hospitalization and quality of life was either low or insufficient. The reduction in exacerbations was demonstrated in both adults and children.

A large body of empirical observational evidence suggested that FeNO changes with the administration of inhaled and oral corticosteroids, leukotriene receptor antagonists, and omalizumab, but not long-acting beta agonists. This is consistent with pharmacologic evidence based on the mechanism of these drugs and can have implication for monitoring the effect of, or adherence to such drugs. We also found that FeNO may also help in selecting patients who may respond to ICS as an initial therapy, and it may be used for predicting exacerbations after ICS withdrawal or reduction, but its response is heterogeneous and its prediction can be enhanced by clinical measures such as ACT.

FeNO testing in early childhood (0-4 years of age) strongly correlates with API; which is not surprising given the relation between atopy and FeNO and the fact that this index is heavily predicated on atopic constitution. FeNO levels are higher in current wheezers and persistent wheezers (compared with non-wheezers and transient wheezers, respectively). This latter evidence can be quite relevant to clinical practice because most transient wheezers outgrow this symptomatic response by 3 years of age. Therefore, toddlers who continue wheezing after that age are more likely to develop asthma in future. However, only three studies ascertained whether these associations translate into subsequent development of a diagnosis of asthma after the age of 5. Two of the studies suggested that FeNO can predict such future diagnosis; one study did not. Therefore, such evidence is of low strength due to these heterogeneous findings, and it should be considered as merely preliminary. This association between FeNO in early childhood and future development of asthma was noted more in infants with atopy or eczema than in those without.

In terms of clinical implications, two scenarios commonly encountered in practice (among others) can benefit the most from FeNO testing. The first is in a patient with compatible symptoms who is clearly atopic (e.g. eczema, postivie skin tests, peripheral blood eosinophilia, positive IgE in the blood; which are routinely available and reimbursable tests). If this patient has elevated FeNO, this would imply that treatment with ICS is indicated; whereas low level (e.g. <20) implies that these compatible symptoms are not likely due to asthma. A caveat in this scenario is that low FeNO does not excluded asthma (clinical judgement and further follow up would be here warranted). The second scenario is about a patient with known asthma, who had a previously documented elevated FeNO level, but has symptoms that are not well controlled on guideline based therapy. In this patient, measuring FeNO as means to monitor adherence to treatment would be helpful.

Findings in Relation to What Is Known

The results of this systematic review are consistent with other systematic reviews that addressed diagnostic performance of FeNO testing (KQ 1.a) and clinical utility of FeNO measurements to select medication option (KQ 1.c); whereas to our knowledge, no systematic reviews have addressed clinical utility of FeNO measurements in monitoring disease activity and asthma outcomes (KQ 1.b), clinical utility of FeNO measurements to monitor response to treatment (KQ 1.d), and FeNO testing in predicting the future development of asthma (KQ 1.e). In terms of diagnostic accuracy, Li et al. reported pooled estimates of sensitivity, specificity, and DOR of 0.78, 0.74 and 11.4.[191] Tang et al. evaluated the diagnosis of asthma in children and reported pooled estimates of sensitivity, specificity, and DOR of 0.79, 0.81 and 16.5.[192] Guo et al reported pooled estimates of sensitivity, specificity, and DOR of 0.72, 0.78 and 15.9.[193] The highest DOR (i.e. diagnostic accuracy) was observed in steroid-naive and nonsmoking patients.[193] In terms of tailoring asthma management using FeNO based algorithms, two recent Cochrane systematic reviews reported that these strategies reduced exacerbations in strategies for adults and children without a significant impact on other outcomes.[194, 195] Although not outcomes of interest in our systematic review, total ICS dose and final mean FeNO level were also not statistically different between the FeNO-based approach and standard management.[194, 195]

Limitations

For several of the key questions (KQ 1.b-e), studies were quite heterogeneous in terms of design, population, control tests, control strategies, and outcome measures; which led to narrative evidence synthesis and narrative rating of the strength of evidence. Narrative evidence synthesis is helpful for decision making; however, it does not provide a single best estimate; which is a limitation. Studies were overall small despite the fact that asthma is a very common condition. We also found limited data on baseline severity and large variations in FeNO protocols, which makes interpretation of the body of evidence challenging.

