Comparative Effectiveness Review
Number 197

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

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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.

This report is based on research conducted by Mayo Clinic Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00013-I). The National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI) sponsor the report. The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ or NIH/NHLBI. Therefore, no statement in this report should be construed as an official position of AHRQ, NIH/NHLBI or of the U.S. Department of Health and Human Services.

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.

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.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact epc@ahrq.hhs.gov.

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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

Arlene Bierman, M.D., M.S.
Director Center for Evidence and Practice Improvement
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

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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Evidence 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?

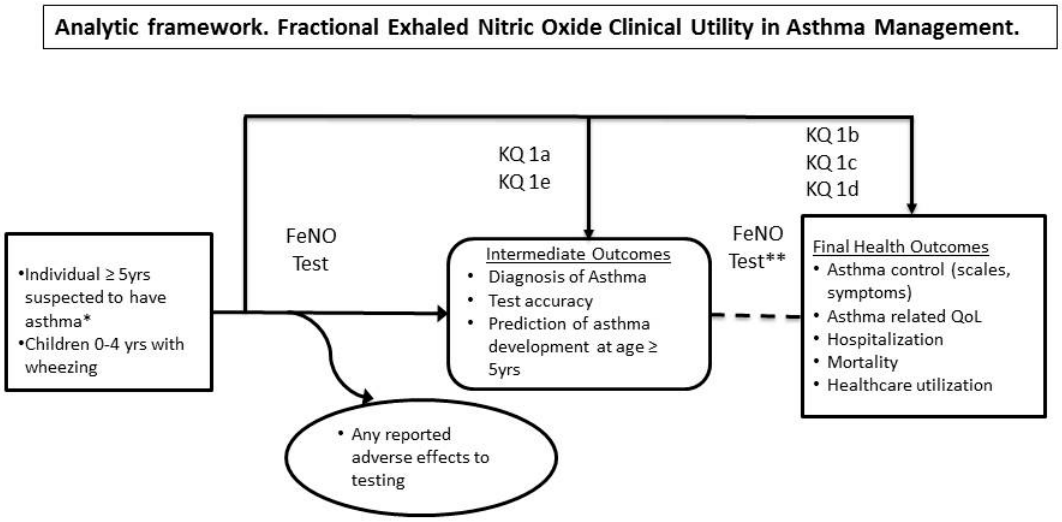
Table 1. PICOTS (population, interventions, comparisons, outcomes, timing, and setting)

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



*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

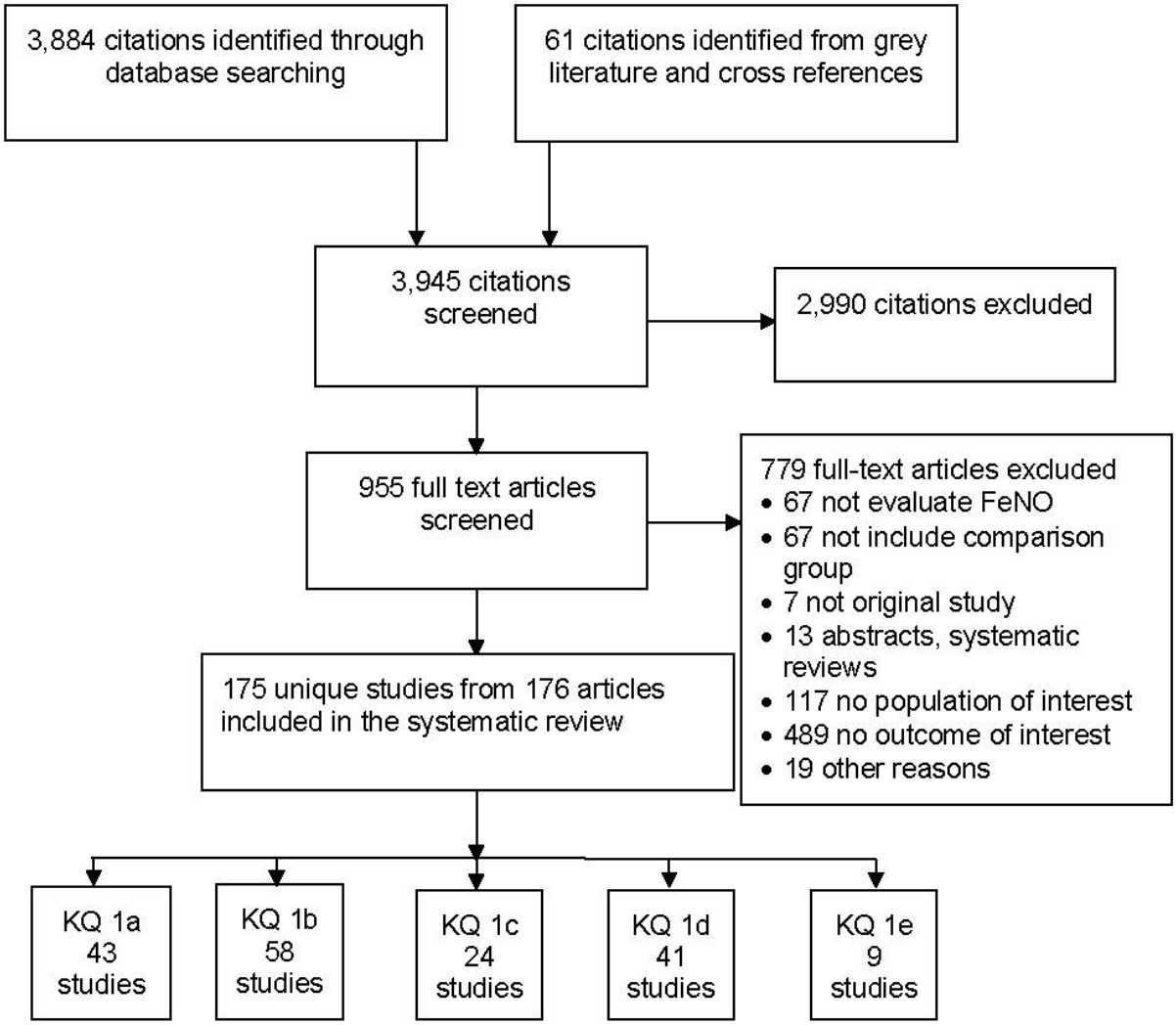


Table 2. Number of studies included per Key Questions, study design, and age group

		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?

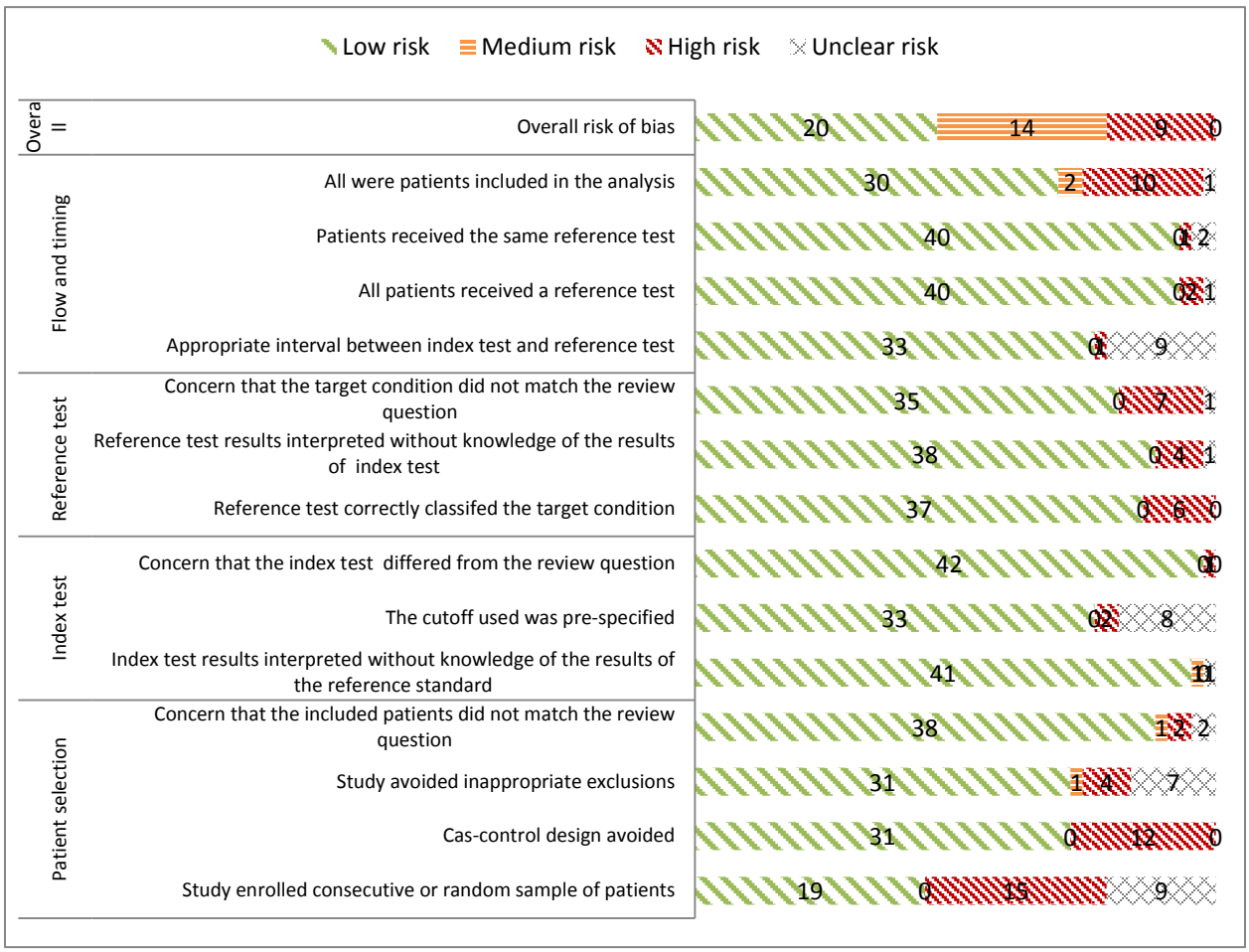
Key Points

- **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)

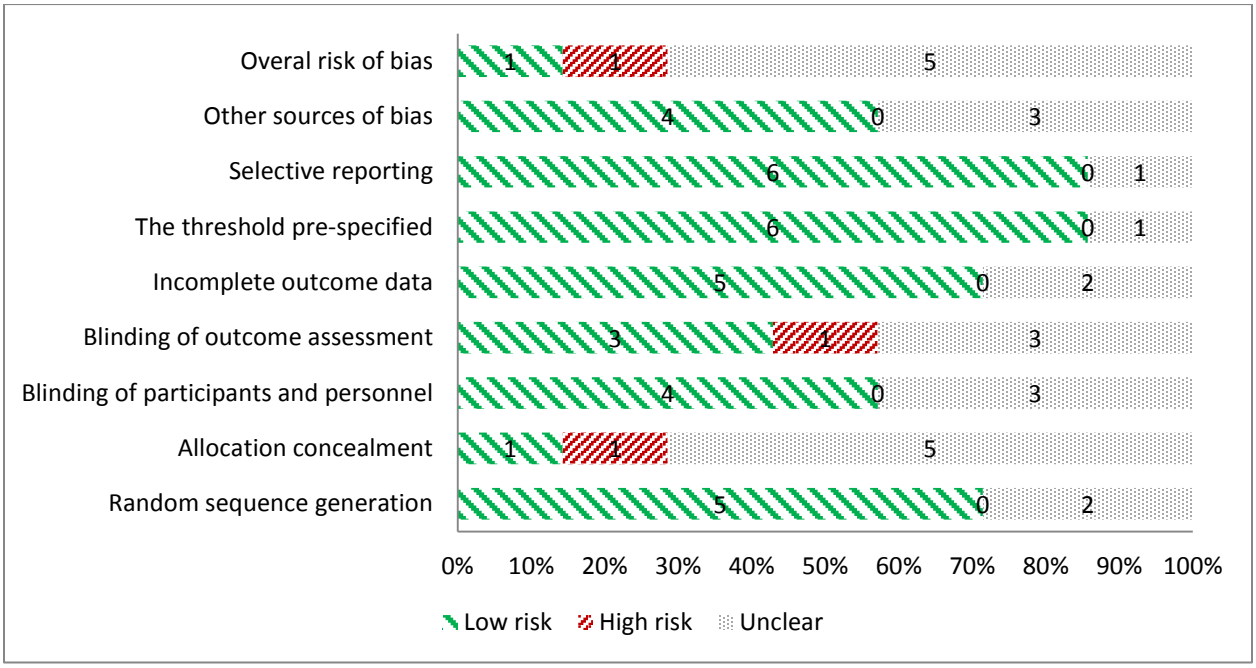
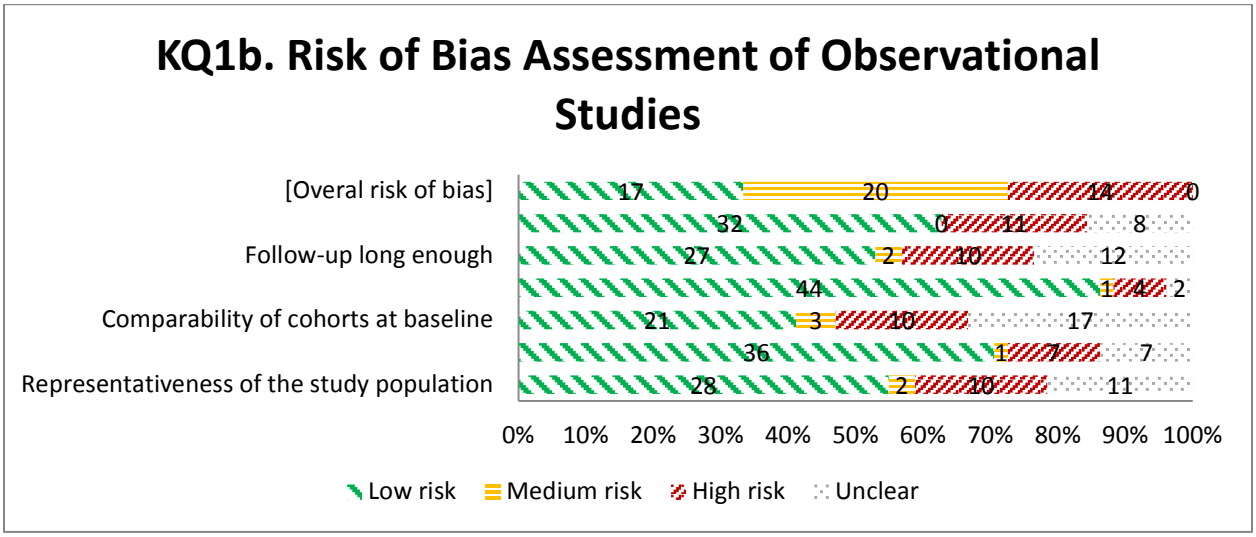