For the diagnostic accuracy question (KQ 1.a), there were several limitations. One challenge relates to the fact that there is no true gold standard of diagnosing asthma. Although we did not rate label studies as having increased risk of bias because of this issue, we recognize that it can impact diagnostic accuracy. In addition, a wide range of reference tests were reported. We categorized these reference tests as clinical diagnosis, positive bronchial challenge test, or a combination of clinical diagnosis, positive bronchial challenge, and/or bronchodilator response. However, significant heterogeneity still exist, such as to how and when these tests were administered. The studies reported a wide range of cutoffs from 0.8 ppb to 85 ppb. Although categorizations of <20, 20-30, 30-40 and >=40 ppb helped reduce heterogeneity and facilitated meta-analyses, we were not able to definitively present a best cutoff overall or within each category. We were also not able to conduct some planned subgroup analyses because of lack of data, including asthma phenotype, adequate testing procedures, body mass index (BMI) or weight, manufacturer and device model, and exhalation flow rate.

Applicability

The age of participants in the studies did not commonly conform to the definitions used in National Heart, Lung and Blood Institute prior asthma guideline (i.e. adults defined as 12 years of age or older)[1]. Therefore, applicability may be affected when guideline developers provide recommendations using diiferent age cutoffs. Otherwise, most studies reported on patients with asthma commonly seen in practice. FeNO measurements in the included studies were for the most part consistent with the American Thoracic Society / European Respiratory Society 2005 guidelines[196] on the measurement of lower respiratory nitric oxide with the standard flow rate of 0.05L/second (body temperature [37° C] and pressure, saturated). The majority of studies did not include specific data on potential confounders including diet, use of mouthwash, and possible respiratory tract infections at the time of measurement. Such information is important for those developing institutional protocols for FeNO testing.

Clinicians considering FeNO as an adjunct to diagnose asthma should expect a fair number of false negatives (that is larger with higher test cutoffs) and an even a larger number of false positives (that is larger with lower test cutoff). The prevalence of asthma in the population being tested also impacts the expected positive and negative predictive values. Using several plausible asthma prevalence values in Figures 13 and 14, we simulate the number of false negative and false positive results expected in 1,000 patients tested for asthma using various FeNO test cutoffs. As the FeNO test sensitivity goes up (i.e. lower cutoff) the percentage of false negatives goes down, but the percentage of false positives goes up. Additionally as the prevalence of asthma increases in the screened population, the positive predictive value for confirmed asthma also increases.