Figure 5. Risk of bias assessment of observational studies using the New-Castle Ottawa Scale (n=51, KQ 1.b)



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)

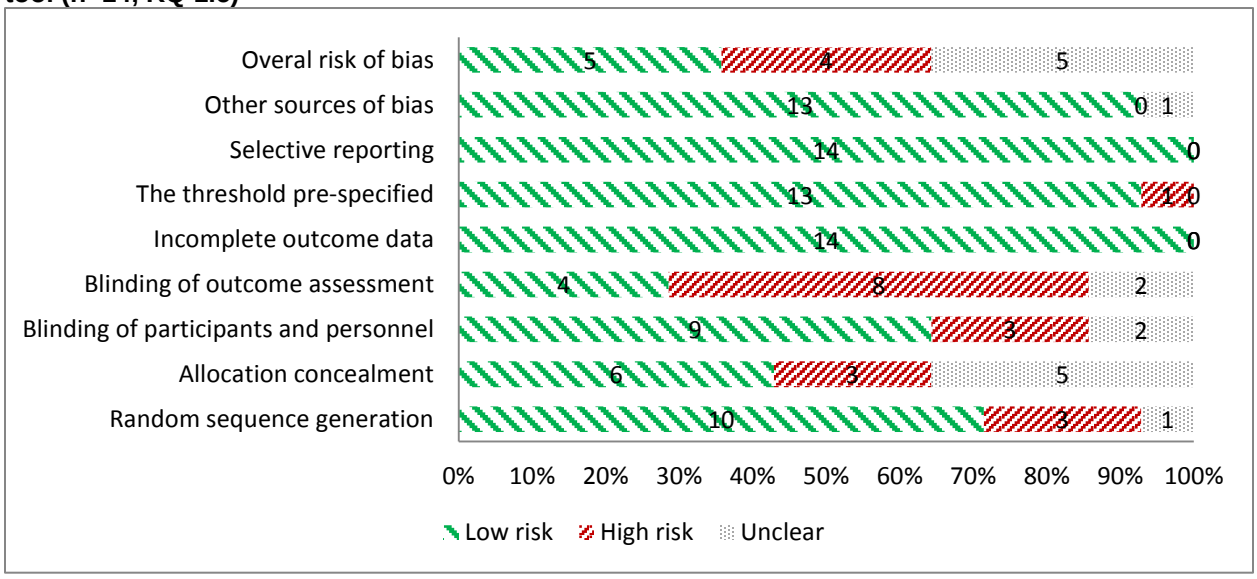
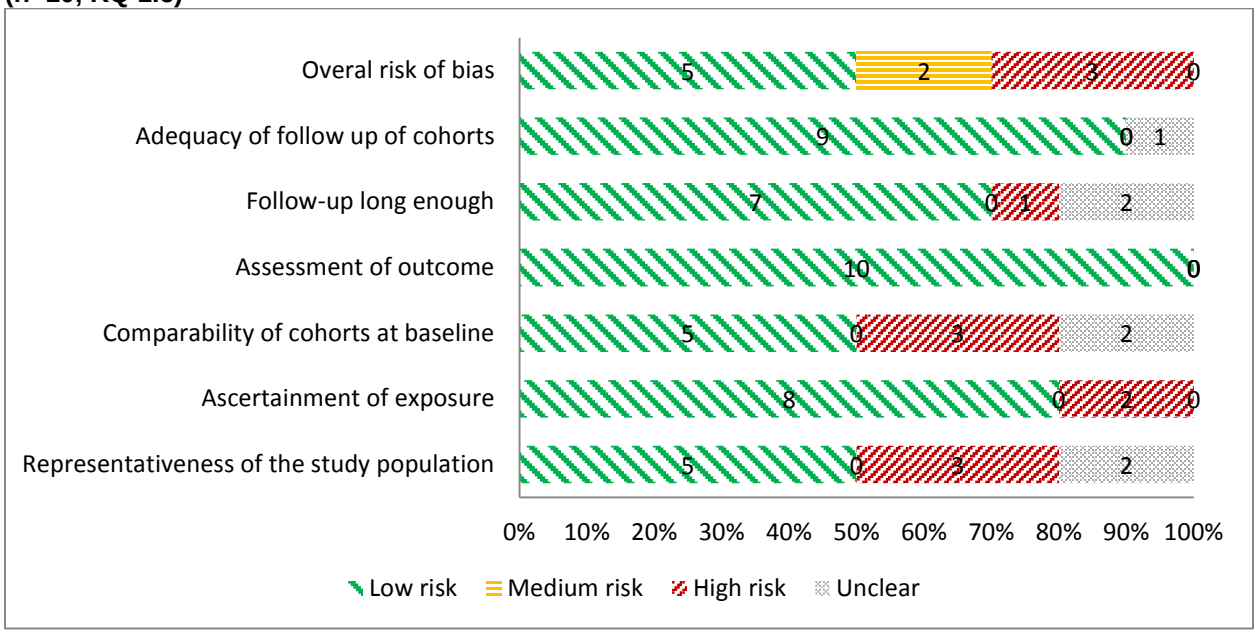


Figure 7. Risk of bias assessment of observational studies using the New-Castle Ottawa Scale (n=10, KQ 1.c)



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)

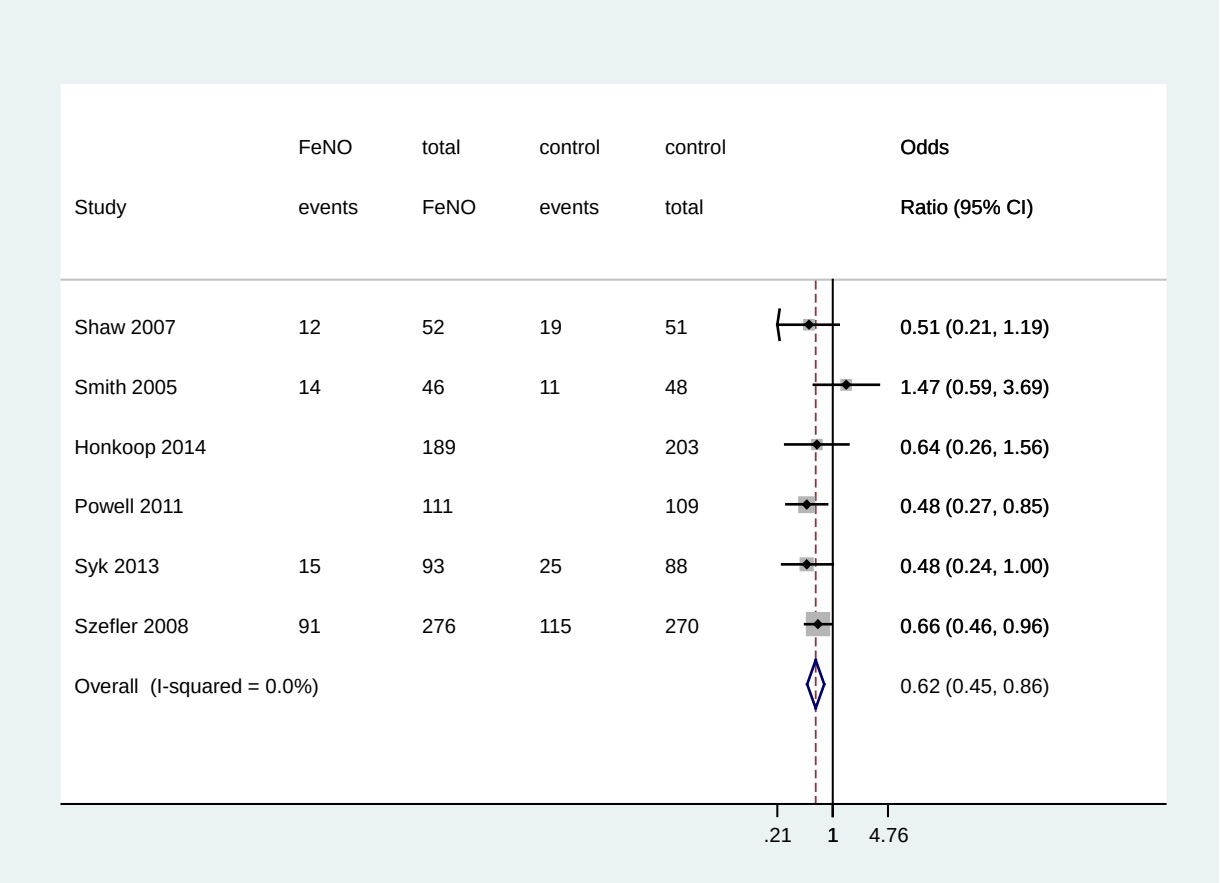


Figure 8 legend: Meta-analysis of the outcome of asthma exacerbations in adults. Columns show the number of exacerbations and sample size for each study (when available) and the odds ratio of every study represented as a square. The diamond reflects the pooled odds ratio. Odds ratio under 1.0 suggests 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)

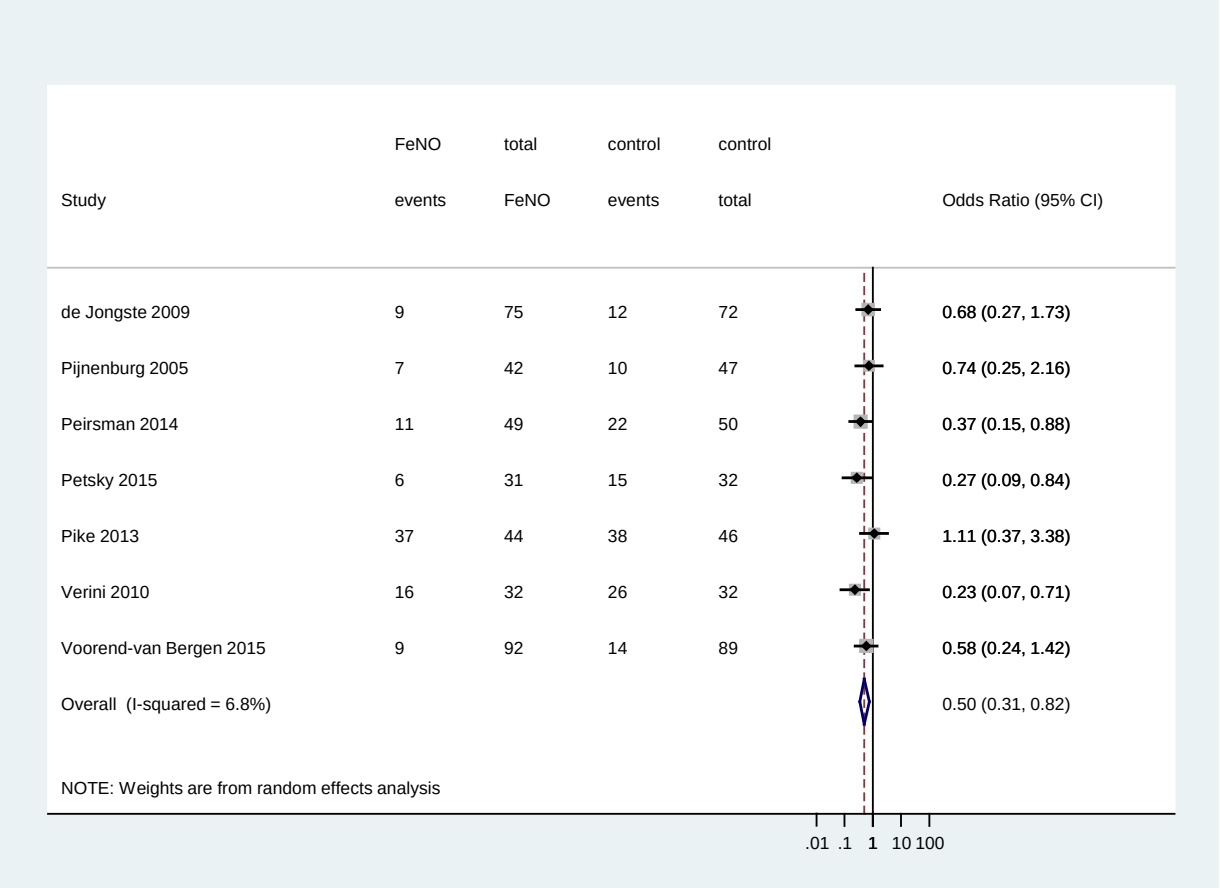


Figure 9 legend: Meta-analysis of the outcome of asthma exacerbations in children. Columns show the number of exacerbations and sample size for each study (when available) and the odds ratio of every study represented as a square. The diamond reflects the pooled odds ratio. Odds ratio under 1.0 suggests 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 Management based on clinical symptoms and/or spirometry. FeNO cutoff (20 to 30 ppb) Followup (6 to 12 months)		patients)	(OR: 0.50; 95% CI 0.31 to 0.82; I^2=7%; 116 events fewer per 1,000)	
	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)

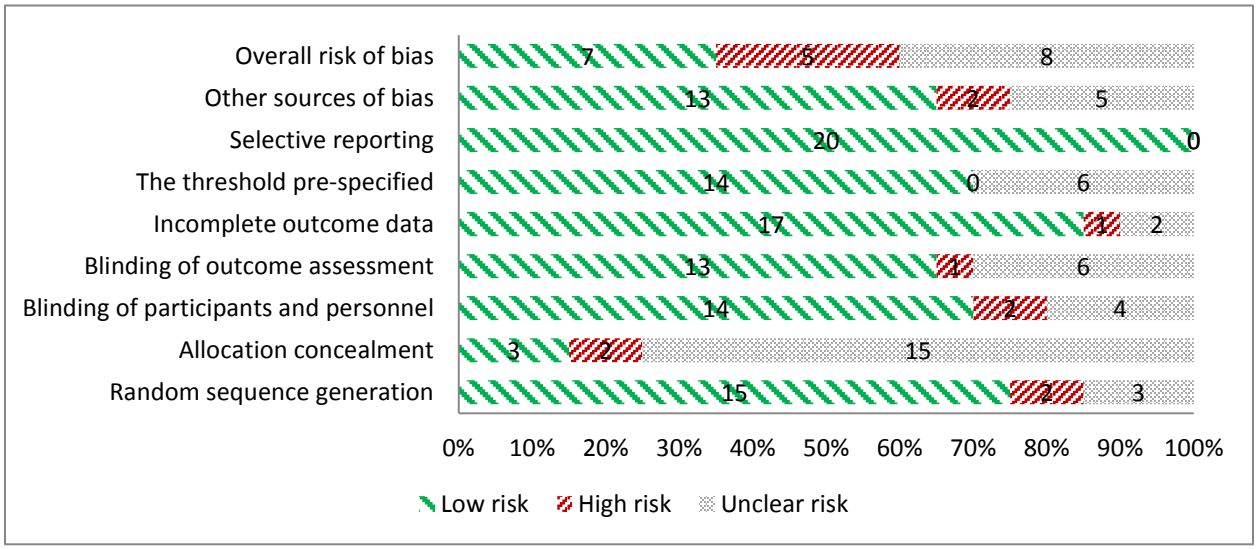
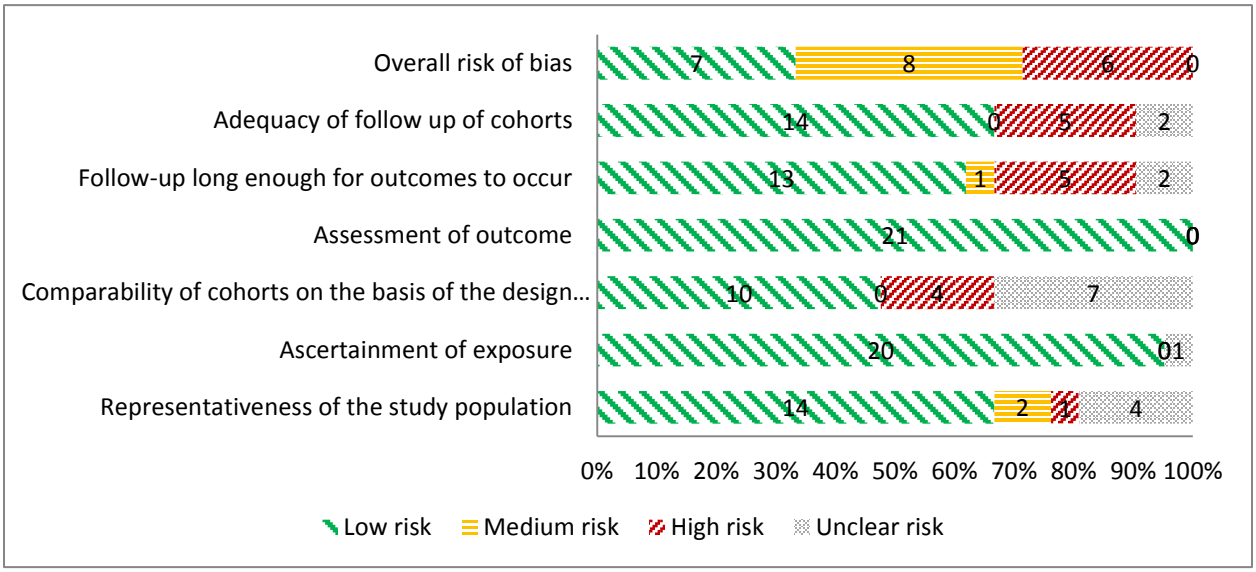


Figure 11. Risk of bias assessment of observational studies using the New-Castle Ottawa Scale (n=21, KQ 1.d)



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?

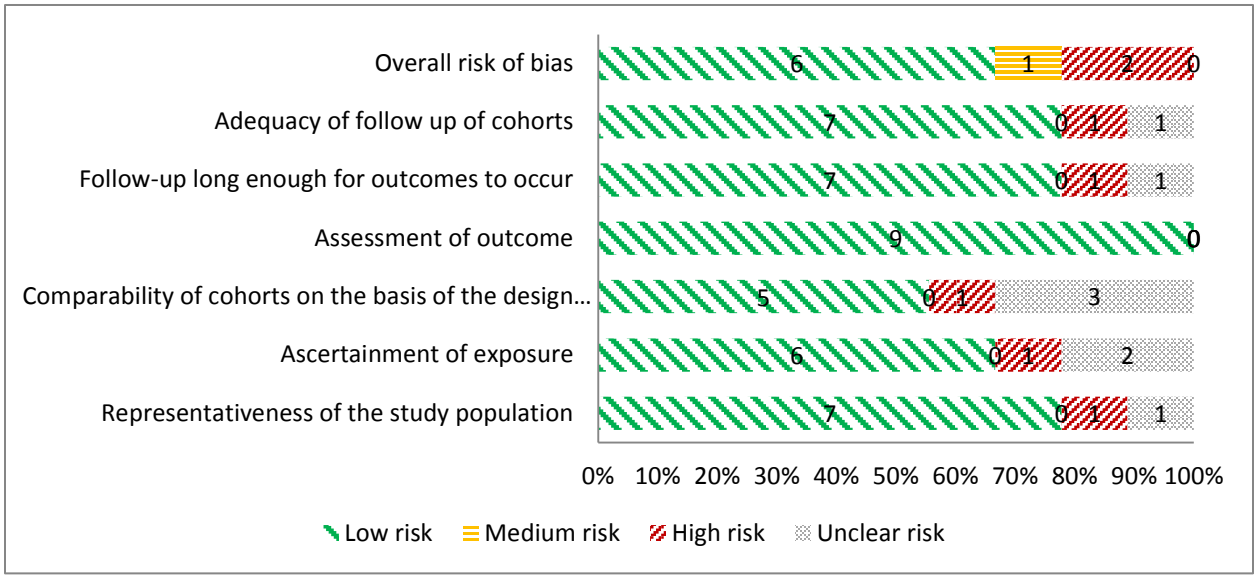
Key Points

- **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

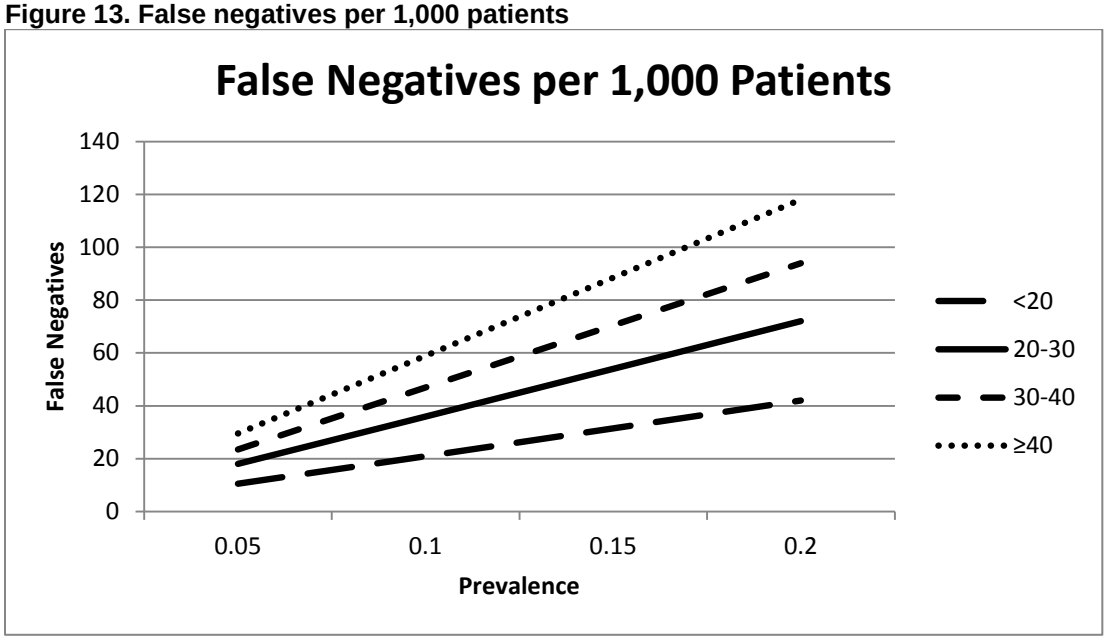
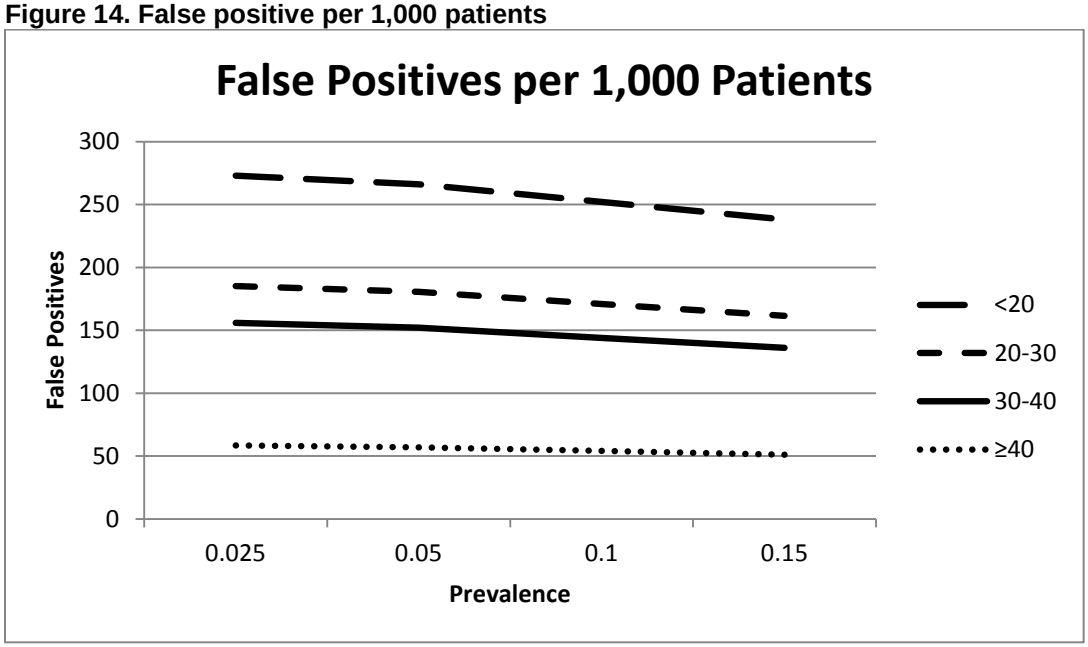


Figure 14. False positive per 1,000 patients



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

Appendixes

Contents

Tables

Figures

Appendix A. Search Strategy

KQ 1a.