Figure 13. False negatives per 1,000 patients

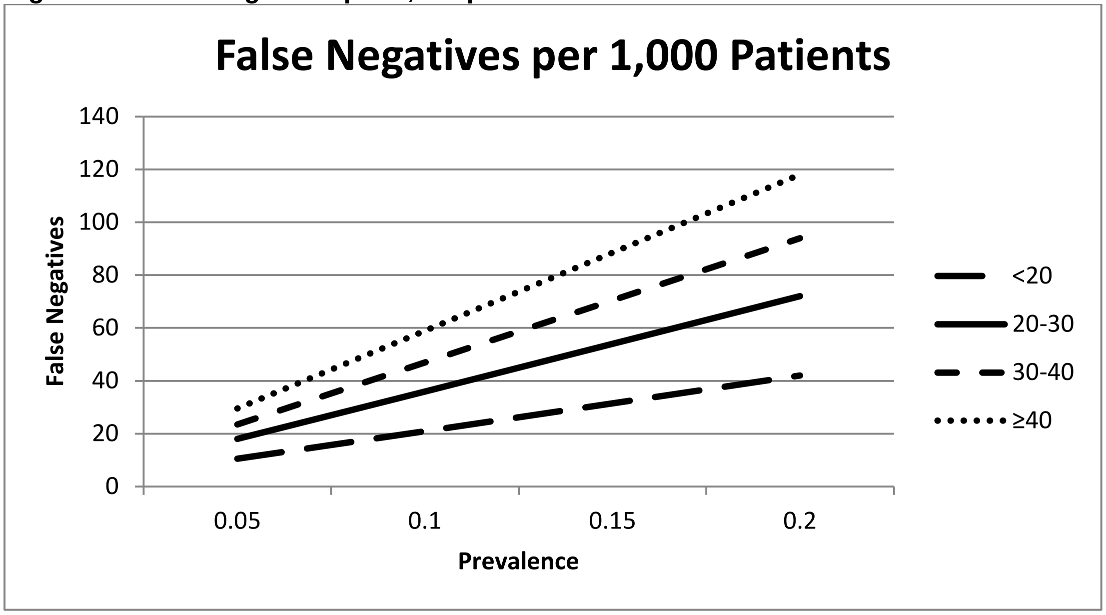
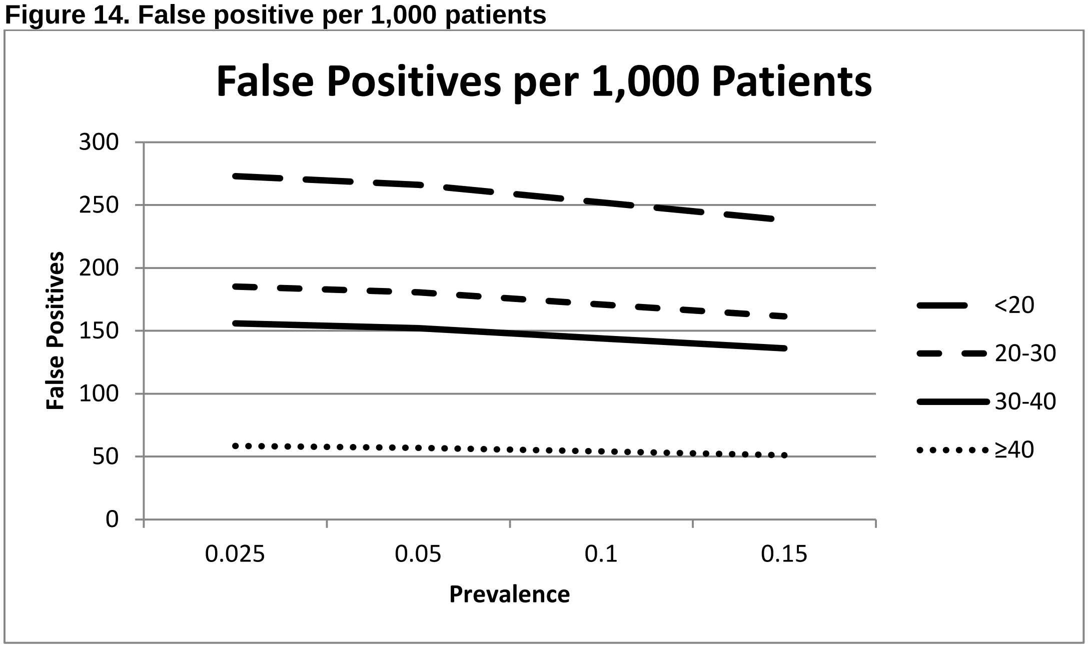


Figure 14. False positive per 1,000 patients



Suggestions for Future Research

Studies with better stratification according to asthma phenotype are needed (eosinophilic/versus non–eosinophilic) to identify populations who may benefit from serial FeNO measurement. Blood eosinophilia and atopy are likely good surrogates for airway eosinophilia and can be used to aid stratification of patients enrolled in studies. The field also needs studies of FeNO-based adherence monitoring programs that specifically evaluate cost effectiveness, acceptability, feasibility, and outcomes of such programs. These studies should also be either group stratified as above, or focus on atopic or eosinophilic patients.

In this review, we demonstrated that FeNO can identify those who will be steroid responsive; therefore, studies of FeNO-based medication titration are needed and should focus on symptomatic patients with previously documented elevated FeNO. Studies evaluating disease activity and outcome, should use validated measures of activity and well defined outcomes.