Ovid

Database(s): Embase 1988 to 2016 Week 30, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials June 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 20, 2016

Search Strategy:

#	Searches	Results
1	exp Asthma/	308141
2	asthma*.mp.	387608
3	1 or 2	387722
4	("airway nitric oxide" or "airway NO" or "airway oxide" or "breath nitric oxide" or "breath NO" or "breath oxide" or "breathed nitric oxide" or "breathed NO" or "breathed oxide" or "breathing nitric oxide" or "breathing NO" or "breathing oxide" or "exhaled nitric oxide" or "exhaled NO" or "exhaled oxide" or FeNO or "lung nitric oxide" or "lung NO" or "lung oxide" or "pulmonary nitric oxide" or "pulmonary NO" or "pulmonary oxide" or "respiration nitric oxide" or "respiration NO" or "respiration oxide" or "respiratory nitric oxide" or "respiratory NO" or "respiratory oxide").mp.	100229
5	exp diagnostic accuracy/	202333
6	exp Spirometry/	48927
7	exp methacholine/	15852
8	exp Eosinophils/	55216
9	exp Eosinophil/	55216
10	exp eosinophil count/	7771
11	exp Peak Expiratory Flow Rate/	17248
12	(("respired air" adj3 pressure) or ((hyperreactiv* or hyperrespons* or respons*) adj3 (SABA or "short-acting beta2 agonist*")) or (breath adj3 measur*) or (diagnos* adj3 (accuracy or accurate)) or bronchoprovocat* or eosinophil* or mecholine or mecholyl or metacholine or methacholine or methacholinium or methylcholine or "peak expiration flow*" or "peak expiratory flow*" or "peak flow*" or spirometr*).mp.	605846
13	or/5-12	606514
14	3 and 4 and 13	8599
15	exp Blood/	2555329
16	blood.fs.	1571711
17	exp Heart/	879900
18	exp Blood Vessels/	1373624

19	exp Heart Diseases/	2263854
20	exp Vascular Diseases/	3255967
21	(arter* or blood or cardiac or cardial or heart or plasma or plasmas or serum or vascular* or vein* or vessel*).mp.	11139543
22	or/15-21	13473717
23	14 not 22	5081
24	exp evidence based medicine/	904342
25	exp meta analysis/	183265
26	exp Meta-Analysis as Topic/	43341
27	exp "systematic review"/	110642
28	exp controlled study/	5161226
29	exp Randomized Controlled Trial/	821123
30	exp triple blind procedure/	132
31	exp Double-Blind Method/	375029
32	exp Single-Blind Method/	59663
33	exp latin square design/	330
34	exp Placebos/	302126
35	exp Placebo Effect/	9028
36	exp comparative study/	2625586
37	exp Cohort Studies/	1940158
38	exp longitudinal study/	303249
39	exp retrospective study/	1069095
40	exp prospective study/	836601
41	case report/	3441589
42	((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case adj3 report)).mp,pt.	17709671
43	or/24-42	19397581
44	23 and 43	4197
45	limit 44 to ("preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or	4118

	"young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	
46	limit 45 to (preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years> or adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	3736
47	from 46 keep 1-1225	1225
48	(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) adj2 (year or years)).mp.	2161044
49	48 and child*.mp.	744191
50	(adult or adults or "middle age" or "middle aged" or elderly or geriatric*).mp.	12223883
51	44 and (49 or 50)	3087
52	47 or 51	3303
53	remove duplicates from 52	2782

Scopus
TITLE-ABS-KEY(asthma*)
TITLE-ABS-KEY("airway nitric oxide" OR "airway NO" OR "airway oxide" OR "breath nitric oxide" OR "breath NO" OR "breath oxide" OR "breathed nitric oxide" OR "breathed NO" OR "breathed oxide" OR "breathing nitric oxide" OR "breathing NO" OR "breathing oxide" OR "exhaled nitric oxide" OR "exhaled NO" OR "exhaled oxide" OR FeNO OR "lung nitric oxide" OR "lung NO" OR "lung oxide" OR "pulmonary nitric oxide" OR "pulmonary NO" OR "pulmonary oxide" OR "respiration nitric oxide" OR "respiration NO" OR "respiration oxide" OR "respiratory nitric oxide" OR "respiratory NO" OR "respiratory oxide")
TITLE-ABS-KEY(("respired air" W/3 pressure) or ((hyperreactiv* or hyperrespons* or respons*) W/3 (SABA or "short-acting beta2 agonist*")) or (breath W/3 measur*) or (diagnos* W/3 (accuracy or accurate)) or bronchoprovocat* or eosinophil* or mecholine or mecholyl or metacholine or methacholine or methacholinium or methylcholine or "peak expiration flow*" or "peak expiratory flow*" or "peak flow*" or spirometr*)
1 and 2 and 3
TITLE-ABS-KEY(arter* OR blood OR cardiac OR cardial OR heart OR plasma OR plasmas OR serum OR vascular* OR vein* OR vessel*)
4 and not 5
TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or

"prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case W/3 report))
TITLE-ABS-KEY(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) W/2 (year or years))
TITLE-ABS-KEY(child*)
TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" or elderly or geriatric*)
6 and 7 and ((8 and 9) or 10)
DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
11 not 12
PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
13 not 14

KQ 1b

Ovid

Database(s): Embase 1988 to 2016 Week 30, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials June 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 20, 2016
Search Strategy:

#	Searches	Results
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3	1 or 2	387722
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5	exp Spirometry/	48927
6	exp Peak Expiratory Flow Rate/	17248
7	exp symptom assessment/	5377
8	(("respired air" adj3 pressure) or ((assess* or evaluat*) adj3 (symptom* or asthma* or control*)) or (breath adj3 measur*) or ACQ or "Asthma Control Questionnaire" or monitor* or "peak expiration flow*" or "peak expiratory flow*" or "peak flow*"	2011076

	or spirometr*).mp.	
9	5 or 6 or 7 or 8	2011755
10	3 and 4 and 9	7945
11	exp Blood/	2555329
12	blood.fs.	1571711
13	exp Heart/	879900
14	exp Blood Vessels/	1373624
15	exp Heart Diseases/	2263854
16	exp Vascular Diseases/	3255967
17	(arter* or blood or cardiac or cardial or heart or plasma or plasmas or serum or vascular* or vein* or vessel*).mp.	11139543
18	or/11-17	13473717
19	10 not 18	5245
20	exp evidence based medicine/	904342
21	exp meta analysis/	183265
22	exp Meta-Analysis as Topic/	43341
23	exp "systematic review"/	110642
24	exp controlled study/	5161226
25	exp Randomized Controlled Trial/	821123
26	exp triple blind procedure/	132
27	exp Double-Blind Method/	375029
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32	exp comparative study/	2625586
33	exp Cohort Studies/	1940158
34	exp longitudinal study/	303249
35	exp retrospective study/	1069095
36	exp prospective study/	836601
37	case report/	3441589
38	((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3	17709671

	(study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case adj3 report)).mp,pt.	
39	or/20-38	19397581
40	19 and 39	4326
41	limit 40 to ("preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	4252
42	limit 41 to (preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years> or adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	3857
43	from 42 keep 1-1267	1267
44	(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) adj2 (year or years)).mp.	2161044
45	44 and child*.mp.	744191
46	(adult or adults or "middle age" or "middle aged" or elderly or geriatric*).mp.	12223883
47	40 and (45 or 46)	3101
48	43 or 47	3346
49	remove duplicates from 48	2797

Scopus

TITLE-ABS-KEY(asthma*)

TITLE-ABS-KEY("airway nitric oxide" OR "airway NO" OR "airway oxide" OR "breath nitric oxide" OR "breath NO" OR "breath oxide" OR "breathed nitric oxide" OR "breathed NO" OR "breathed oxide" OR "breathing nitric oxide" OR "breathing NO" OR "breathing oxide" OR "exhaled nitric oxide" OR "exhaled NO" OR "exhaled oxide" OR FeNO OR "lung nitric oxide" OR "lung NO" OR "lung oxide" OR "pulmonary nitric oxide" OR "pulmonary NO" OR "pulmonary oxide" OR "respiration nitric oxide" OR "respiration NO" OR "respiration oxide" OR "respiratory nitric oxide" OR "respiratory NO" OR "respiratory oxide")

TITLE-ABS-KEY(("respired air" W/3 pressure) or ((assess* or evaluat*) W/3 (symptom* or asthma* or control*)) or (breath W/3 measur*) or ACQ or "Asthma Control Questionnaire" or monitor* or "peak expiration flow*" or "peak expiratory flow*" or "peak flow*" or spirometr*)

1 and 2 and 3

TITLE-ABS-KEY(arter* OR blood OR cardiac OR cardial OR heart OR plasma OR plasmas OR serum OR vascular* OR vein* OR vessel*)

4 and not 5

TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3

trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case W/3 report))
TITLE-ABS-KEY(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) W/2 (year or years))
TITLE-ABS-KEY(child*)
TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" or elderly or geriatric*)
6 and 7 and ((8 and 9) or 10)
DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
11 and not 12
PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
#13 and not #14

KQ 1c

Ovid

Database(s): Embase 1988 to 2016 Week 30, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials June 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 20, 2016
Search Strategy:

#	Searches	Results
1	exp Asthma/dh, dt, rt, su, th [Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]	47695
2	exp asthma/dm, dt, rt, su, th [Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	56442
3	asthma*.mp.	387624
4	(drug* or pharmacotherap* or medication* or agent* or chemotherap* or intervention* or manag* or microbicid* or prevent* or radiotherap* or surg* or resect* or operat* or repair* or reconstruction* or therap* or treat*).mp.	24384025
5	3 and 4	249963
6	1 or 2 or 5	261247
7	("airway nitric oxide" or "airway NO" or "airway oxide" or "breath nitric oxide" or	100229

	"breath NO" or "breath oxide" or "breathed nitric oxide" or "breathed NO" or "breathed oxide" or "breathing nitric oxide" or "breathing NO" or "breathing oxide" or "exhaled nitric oxide" or "exhaled NO" or "exhaled oxide" or FeNO or "lung nitric oxide" or "lung NO" or "lung oxide" or "pulmonary nitric oxide" or "pulmonary NO" or "pulmonary oxide" or "respiration nitric oxide" or "respiration NO" or "respiration oxide" or "respiratory nitric oxide" or "respiratory NO" or "respiratory oxide").mp.	
8	exp Eosinophils/	55216
9	exp Eosinophil/	55216
10	exp eosinophil count/	7771
11	exp sputum examination/ or exp sputum/ or exp sputum level/ or exp sputum analysis/	53693
12	exp Bronchoalveolar Lavage Fluid/	66065
13	exp Skin Tests/	109868
14	exp Hypersensitivity/di [Diagnosis]	94630
15	exp sensitization/	49920
16	exp allergy test/	3670
17	exp Immunoglobulin E/	95525
18	(((allerg* or skin or hypersensitivit* or sensitiz*) adj3 test*) or "alveolar lavage" or "bronchial lavage" or "bronchoalveolar lavage" or eosinophil* or expectorate or IgE or "immunoglobulin e" or "lung lavage" or "lung washing" or "pulmonary lavage" or "pulmonary washing" or sputum).mp.	495523
19	or/8-18	619799
20	6 and 7 and 19	4530
21	exp Blood/	2555329
22	blood.fs.	1571711
23	exp Heart/	879900
24	exp Blood Vessels/	1373624
25	exp Heart Diseases/	2263854
26	exp Vascular Diseases/	3255967
27	(arter* or blood or cardiac or cardial or heart or plasma or plasmas or serum or vascular* or vein* or vessel*).mp.	11140330
28	or/21-27	13474504
29	20 not 28	2127
30	exp evidence based medicine/	904342
31	exp meta analysis/	183265
32	exp Meta-Analysis as Topic/	43341
33	exp "systematic review"/	110642
34	exp controlled study/	5161226
35	exp Randomized Controlled Trial/	821123

36	exp triple blind procedure/	132
37	exp Double-Blind Method/	375029
38	exp Single-Blind Method/	59663
39	exp latin square design/	330
40	exp Placebos/	302126
41	exp Placebo Effect/	9028
42	exp comparative study/	2625586
43	exp Cohort Studies/	1940158
44	exp longitudinal study/	303249
45	exp retrospective study/	1069095
46	exp prospective study/	836601
47	case report/	3441591
48	((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case adj3 report)).mp,pt.	17710846
49	or/30-48	19398758
50	29 and 49	1584
51	limit 50 to ("preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	1527
52	limit 51 to (preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years> or adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	1324
53	from 52 keep 1-652	652
54	(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) adj2 (year or years)).mp.	2161258
55	54 and child*.mp.	744238
56	(adult or adults or "middle age" or "middle aged" or elderly or geriatric*).mp.	12224142

57 50 and (55 or 56)	1050
58 53 or 57	1191
59 remove duplicates from 58	1007

Scopus
TITLE-ABS-KEY(asthma*)
TITLE-ABS-KEY(drug* or pharmacotherap* or medication* or agent* or chemotherap* or intervention* or manag* or microbicid* or prevent* or radiotherap* or surg* or resect* or operat* or repair* or reconstruction* or therap* or treat*)
TITLE-ABS-KEY("airway nitric oxide" OR "airway NO" OR "airway oxide" OR "breath nitric oxide" OR "breath NO" OR "breath oxide" OR "breathed nitric oxide" OR "breathed NO" OR "breathed oxide" OR "breathing nitric oxide" OR "breathing NO" OR "breathing oxide" OR "exhaled nitric oxide" OR "exhaled NO" OR "exhaled oxide" OR FeNO OR "lung nitric oxide" OR "lung NO" OR "lung oxide" OR "pulmonary nitric oxide" OR "pulmonary NO" OR "pulmonary oxide" OR "respiration nitric oxide" OR "respiration NO" OR "respiration oxide" OR "respiratory nitric oxide" OR "respiratory NO" OR "respiratory oxide")
TITLE-ABS-KEY(((allerg* or skin or hypersensitivit* or sensitiz*) W/3 test*) or "alveolar lavage" or "bronchial lavage" or "bronchoalveolar lavage" or eosinophil* or expectorate or IgE or "immunoglobulin e" or "lung lavage" or "lung washing" or "pulmonary lavage" or "pulmonary washing" or sputum)
1 and 2 and 3 and 4
TITLE-ABS-KEY(arter* OR blood OR cardiac OR cardial OR heart OR plasma OR plasmas OR serum OR vascular* OR vein* OR vessel*)
5 and not 6
TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case W/3 report))
TITLE-ABS-KEY(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) W/2 (year or years))
TITLE-ABS-KEY(child*)
TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" or elderly or geriatric*)
7 and 8 and ((9 and 10) or 11)
DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
12 and not 13

PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
14 and not 15

KQ 1d

Ovid

Database(s): Embase 1988 to 2016 Week 30, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials June 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 20, 2016
Search Strategy:

#	Searches	Results
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2	exp asthma/dm, dt, rt, su, th [Disease Management, Drug Therapy, Radiotherapy, Surgery, Therapy]	56442
3	asthma*.mp.	387624
4	(drug* or pharmacotherap* or medication* or agent* or chemotherap* or intervention* or manag* or microbicid* or prevent* or radiotherap* or surg* or resect* or operat* or repair* or reconstruction* or therap* or treat*).mp.	24384025
5	3 and 4	249963
6	1 or 2 or 5	261247
7	("airway nitric oxide" or "airway NO" or "airway oxide" or "breath nitric oxide" or "breath NO" or "breath oxide" or "breathed nitric oxide" or "breathed NO" or "breathed oxide" or "breathing nitric oxide" or "breathing NO" or "breathing oxide" or "exhaled nitric oxide" or "exhaled NO" or "exhaled oxide" or FeNO or "lung nitric oxide" or "lung NO" or "lung oxide" or "pulmonary nitric oxide" or "pulmonary NO" or "pulmonary oxide" or "respiration nitric oxide" or "respiration NO" or "respiration oxide" or "respiratory nitric oxide" or "respiratory NO" or "respiratory oxide").mp.	100229
8	exp Spirometry/	48927
9	exp Peak Expiratory Flow Rate/	17248
10	exp symptom assessment/	5377
11	(("respired air" adj3 pressure) or ((assess* or evaluat*) adj3 (symptom* or asthma* or control*)) or (breath adj3 measur*) or ACQ or "Asthma Control Questionnaire" or monitor* or "peak expiration flow*" or "peak expiratory flow*" or "peak flow*" or spirometr*).mp.	2011281
12	8 or 9 or 10 or 11	2011960
13	6 and 7 and 12	6539
14	exp Blood/	2555329
15	blood.fs.	1571711

16	exp Heart/	879900
17	exp Blood Vessels/	1373624
18	exp Heart Diseases/	2263854
19	exp Vascular Diseases/	3255967
20	(arter* or blood or cardiac or cardial or heart or plasma or plasmas or serum or vascular* or vein* or vessel*).mp.	11140330
21	or/14-20	13474504
22	13 not 21	4246
23	exp evidence based medicine/	904342
24	exp meta analysis/	183265
25	exp Meta-Analysis as Topic/	43341
26	exp "systematic review"/	110642
27	exp controlled study/	5161226
28	exp Randomized Controlled Trial/	821123
29	exp triple blind procedure/	132
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42	or/23-41	19398758

43	22 and 42	3621
44	limit 43 to ("preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	3567
45	limit 44 to (preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years> or adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	3268
46	from 45 keep 1-897	897
47	(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) adj2 (year or years)).mp.	2161258
48	47 and child*.mp.	744238
49	(adult or adults or "middle age" or "middle aged" or elderly or geriatric*).mp.	12224142
50	43 and (48 or 49)	2627
51	46 or 50	2789
52	remove duplicates from 51	2389

Scopus

TITLE-ABS-KEY(asthma*)

TITLE-ABS-KEY(drug* or pharmacotherap* or medication* or agent* or chemotherap* or intervention* or manag* or microbicid* or prevent* or radiotherap* or surg* or resect* or operat* or repair* or reconstruction* or therap* or treat*)

TITLE-ABS-KEY("airway nitric oxide" OR "airway NO" OR "airway oxide" OR "breath nitric oxide" OR "breath NO" OR "breath oxide" OR "breathed nitric oxide" OR "breathed NO" OR "breathed oxide" OR "breathing nitric oxide" OR "breathing NO" OR "breathing oxide" OR "exhaled nitric oxide" OR "exhaled NO" OR "exhaled oxide" OR FeNO OR "lung nitric oxide" OR "lung NO" OR "lung oxide" OR "pulmonary nitric oxide" OR "pulmonary NO" OR "pulmonary oxide" OR "respiration nitric oxide" OR "respiration NO" OR "respiration oxide" OR "respiratory nitric oxide" OR "respiratory NO" OR "respiratory oxide")

TITLE-ABS-KEY(("respired air" W/3 pressure) or ((assess* or evaluat*) W/3 (symptom* or asthma* or control*)) or (breath W/3 measur*) or ACQ or "Asthma Control Questionnaire" or monitor* or "peak expiration flow*" or "peak expiratory flow*" or "peak flow*" or spirometr*)

1 and 2 and 3 and 4

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5 and not 6

TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative

analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case W/3 report))
TITLE-ABS-KEY(("5" or "6" or "7" or "8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen) W/2 (year or years))
TITLE-ABS-KEY(child*)
TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" or elderly or geriatric*)
7 and 8 and ((9 and 10) or 11)
DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
12 and not 13
PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
14 and not 15

KQ 1e

Ovid

Database(s): Embase 1988 to 2016 Week 30, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials June 2016, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 20, 2016
Search Strategy:

#	Searches	Results
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2	exp Respiratory Sounds/	51820
3	(rhonchi or rhonchus or wheez*).mp.	37161
4	2 or 3	64711
5	exp "Predictive Value of Tests"/	269135
6	(predict* or API).mp.	2747478
7	5 or 6	2747478
8	1 and 4 and 7	499
9	exp Blood/	2555329

10	blood.fs.	1571711
11	exp Heart/	879900
12	exp Blood Vessels/	1373624
13	exp Heart Diseases/	2263854
14	exp Vascular Diseases/	3255967
15	(arter* or blood or cardiac or cardial or heart or plasma or plasmas or serum or vascular* or vein* or vessel*).mp.	11140330
16	or/9-15	13474504
17	8 not 16	282
18	exp evidence based medicine/	904342
19	exp meta analysis/	183265
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21	exp "systematic review"/	110642
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23	exp Randomized Controlled Trial/	821123
24	exp triple blind procedure/	132
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37	or/18-36	19398758
38	17 and 37	247
39	limit 38 to ("all infant (birth to 23 months)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)") [Limit not valid in Embase,CCTR,CDSR; records were retained]	234
40	limit 39 to (infant or preschool child <1 to 6 years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process,CCTR,CDSR; records were retained]	182
41	from 40 keep 1-31	31
42	(("1" or "2" or "3" or "4" or one or two or three or four) adj2 (year or years)).mp.	1727622
43	42 and child*.mp.	432826
44	(newborn* or neonat* or infant* or toddler*).mp.	2225413
45	38 and (43 or 44)	113
46	41 or 45	117
47	remove duplicates from 46	105

Scopus
TITLE-ABS-KEY("airway nitric oxide" OR "airway NO" OR "airway oxide" OR "breath nitric oxide" OR "breath NO" OR "breath oxide" OR "breathed nitric oxide" OR "breathed NO" OR "breathed oxide" OR "breathing nitric oxide" OR "breathing NO" OR "breathing oxide" OR "exhaled nitric oxide" OR "exhaled NO" OR "exhaled oxide" OR FeNO OR "lung nitric oxide" OR "lung NO" OR "lung oxide" OR "pulmonary nitric oxide" OR "pulmonary NO" OR "pulmonary oxide" OR "respiration nitric oxide" OR "respiration NO" OR "respiration oxide" OR "respiratory nitric oxide" OR "respiratory NO" OR "respiratory oxide")
TITLE-ABS-KEY(rhonchi or rhonchus or wheez*)
TITLE-ABS-KEY(predict* or API)
1 and 2 and 3
TITLE-ABS-KEY(arter* OR blood OR cardiac OR cardial OR heart OR plasma OR plasmas OR serum OR vascular* OR vein* OR vessel*)
4 and not 5
TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or "comparative study" or "comparative survey" or "comparative analysis" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "clinical study" or "clinical trial" or "multicenter study" or "multi-center study" or ((study or trial or random* or control*) and compar*) or (case W/3 report))
TITLE-ABS-KEY (("1" or "2" or "3" or "4" or one or two or three or four) W/2 (year or years))
TITLE-ABS-KEY(child*)

TITLE-ABS-KEY(newborn* or neonat* or infant* or toddler*)
6 and 7 and ((8 and 9) or 10)
DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
11 and not 12
PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*)
13 and not 14

Appendix B. Excluded Studies

Abuzayan I, Turner SW. Changes in exhaled nitric oxide after ingestion of L-arginine in children: a pilot study. Pediatr Pulmonol. 2010 Mar;45(3):236-40. doi: 10.1002/ppul.21110. PMID: 20131381. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Acouetey DS, Zmirou-Navier D, Avogbe PH, et al. Genetic predictors of inflammation in the risk of occupational asthma in young apprentices. Ann Allergy Asthma Immunol. 2013 Jun;110(6):423-8 e5. doi: 10.1016/j.anai.2013.04.005. PMID: 23706710.. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Adar SD, D'Souza J, Sheppard L, et al. Adopting Clean Fuels and Technologies on School Buses. Pollution and Health Impacts in Children. Am J Respir Crit Care Med. 2015 Jun 15;191(12):1413-21. doi: 10.1164/rccm.201410-1924OC. PMID: 25867003 *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Adema, A Y, Verwey, et al. Effect of a short-term stay in a high altitude clinic. Tijdschrift voor Kindergeneeskunde. 2009;77(1):30-6. *The study does not evaluate FeNO.*

Adisesh LA, Kharitonov SA, Yates DH, et al. Exhaled and nasal nitric oxide is increased in laboratory animal allergy. Clinical and Experimental Allergy. 1998 Jul;28(7):876-80. DOI: 10.1046/j.1365-2222.1998.00332.x. PMID: WOS:000075104800014. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Akamatsu T, Shirai T, Kato M, et al. Effect of switching from salmeterol/fluticasone to formoterol/ budesonide combinations in patients with uncontrolled asthma. Allergol Int. 2012 Jun;61(2):323-9. doi: 10.2332/allergolint.11-OA-0384. PMID: 22441635. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Akamatsu T, Shirai T, Kato M, et al. Switching from salmeterol/fluticasone to formoterol/budesonide combinations improves peripheral airway/alveolar inflammation in asthma. Pulm Pharmacol Ther. 2014 Feb;27(1):52-6. doi: 10.1016/j.pupt.2013.04.001. PMID: 23583566. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Akashi K, Mezawa H, Tabata Y, et al. Optimal step-down approach for pediatric asthma controlled by salmeterol/fluticasone: A randomized, controlled trial (OSCAR study). Allergol Int. 2016 Jul;65(3):306-11. doi: 10.1016/j.alit.2016.02.010. PMID: 27155753. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Al-Ali MK, Eames C, Howarth PH. Exhaled nitric oxide; relationship to clinicophysiological markers of asthma severity. Respiratory Medicine. 1998 Jul;92(7):908-13. doi: Doi 10.1016/S0954-6111(98)90189-5. PMID: WOS:000075609700003. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Al-Ali MK, Howarth PH. Exhaled nitric oxide levels in exacerbations of asthma, chronic obstructive pulmonary disease and pneumonia. Saudi Med J. 2001 Mar;22(3):249-53. PMID: 11307112. *The study does not have a comparison group (studies must have a comparison group or pre/post design)*

Alcazar-Navarrete B, Romero-Palacios PJ, Ruiz-Sancho A, et al. Diagnostic performance of the measurement of nitric oxide in exhaled air in the diagnosis of COPD phenotypes. Nitric Oxide-Biology and Chemistry. 2016 Apr 1;54:67-72. doi: 10.1016/j.niox.2016.02.003. PMID: WOS:000373658000008. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Ali M, Khoo SK, Turner S, et al. NOS1 polymorphism is associated with atopy but not exhaled nitric oxide levels in healthy children. Pediatr Allergy Immunol. 2003 Aug;14(4):261-5. doi: 10.1034/j.1399-3038.2003.00065.x. PMID: 12911502. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Allen RW, Mar T, Koenig J, et al. Changes in lung function and airway inflammation among asthmatic children residing in a woodsmoke-impacted urban area. Inhalation Toxicology. 2008 February;20(4):423-33. doi: 10.1080/08958370801903826. PMID: WOS:000253642800006. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Alvarez-Gutierrez FJ, Medina-Gallardo JF, Perez-Navarro P, et al. [Comparison of the Asthma Control Test (ACT) with lung function, levels of exhaled nitric oxide and control according to the Global Initiative for Asthma (GINA)]. Arch Bronconeumol. 2010 Jul;46(7):370-7. doi: 10.1016/j.arbres.2010.04.003. PMID: 20605310. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Alvarez-Puebla MJ, Olaguibel JM, Almudevar E, et al. Mannitol versus hypertonic saline: Safety and efficacy of mannitol and hypertonic saline in sputum induction and bronchial hyperreactivity assessment. Chronic Respiratory Disease. 2015 Aug;12(3):197-203. doi: 10.1177/1479972315576144. PMID: WOS:000358381700003. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Amer, M, Cowan, et al. Effect of inhaled beta2-agonist on exhaled nitric oxide in chronic obstructive pulmonary disease. PLoS ONE. 2016 01 Jun;11 (6) (no pagination)(e0157019). doi: 10.1371/journal.pone.0157019. PMID: 20160431719. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Amimoto, Y, Arakaki, et al. Relationship between compliance with inhaled corticosteroids and changes in the fraction of exhaled nitric oxide during summer camp for asthmatic children. Japanese Journal of Allergology. 2011;60(12):1641-5. doi: 10.15036/arerugi.60.1641. *The study is not original (commentaries, letters, etc. should be excluded)*