The role of serial FeNO measurements in children ages 0-5 year who develop illness associated with wheezing remains unclear. Cohort studies of such infants with follow up into later years of childhood and adolescence are needed to establish if persistently elevated levels correlate with increased risk of ultimate asthma diagnosis. This question is of particular importance, because the best biomarker we have at this time to predict asthma in this setting is the presence of eczema, which can be subjective. In addition, some children (regardless of age) often suffer from wheezy bronchitis, also known as wheezing associated respiratory infections. These are discrete illnesses with good prognosis that are quite common in pre-school age. Despite the benign outcome, many of these children still receive oral steroids. Would point of care FeNO measurements identify the children who do not require oral steroids? Such knowledge might address a very common clinical problem and spare children and their parents the adverse effects of steroids.

This review has yeilded a very small body of evidence on geriatric asthma. It will be important to determine the clinical utility of FeNO in a population that was underrepresented in the current literature.

Future research should also address the effect of emerging treatments such as anti-IL13 and anti-IL5 drugs on FeNO levels. Knowledge of such effect may demonstrate a role of FeNO in monitoring the use and adherence to some of these treatments and not others.

A challenge we faced in this review is to define the reference test for asthma diagnosis. Future studies should be explicit in describing the reference standard and use the modern testing approach recommended in current clinical practice guidelines; which may improve accuracy of diagnosis and make evidence more relevant. Similarily, studies should attempt to be consistent with guideline recommendations in definition of variables such as age, FeNO protocols and cutoffs, and asthma control categories, to further enhance applicability. Studies should also investigate factors that may affect FeNO diagnostic accuracy, including asthma phenotype, adequate testing procedures, body mass index (BMI) or weight, manufacturer and device model, and exhalation flow. More research should be done to evaluate diagnostic utility of FeNO testing in picking up asthma in a general population not on any type of treatment.

Conclusion

FeNO has moderate accuracy to diagnose asthma in people ages 5 years and older. Test performance is modestly better in steroid-naïve asthmatics, children, and nonsmokers than the general population with suspected asthma. Algorithms that include FeNO measurements can help in monitoring response to anti-inflammatory or long-term control medications, including dose titration, weaning, or treatment adherence. At this time, there is insufficient evidence supporting the measurement of FeNO in children under the age of 5 as a means for predicting a future diagnosis of asthma.

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Abbreviations

Abbreviation	Definition
ACT	Asthma control test
ACQ	Asthma Control Questionnaire
AUC	Area under the curve
API	Asthma predictive index
AQLQ	Asthma quality of life questionnaire
ATS	American Thoracic Society
AUC	Area under the curve
BMI	Body mass index
DOR	Diagnostic odds ratio
EBC	Exhaled breath condensate
ED	Emergency Department
ERS	European Respiratory Society
FEF25–75	Forced expiratory flow at 25–75% of forced vital capacity
FeNO	Fraction exhaled nitric oxide
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
HSROC	Hierarchical summary receiver operating characteristic
ICS	Inhaled corticosteroid
ICU	Intensive care unit
IgE	Immunoglobulin E
IQR	Interquartile range
KQ	Key question
LABA	Long acting beta agonist
LR+	Positive likelihood ratio
LR-	Negative likelihood ratio
LTRA	Leukotriene receptor antagonist
NO	Nitric oxide
NPV	Negative predictive value
OR	Odds ratio
PACQLQ	Pediatric asthma caregiver's quality of life questionnaire
PAQLQ	Pediatric asthma quality of life questionnaire
PC15	Provocation concentration causing a 15% fall in FEV_1
PC20	Provocation concentration causing a 20% fall in FEV_1
PD15	Provocation dose causing a 15% decline in FEV_1
PD20	Provocation dose causing a 20% decline in FEV_1
PEF	Peak expiratory flow
PH	Potential hydrogen
PIAMA	Prevention and Incidence of Asthma and Mite Allergy
PICOTS	Patient, Intervention, Comparison, Outcome, Timing, Settings
ppb	Part per billion
PPV	Positive predictive value
QALY	Quality-adjusted life year
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2
R	Correlation
RCT	Randomized controlled trial
ROC curve	Receiver operating characteristic curve
SD	Standard deviation
SOE	Strength of evidence