Amore M, Antonucci C, Bettini E, et al. Disease Control in Patients with Asthma is Associated with Alexithymia but not with Depression or Anxiety. Behavioral Medicine. 2013 Oct 1;39(4):138-45. doi: 10.1080/08964289.2013.818931. PMID: WOS:000327945800006. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Anderson WJ, Lipworth BJ. Does body mass index influence responsiveness to inhaled corticosteroids in persistent asthma? Ann Allergy Asthma Immunol. 2012 Apr;108(4):237-42. doi: 10.1016/j.anai.2011.12.006. PMID: 22469442. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Anderson WJ, Lipworth BJ. Relationship of mannitol challenge to methacholine challenge and inflammatory markers in persistent asthmatics receiving inhaled corticosteroids. Lung. 2012 Oct;190(5):513-21. doi: 10.1007/s00408-012-9396-6. PMID: 22684880. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Ansarin, K, Chatkin, et al. Exhaled nitric oxide in chronic obstructive pulmonary disease: Relationship to pulmonary function. European Respiratory Journal. 2001;17(5):934-8. PMID: 2001232784. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Antczak A, Kharitonov SA, Montuschi P, et al. Inflammatory response to sputum induction measured by exhaled markers. Respiration. 2005 Nov-Dec;72(6):594-9. doi: 10.1159/000086721. PMID: 15988171. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Arabkhazaeli A, Vijverberg SJ, van Erp FC, et al. Characteristics and severity of asthma in children with and without atopic conditions: a cross-sectional study. BMC Pediatr. 2015 Nov 06;15:172. doi: 10.1186/s12887-015-0481-x. PMID: 26545978. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Araujo L, Jacinto T, Moreira A, et al. Clinical efficacy of web-based versus standard asthma self-management. J Investig Allergol Clin Immunol. 2012;22(1):28-34. PMID: 22448451. *Other reason*

Araujo L, Moreira A, Palmares C, et al. Induced sputum in children: success determinants, safety, and cell profiles. J Investig Allergol Clin Immunol. 2011;21(3):216-21. PMID: 21548450. *The study does not evaluate FeNO*

Arga M, Bakirtas A, Topal E, et al. Can exhaled nitric oxide be a surrogate marker of bronchial hyperresponsiveness to adenosine 5'-monophosphate in steroid-naive asthmatic children? Clin Exp Allergy. 2015 Apr;45(4):758-66. doi: 10.1111/cea.12447. PMID: 25378028. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Arnold DH, Gebretsadik T, Abramo TJ, et al. Noninvasive testing of lung function and inflammation in pediatric patients with acute asthma exacerbations. J Asthma. 2012 Feb;49(1):29-35. doi: 10.3109/02770903.2011.637599. PMID: 22133263. *The study does not have a comparison group (studies must have a comparison group or pre/post design)*

Aronsson D, Tufvesson E, Bjermer L. Allergic rhinitis with or without concomitant asthma: difference in perception of dyspnoea and levels of fractional exhaled nitric oxide. Clin Exp Allergy. 2005 Nov;35(11):1457-61. doi: 10.1111/j.1365-2222.2005.02363.x. PMID: 16297142. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Arroyave, W D, Rabito, et al. Asthma severity, not asthma control, is worse in atopic compared with nonatopic adolescents with asthma. Annals of Allergy, Asthma and Immunology. 2016 01 Jan;116(1):18-25. doi: 10.1016/j.anai.2015.10.015. PMID: 20160035478. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Arshad SH, Raza A, Lau L, et al. Pathophysiological characterization of asthma transitions across adolescence. Respir Res. 2014 Nov 29;15:153. doi: 10.1186/s12931-014-0153-7. PMID: 25472820. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Badorrek P, Dick M, Emmert L, et al. Pollen starch granules in bronchial inflammation. Ann Allergy Asthma Immunol. 2012 Sep;109(3):208-14 e6. doi: 10.1016/j.anai.2012.06.019. PMID: 22920077. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Baines KJ, Simpson JL, Wood LG, et al. Transcriptional phenotypes of asthma defined by gene expression profiling of induced sputum samples. J Allergy Clin Immunol. 2011 Jan;127(1):153-60, 60 e1-9. doi: 10.1016/j.jaci.2010.10.024. PMID: 21211650. *Other reason*

Balboa de P, F, Rueda E, et al. Exhaled nitric oxygen in healthy and asthmatic children. [Spanish]. Anales Espanoles de Pediatria. 2002;57(1):12-7. PMID: 2002277965. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Baptist, A P, Ross, et al. Older adults with asthma: Does age of asthma onset make a difference? Journal of Asthma. 2013 October;50(8):836-41. doi: 10.3109/02770903.2013.816967. PMID: 2013584398. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Baptist AP, Li L, Dichiaro CA. The importance of atopy on exhaled nitric oxide levels in African American children. Ann Allergy Asthma Immunol. 2015 May;114(5):399-403. doi: 10.1016/j.anai.2015.02.005. PMID: 25752733. *The study does not have a comparison group (studies must have a comparison group or pre/post design)*

Baptist AP, Sengupta R, Pranathiageswaran S, et al. Evaluation of exhaled nitric oxide measurements in the emergency department for patients with acute asthma. Ann Allergy Asthma Immunol. 2008 May;100(5):415-9. doi: 10.1016/S1081-1206(10)60464-4. PMID: 18517071. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Baptist AP, Shah B, Wang Y, et al. Exhaled nitric oxide levels during treatment in patients hospitalized with asthma. Allergy Asthma Proc. 2008 Mar-Apr;29(2):171-6. doi: 10.2500/aap.2008.29.3098. PMID: 18430315. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Baptist AP, Ross JA, Yang Y, et al. A randomized controlled trial of a self-regulation intervention for older adults with asthma. J Am Geriatr Soc. 2013 May;61(5):747-53. doi: 10.1111/jgs.12218. PMID: 23617712. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Baptist, Alan P, Shah, et al. Exhaled nitric oxide levels during treatment in patients hospitalized with asthma. Allergy & Asthma Proceedings. 2008 Mar-Apr;29(2):171-6. PMID: 18430315. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Baraket, Melissa, Oliver, et al. Is low dose inhaled corticosteroid therapy as effective for inflammation and remodeling in asthma? A randomized, parallel group study. Respiratory Research. 2012;13:11. PMID: 22300506. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Baraket M, Oliver BG, Burgess JK, et al. Is low dose inhaled corticosteroid therapy as effective for inflammation and remodeling in asthma? A randomized, parallel group study. Respir Res. 2012 Feb 02;13:11. doi: 10.1186/1465-9921-13-11. PMID: 22300506. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Baraldi E, Carra S, Dario C, et al. Effect of natural grass pollen exposure on exhaled nitric oxide in asthmatic children. Am J Respir Crit Care Med. 1999 Jan;159(1):262-6. doi: 10.1164/ajrccm.159.1.9804063. PMID: 9872848. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Baraldi E, Carraro S, Alinovi R, et al. Cysteinyl leukotrienes and 8-isoprostane in exhaled breath condensate of children with asthma exacerbations. Thorax. 2003 Jun;58(6):505-9. doi: 10.1136/thorax.58.6.505. PMID: 12775861. *The study does not have a comparison group (studies must have a comparison group or pre/post design)*

Baraldi E, Ghiro L, Piovan V, et al. Safety and success of exhaled breath condensate collection in asthma. Arch Dis Child. 2003 Apr;88(4):358-60. doi: 10.1136/adc.88.4.358. PMID: 12651772. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Baraldi E, Giordano G, Pasquale MF, et al. 3-Nitrotyrosine, a marker of nitrosative stress, is increased in breath condensate of allergic asthmatic children. Allergy. 2006 Jan;61(1):90-6. doi: 10.1111/j.1398-9995.2006.00996.x. PMID: 16364162. *Other reason*

Baraldi E, Scollo M, Zaramella C, et al. A simple flow-driven method for online measurement of exhaled NO starting at the age of 4 to 5 years. Am J Respir Crit Care Med. 2000 Nov;162(5):1828-32. doi: 10.1164/ajrccm.162.5.2002014. PMID: 11069821. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Baraldi E, Bonetto G, Zacchello F, et al. Low exhaled nitric oxide in school-age children with bronchopulmonary dysplasia and airflow limitation. Am J Respir Crit Care Med. 2005 Jan 01;171(1):68-72. doi: 10.1164/rccm.200403-298OC. PMID: 15477497. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Baraldi E, Ghiro L, Piovan V, et al. Increased exhaled 8-isoprostane in childhood asthma. Chest. 2003 Jul;124(1):25-31. doi: 10.1378/chest.124.1.25. PMID: 12853498. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Barben J, Strippoli MP, Trachsel D, et al. Effect of mannitol dry powder challenge on exhaled nitric oxide in children. PLoS One. 2013 18 Jan;8(1):e54521. doi: 10.1371/journal.pone.0054521. PMID: 23349918. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Bardin P, Kanniess F, Gauvreau G, et al. Roflumilast for asthma: Efficacy findings in mechanism of action studies. Pulm Pharmacol Ther. 2015 Dec;35 Suppl:S4-10. doi: 10.1016/j.pupt.2015.08.006. PMID: 26296794. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Barraza-Villarreal A, Sunyer J, Hernandez-Cadena L, et al. Air pollution, airway inflammation, and lung function in a cohort study of Mexico City schoolchildren. Environ Health Perspect. 2008 Jun;116(6):832-8. doi: 10.1289/ehp.10926. PMID: 18560490. *The study does not evaluate FeNO*

Barreto M, Bonafoni S, Barberi S, et al. Does a parent-reported history of pneumonia increase the likelihood of respiratory symptoms needing therapy in asthmatic children and adolescents? J Asthma. 2011 Sep;48(7):714-20. doi: 10.3109/02770903.2011.601779. PMID: 21793780. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Barreto M, Rennerova Z, Montesano M, et al. Variations in exhaled nitric oxide in children with asthma during a 1-week stay in a mountain village sanatorium. J Asthma. 2008 Aug;45(6):453-8. doi: 10.1080/02770900802040035. PMID: 18612896. *The study does not have a comparison group (studies must have a comparison group or pre/post design)*

Barreto M, Villa MP, Olita C, et al. 8-Isoprostane in exhaled breath condensate and exercise-induced bronchoconstriction in asthmatic children and adolescents. Chest. 2009 Jan;135(1):66-73. doi: 10.1378/chest.08-0722. PMID: 18753466. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Barreto M, Villa MP, Montesano M, et al. Reduced exhaled nitric oxide in children after testing of maximal expiratory pressures. Pediatr Pulmonol. 2006 Feb;41(2):141-5. doi: 10.1002/ppul.20358. PMID: 16358341. *The study does not have a comparison group (studies must have a comparison group or pre/post design)*

Barros R, Moreira A, Fonseca J, et al. Adherence to the Mediterranean diet and fresh fruit intake are associated with improved asthma control. Allergy. 2008 Jul;63(7):917-23. doi: 10.1111/j.1398-9995.2008.01665.x. PMID: 18588559. *Other reason*

Barros R, Moreira A, Fonseca J, et al. Dietary intake of alpha-linolenic acid and low ratio of n-6:n-3 PUFA are associated with decreased exhaled NO and improved asthma control. British Journal of Nutrition. 2011 Aug 14;106(3):441-50. doi: 10.1017/S0007114511000328. PMID: 2011524628. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Battaglia S, den Hertog H, Timmers MC, et al. Small airways function and molecular markers in exhaled air in mild asthma. Thorax. 2005 Aug;60(8):639-44. doi: 10.1136/thx.2004.035279. PMID: 16061704. *The study does not have a comparison group (studies must have a comparison group or pre/post design)*

Beck-Ripp J, Latzin P, Griese M. Exhaled carbon monoxide is not flow dependent in children with cystic fibrosis and asthma. Eur J Med Res. 2004 Nov 29;9(11):518-22. PMID: 15649862. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Beck J, Griese M, Latzin P, et al. Characteristics of flow dependency of nitric oxide in exhaled air in children with cystic fibrosis and asthma. Eur J Med Res. 1999 Aug 25;4(8):335-40. PMID: 10471545. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Beg MF, Alzoghaibi MA, Abba AA, et al. Exhaled nitric oxide in stable chronic obstructive pulmonary disease. Ann Thorac Med. 2009 Apr;4(2):65-70. doi: 10.4103/1817-1737.44649. PMID: 19561927. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Behndig AF, Larsson N, Brown JL, et al. Proinflammatory doses of diesel exhaust in healthy subjects fail to elicit equivalent or augmented airway inflammation in subjects with asthma. Thorax. 2011 Jan;66(1):12-9. doi: 10.1136/thx.2010.140053. PMID: 20837873. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

Beier J, Beeh KM, Kornmann O, et al. Sputum induction leads to a decrease of exhaled nitric oxide unrelated to airflow. Eur Respir J. 2003 Aug;22(2):354-7. doi: 10.1183/09031936.03.00118602. PMID: 12952273. *The study does not have patients of interest (suspected to have asthma, have wheezing, 0-4 years old who may develop asthma in the future)*

Benor S, Alcalay Y, Domany KA, et al. Ultrafine particle content in exhaled breath condensate in airways of asthmatic children. J Breath Res. 2015 Apr 01;9(2):026001. doi: 10.1088/1752-7155/9/2/026001. PMID: 25830607. *The study does not report any outcomes of interest (diagnosis of asthma, clinical asthma outcomes, healthcare utilization, harms due to over-/under-diagnosis or other side effects)*

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Appendix C. Description of Included Studies

Table C.1. Characteristics of the included studies in KQ 1a

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)
Arora, 2006[1]	United States, cross section study, low risk of bias.	Reference test; positive bronchial challenge histamine broncho-provocation, N= 172	138 asthmatic patients; mean age of 20 years, 47% males. 34 non-asthmatic patients a mean age of 21 years, 59% males.	Histamine challenge used to confirm or refute asthma diagnosis in subjects with compatible symptoms; i.e. used as part of gold standard diagnosis. PC20 <8 mg/mL.	FeNO at 17 ppb cut-off, compared with histamine broncho-provocation test had sensitivity: 63%, specificity: 59%, PPV: 86%, NPV: 28%. AUC=0.63. FeNO at 20 ppb cut-off, compared with histamine broncho-provocation test had sensitivity: 53%, specificity: 68%, PPV: 87%, NPV: 26%.
		FeNO, N= 172		Measured by NIOX system (Aerocrine AB, Stockholm, Sweden) at a flow rate of 50 mL/sec. FeNO measurement occurred before start of the standard asthma evaluation, including spirometry, to avoid any influence of baseline spirometry on FeNO values.	
Avital, 2001[2]	Israel, longitudinal nonrandomized, outpatient setting, medium risk of bias.	Reference test; positive bronchial challenge adenosine-5' monophosphat e (AMP) challenge test, N= 71	36 children with mild intermittent asthma Mean age 4.4 years (SD: 0.2). 20 non-asthmatic children with chronic cough with a mean age of 4.2 years (SD: 0.3) and 15 healthy children with a mean age of 5.1 years (SD: 0.2).	Positive test was defined as a clear wheeze heard over the chest by auscultation, a drop in oxygen saturation of 5% or more from baseline, or an increase of >50% over the baseline respiratory rate.	Mild intermittent asthma vs. Chronic cough: Compared to AMP challenge test, FeNO 3.8 ppb had sensitivity 77% and specificity 77%. Mild intermittent asthma vs. healthy children: Compared to AMP challenge test, FeNO 2.9 ppb had sensitivity 88% and specificity 88%.
		FeNO, N= 71		Measured using chemiluminescence analyzer (LR 2000, Logan Research, Rochester, UK). FeNO measured before bronchial challenge. Salbutamol inhalation was administered at end of test ex. beta-agonist was given at end of bronchoprovocation challenge and	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)
				after FeNO measured.	
Backer, 2014[3]	Denmark, retrospective study, outpatient setting, medium risk of bias.	Reference test; positive bronchial challenge mannitol challenge test, N= 141	Overall mean age 28.3 years, 41% males, 4% current smokers, 90% atopic.	Positive challenge test when >15% reduction in FEV1. Negative challenge, max dose reached (635 mg). PD15 computed by interpolation.	FeNO at 25 ppb cut-off, compared with mannitol with PD15 <635 mg had sensitivity of 64% and specificity of 87% to diagnose asthma.
		FeNO, N= 141		Aerocrine (NioxMinor, Solna, Sweden) following the recommendations of the ERS and ATS.	
Berkman, 2005[4]	Israel, cross-sectional study, outpatient setting, low risk of bias.	Reference test; positive bronchial challenge adenosine 5 'monophosphate (AMP), N= 85	40 asthmatics Mean age 21.9 years (SD: 1.6), 60% males. 45 healthy subjects Mean age 29.3 years (SD: 2.4), 53.3% males.	Musing Sigma-Aldridge, Rehovot, Israel. The test was positive if AMP < 150 mg/mL.	FeNO 7 ppb vs. AMP had sensitivity 86.5% and specificity 81.5%
		Reference test; clinical diagnosis, N= 85		Determined 24 months after performing FeNO and provocation studies.	FeNO 7 ppb vs. clinical diagnosis had sensitivity 88.9% and specificity 82.5%
		Reference test; positive bronchial challenge exercise-induced bronchochonstriction		The test was positive if exercise change FEV_1 >10%.	FeNO 7 ppb vs. Exercise-induced bronchoconstriction had sensitivity 91.3% and specificity 70.1%
		Reference test; Positive bronchial challenge		Using (Spectrum Chemical Corp, Gardena, CA, USA). The test was considered positive if MCH < 3 mg/ mL.	FeNO 7 ppb vs. MCH had sensitivity 66.7% and specificity 72.9%

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)
		Methacoline challenge, N= 85			
		FeNO, N= 85		Measured using a chemiluminescence analyser (LR 2000, Logan Research, Rochester, UK). Resistance, mouth pressure (5 cm H2O), and flow rate (250 ml/s) Three successive recordings were made and the mean value was recorded.	
Berlyne, 2000[5]	Canada, cross sectional study, outpatient setting, high risk of bias.	Reference test; combined (Positive bronchial challenge + Bronchodilator response) airway hyperresponsiveness and methacholine challenge test, N= 123	Healthy (N= 50) and patients (N=73) Overall mean age 38.1 years, 42% males, 85% atopic.	Methacholine airway hyperresponsiveness with a PC20 of less than 8 mg/mL if the FEV_1/FVC was 70% or greater or an improvement of the FEV_1 from predicted of 15% or greater after 200 µg of inhaled salbutamol if the FEV_1/FVC was less than 70%.	Compared with airway hyperresponsiveness and methacholine challenge test, FeNO levels of 17.1 ppb had a sensitivity of 81% and a specificity of 90% for diagnosing asthma in patients without steroid treatment. However, the sensitivity and specificity were lower when the patients were taking ICSs (sensitivity and specificity of FeNO at 15.1 ppb were 51% and 86%, respectively.
		FeNO, N= 123		Measured by rapid linear-response chemiluminescence analyzer (Sievers 240, Boulder, Colo) at fixed flow of 45 mL/s. FeNO was not used to diagnose asthma, but to distinguish asthmatics (steroid naive or on ICS) from atopic non-asthmatics, and to distinguish these groups from the healthy nonatopic group.	
Bommarito, 2007[6]	Italy, cross sectional study, low risk of bias.	Reference test; clinical diagnosis European	13 asthmatic, mean age 43.6 years (SD: 0.72), 46.2% males, 23.1% current	A short, self-completed questionnaire identical to that used for stage 1 in the ECRHS I. Subjects with 'current asthma' were defined as those	Compared with ECRHS II, FeNO > 18.7 ppb had the best combination of sensitivity (69.2%) and specificity (71%), with a

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)
		Community Respiratory Health Survey II (ECRHS II) questionnaire, N= 55	smokers. 42 controls (rhinitis and atopics) 17 had rhinitis; mean age 40.6 years (SD: 1.5), 47.1% males, 5.8% current smokers and 25 were atopics; mean age 41 years (SD:1.35), 64% males, 20% current smokers.	reporting asthma in life + at least 1 of these asthma-like symptoms in the last 12 months: wheezing/whistling, tightness in chest, asthma attacks or treatment for MD-diagnosed asthma.	positive predictive value of 24% and a negative predictive value of 95% for the diagnosis of asthma.
		FeNO, N= 55		Measured by offline Chemiluminescent analyzer (model 280; Sievers) at a flow rate of 350 mL/sec. Order of tests, & specifics e.g. beta-agonists witheld, were not specified, but ATS guidelines referenced.	
Cordeiro, 2011[7]	Netherlands, longitudinal nonrandomized, outpatient setting, medium risk of bias.	Reference test; clinical diagnosis, N=114	42 in Asthma group Mean age 39 years, (range 7-83), 33% males, 93% atopic. 10% smokers. 72 non-asthmatics mean age 38 years (range 7-87), 40% males, 58% atopic. 10% smokers.	Clinical assessment of the diagnosis of asthma was based on a history of typical respiratory symptoms and an FEV_1 improvement of >12% (of the percent predicted value) and >200 mL or PC20 histamine of ≤8 mg/Ml, according to the Global Initiative for Asthma guidelines. SABA withheld 8 hours, LABA withheld 48 hours	Asthmatic patients had a higher mean FeNO level than healthy controls (44 ppb versus 17 ppb; $p < 0.001$). The ROC curve for FeNO to diagnose asthma showed area under curve (AUC) was 0.88 (CI, 0.80 to 0.95). The highest cutoff sum of sensitivity and specificity was 27 ppb. It had a sensitivity of 78%, specificity of 92%, a PPV of 86% and a NPV of 87% for a diagnosis of asthma. Diagnostic accuracy was 0.86.
		FeNO, N=114		FeNO was measured online at a constant flow rate of 50 mL/s and expressed as ppb. FeNO measurements were performed with the Niox Flex before any PFT done	
Deykin, 2002[8]	United States, cross sectional study,outpatient setting, medium risk of bias.	Reference test; positive bronchial challenge positive methacoline challenge test, N= 62	34 asthmatic patients, mean age 29.6 years (SD: 1.6), 41% males. 28 healthy individuals, mean age 27.3 years (SD: 1.3), 43% males.	Asthma diagnosed with either a 12% improvement in FEV_1 after inhalation of a β-agonist or a methacholine PC20 of ≤ 8 mg/mL.	Compared to Methacoline challenge test, Offline FeNO 30.7 ppb: sensitivity 70.6%; specificity 75% Offline FeNO 19.2 ppb: sensitivity 64.7%; specificity 67.7% Offline FeNO 13.2 ppb: sensitivity 73.5%; specificity 71.4%

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)
		FeNO, N= 62		Offline: Measured at a single visit using a chemiluminescence analyzer (model 280; Sievers, Boulder, CO) within 12 hours of collections that made at 50, 100, 200, 350, and 500 ml/second in triplicate. Online: Measured using a NOA 280 (Sievers) at a pressure of 10 mm Hg, the flow through the system was 43, 108, 210, and 250 ml/second.	Offline FeNO 10.4 ppb: sensitivity 79.4%; specificity 71.4% Offline FeNO 8.7 ppb: sensitivity 66.7%; specificity 71.4% Online FeNO 30.9 ppb: sensitivity 72.2%; specificity 70.6% Online FeNO 14.4 ppb: sensitivity 66.7%; specificity 70.6% Online FeNO 10.0 ppb: sensitivity 66.7%; specificity 70.6% Online FeNO 9.9 ppb: sensitivity 72.2%; specificity 76.5%
Dupont, 2003[9]	Belgium, prospective cohort, outpatient setting, medium risk of bias.	Reference test; combined (Positive bronchial challenge + Bronchodilator response) Airways hyperresponsiveness (PC20) and/or spirometry response to salbutamol, N= 240	160 Asthmatic patients; Mean Age 41 years (SD: 17), 48.1% male, 0% smoker. 80 healthy control; Mean age 43 years (SD: 14), 42.5% male, 0% smoker.	Airways hyperresponsiveness defined as histamine PC20 < 8 mg/mL. Standard spirometric methods to assess bronchodilator reversibility (FEV1 reversibility to beta-2-agonist >12%).	Compared with airways hyperresponsiveness (PC20) and/or spirometry response to salbutamol, the best FeNO cutoff associated with highest accuracy was 13 ppb with: Sensitivity: 85%. Specificity: 80%. PPV: 89.5%. NPV: 89.5%. Accuracy: 0.83. Other cutoffs results were reported in the analysis as well.
		FeNO, N= 240		Flow rate of 200 mL/s using an Eco Physics CLD 700 AL MED chemiluminescence analyzer (Eco Physics; Durnten, Switzerland) adapted for on-line recording. Patients and subjects did not consume any alcohol-containing or caffeinated beverages in the 4 h before the test, nor did they receive inhaled short-	

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				acting B2-mimetics in the 8 h prior to the measurements.	
Florentin, 2014[10]	France, case-control study, outpatient setting, high risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) clinical diagnosis, Spirometry, Bronchodilator reversibility or work-related specific IgE, N= 178	19 Occupational asthmatics and 159 controls mean age 25 years (SD: 2.9), 56.2% males, 49.4% smokers, 43.3% atopic.	Asthma diagnosis was based on the combination of standardized questionnaire derived from the Epidemiological study on the genetics and environment of asthma, bronchial hyper-responsiveness and atopy (EGEA) study, and undergo clinical specific IgE (sIgE) testing and lung function investigations, including carbon monoxide and spirometry measurements.	Compared to clinical diagnosis, Spirometry, Bronchodilator reversibility or work-related specific IgE; FeNO 8.5 ppb had sensitivity 78.9%; specificity 42.8%. FeNO 10.5 ppb: sensitivity 68.4%; specificity 56%. FeNO 25 ppb: sensitivity 42.1%; specificity 92.4%. FeNO 50 ppb: sensitivity 21%; specificity 98.7%. FeNO 8.5 ppb combined with positive clinical examination had sensitivity 79% and specificity 80.5% in asthma diagnosis.
		FeNO, N= 178		Measured using Niox-Mino Analyser; Aerocrine, Stockholm, Sweden.	
Fortuna, 2007[11]	Spain, prospective study, outpatient setting, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) clinical history and positive Methacholine challenge, N=	28 Asthmatic Median age 37 years, range 18-68, 10.7% smokers and 14.3% ex-smokers. 22 Control Mean age 38 years, range 18-64, 14.3% smokers and 10.7% ex-smokers.	Day 1 patient filled in clinical symptom questionnaire and underwent FeNO, spirometry with bronchodilator, & induced sputum. Methacholine challenge test was performed next day – positive if PD20 ≤16 mg/mL.	Compared with clinical history and methacholine challenge test, FeNO at 20 ppb had sensitivity 77%, specificity 64%, PPV 62% and NPV 78% in the diagnosis of asthma. Cutoff that best distinguished between asthmatics and non-asthmatics was FeNO 23 ppb

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		57 FeNO, N= 57		Aerocrine (NioxMinor, Solna, Sweden) following the recommendations of the ERS and ATS.	
Fukuhara, 2011[12]	Japan, prospective study, outpatient setting, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) Conventional criteria:, N= 61 FeNO, N= 61	42 asthmatics; mean age 54.8 years, range 50-59.7, 52.4% males, 7% current smokers, 21.4% former smokers and 71.4% non-smokers. 19 controls; mean age 57.4 years, range 48.5-66.2, 47.3% males, 15.8% current smokers, 21% former smokers and 66.7% non-smokers.	Asthma diagnosis was based on diagnosed by conventional criteria. It includes subjective symptoms and any two positive tests (Airway hyper-responsiveness (AHR) or Bronchodilator reversibility (BDR) or Eosinophil count in induced sputum). Positive bronchodilator reversibility is defined as an increase in FEV_1 of 200 mL and ≥ 12% from baseline after inhalation of a short-acting β-2 agonist. Positive airway hyper-responsiveness was defined as a value <12.5 units. . FeNO cutoff levels for diagnosing asthma from 3 prior studies from same authors ~40 ppb. Measured using an online chemiluminescence analyzer (NA623N; Chest MI, Tokyo, Japan) at a constant mouth pressure of 16 cm H2O and a flow of 50 mL/sec.	Compared to conventional criteria or AHR or BDR or Eos%, FeNO 40 ppb had sensitivity 78.6% and specificity 89.5% in asthma diagnosis.
Grzelewski, 2014[13]	Poland, retrospective, cross sectional, outpatient setting, medium risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response)	60.3% asthmatic and 39.7% control. Mean age 10.4 year, 60.4% males.	Diagnosis of asthma was made by allergy specialists based on symptoms of asthma, findings on examination of respiratory system, & improvement in FEV1 ≥12% after administration of salbutamol.	FeNO cutoff of 15.8 ppb, clinical symptoms plus bronchodilator response, had 59% sensitivity and 46% specificity. Overall study showed more helpful data to exclude asthma in

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		clinical symptoms plus bronchodilator response, N= 3612			schoolchildren with allergic rhinitis or positive specific IgE: 70%<NPV<80%
		FeNO, N= 3612		Measured by chemiluminescence analyzer (model 280i nitric oxide analyzer; Sievers, Boulder, CO) t flow rate (50 ml/ sec) As a standard procedure in Allergy outpatient clinic, sequence of tests was: FeNO, Rint, whole body plethysmography, spirometry.	
Heffler, 2006[14]	Italy, prospective study, outpatient setting, low risk of bias.	Reference test; Combined (Positive bronchial challenge + Bronchodilator response) Positive Methacoline challenge (PD20) or Bronchial reversibility, N= 48	Patients referred to Specialty Clinic with persistent rhinitis & lower airways symptoms. 18 asthmatic, mean age 42.33 years, range 17–69, 50% males, All nonsmokers, 77.8% atopic. 30 healthy subjects, mean age 38.73 years, range 11–75, 40% males, All nonsmokers, 70% atopic.	Asthma diagnosed with either a 12% improvement in FEV_1 after inhalation of a β-agonist or a methacholine PC20 of $\leq$ 8 mg/mL.	Compared with Methacholine challenge test, the cut-off point of FeNO 36 ppb was associated with the highest combination of specificity 60.0% and sensitivity (77.8%), resulting in a NPV of 81.8% and in a PPV of 54%. All other cutoffs results were reported in the analysis.
		FeNO, N= 48		Measurement after mouthwash using a chemiluminescence analyser (NiOX, Aerocrine AB, Solna, Sweden) calibrated with a certified FeNO calibration gas mixture at a flow rate of 50 ml/sec.	
Henriksen, 2000[15]	Norway, cross sectional study, outpatient setting, high risk	Reference test, Combined (Clinical Diagnosis	Suspected asthma (N=138) Mean age 16.3 years, 44% males,	Methacholine reactivity defined as >20% drop FEV1 (PD20). If baseline spiro showed obstruction, broncho-dilator response defined as >15%	52% of the suspected asthmatics and 20% of the control subjects had elevated levels of FeNO (>8 ppb).

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	of bias.	+Positive bronchial challenge) Survey and methacholine challenge test, N= 331	21% Smokers, BMI 22.5 Kg/m^2. Control subjects (N= 193) Mean age 16 years, 46% male, 13% smokers, BMI 21.9 Kg/m^2.	improvement in FEV1. A large-scale epidemiological survey (Young Helseundersùkelsen i Nord-Trùndelag (Health Survey in NorthTrùndelag; HUNT). It was conducted by the Norwegian State Institute of Public Health.	45% of the suspected asthmatics and 11% of the control subjects had elevated levels of FeNO (>11 ppb).
		FeNO, N=331		Measured by LR 2000 NO gas analyzer (Logan Research Ltd, London, UK). The sampling flow rate was 250 mL/min at One visit.	
Ishizuka, 2011[16]	Japan, cross sectional study, outpatient setting, high risk of bias.	Reference test; Clinical Diagnosis European Community Respiratory Health Survey (ECRHS) questionnaire, N= 584	Mean age 19.6 years; range 18-24 years, 46% males.	Japanese version of the ECRHS questionnaire.	FeNO at 38 ppb cut-off, compared with ECRHS, had sensitivity of 87% and specificity of 74%.
		FeNO, N= 584		Measured using an offline kit produced by the Center for Environmental Information Science (Tokyo, Japan) expiratory flow rate is adjusted to 50 mL/sec.	
Jerzynska, 2014[17]	Poland, cross sectional study, outpatient setting, high risk of bias	Reference test; Combined (Clinical Diagnosis + Bronchodilator response) clinical symptoms and Spirometry, N= 1767	1053 asthmatic and 714 controls. Mean age 11.2 years, 59.3% males, 64.6% atopic.	Pulmonary function testing was done with a Master Screen unit (Erich Jaeger Gmbh-Hochberg, Germany). An improvement in the pre-bronchodilator FEV_1 > 12% after administration of salbutamol (200 ug) in all the patients considered diagnostic.	For patients with atopy and allergic rhinitis (389 patients), FeNO at 23 ppb cut-off had: sensitivity: 90% (95% CI: 68 to 98%), specificity 52% (95% CI: 42 to 61%), PPV 25% (95% CI: 16 to 37%), and NPP: 97% (95% CI: 88 to 99%).

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		FeNO, N= 1767		Using a chemiluminescence analyzer (model 280i nitric oxide analyzer; Sievers, Boulder, CO, USA) provides on-line continuous measurement of NO in a single exhalation with a detection range of 0.1–500 ppb, and exhaled at a constant flow rate (50 mL/s) from total lung capacity to residual volume without breath holding.	
Katsoulis, 2013[18]	Greece, longitudinal nonrandomized study, outpatient setting, medium risk of bias.	Reference test; Positive bronchial challenge methacholine challenge test, N =122 FeNO, N =122	112 symptomatic patients, mean age of 25 years, 85% males, 30% smokers, 46% atopic.	PD20 of methacholine <800 µg was considered diagnostic for asthma. Measured by (NIOX MINO, airway inflammation monitor; Aerocrine, Solna, Sweden) that provides measurements at 50 ml/sec exhalation flow rate.	FeNO at 32 ppb cut-off, compared with Methacholine with PD20 <800 µg had sensitivity of 47% and a specificity of 85%, AUC = 0.691. In smokers, FeNO at 11 ppb was associated with a sensitivity of 85% and a specificity of 5%, AUC = 0.625. In atopic patients: FeNO at 26 ppb was associated with a sensitivity of 55% and a specificity of 85%, AUC = 0.677.
Kostikas 2008[19]	Greece, cross sectional study, medium risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) clinical diagnosis, bronchodilator	63 asthmatics mean age 21.6 years (SD: 2.7), 53.9% males, 36.5% smokers. 86 controls (57 rhinitis and 29 with non-specific symptoms) 57 with rhinitis; mean age 21.8 years (SD: 3),	Diagnosis of asthma made after FeNO measurements, based on evaluation by a respiratory physician blinded to FeNO results using prespecified criteria: Hx of relevant lower respiratory tract symptoms, along with 1 of: bronchodilator response (increase in FEV1 >12% and >200 mL) or positive methacholine bronchial challenge test, or clinical and spirometric response to a 4-week trial ICS.	In comparison with bronchodilator response and bronchial challenge, FeNO values >25 ppb had specificity 90% for the diagnosis of asthma in all study groups; specificity rises further to approximately > 95% for FeNO values > 30 ppb. In contrast, a cut-off point > 10 ppb presents sensitivity of 85% in the whole study group, rising to approximately 95% in

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		response and bronchial challenge, N= 149	33.3% smokers. 29 non-specific symptoms; mean age 22.1 years (SD: 3.1), 37.9% smokers.		nonsmokers. All cutoffs results are reported in detailed in the analysis as well.
		FeNO, N= 149		FeNO was measured once per month, using an exhaled NO (eNO) monitoring system NIOX (Aerocrine, Solna, Sweden) via chemiluminescence according to ATS guidelines at 50 mL/sec exhalation flow rate.	
Lemiere, 2010[20]	Canada and Belgium, cross sectional study, low risk of bias.	Reference test; Positive bronchial challenge Specific inhalation challenges (SICs) , N= 43	24 Occupational asthmatics mean age 40.5 years (SD: 10.1) 76.9% males, 38.4% current smokers, 65.4% atopic.	SIC was considered positive if a reproducible fall in FEV 1 of 20% or more occurred after exposure to the offending agent along with a characteristic pattern of an asthmatic reaction.	In comparison with SICs, 10 ppb change in FeNO between baseline and 7 hours post-exposure had sensitivity: 21% and specificity 87.5%. In comparison with SICs, 10 ppb change in FeNO between baseline and 24 hours post-exposure had sensitivity: 36.8% and specificity 81.2%.
		FeNO, N= 43	19 non-asthmatics mean age 44.8 years (SD: 10.8) 63.4% males, 26.8% current smokers, 53.8% atopic.	Canada; measured at multiple visits using offline Chemiluminescent analyzers (280i Sievers; GE; Boulder, CO). Belgium; measuredy at multiple visits using an online (NiOX; Aerocrine AB; Solna, Sweden). Sputum cell counts & FeNO were collected at end of control day and at 7 hours and 24 hours after exposure to offending agent.	
Malinovschi, 2012[21]	Denmark, cross sectional study, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response +	96 asthmatic patients mean age of 32.7 years, 40.6% males, 53.1% ever smoked.	All subjects were interviewed by a respiratory specialist who diagnosed asthma based on presence of compatible Sx + at least 1 of following 1) Airway hyper-responsiveness to methacholine < 8.0 µmol.	Non-smokers (N= 108): In comparison with Methacoline challenge test or asthma symptoms, FeNO at 15 ppb cut-off had a sensitivity of 77.8%, a specificity of 63.5%, PPV of 60%,

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		Positive bronchial challenge) Methacoline challenge test or asthma symptoms, N=282 FeNO, N=282	186 symptomatic non-asthmatic patients mean age of 32.7 years, 39.8% males, 64.1% ever smoked.	2) At least 250 ml increase in FEV1 after bronchodilator. 3) Daily use of systemic steroid, ICS, or inhaled beta2-agonist. 4) Asthma symptoms during but not outside pollen season if patient had allergic rhinitis. Measured by using an online technique at a exhalation flow-rate of 50 mL/s, based on electrochemical sensor (NIOX Mino, Aerocrine AB, Solna, Sweden) before any lung function tests.	NPV 80%, AUC of 0.72. Ex- Smokers (N= 62): FeNO at 22 ppb cut-off had a sensitivity of 63.2%, a specificity of 86.1%, PPV of 67%, NPV 84%, AUC of 0.74. Current smokers (N= 112): FeNO at 17 ppb cut-off had a sensitivity of 56.3%, a specificity of 82.5%, PPV of 57%, NPV 82%, AUC of 0.70.
Martin, 2016[22]	United Kingdom, longitudinal nonrandomized, high risk of bias.	Reference test; Combined (Clinical Diagnosis + Positive bronchial challenge) clinical diagnosis and positive bronchial challenge test, N= 74 FeNO, N= 74	28 asthma patients, median age 29 years; range 18-70, 39% males, 17.9% current smoker, 14.3% ex-smoker, 14.3% atopics (eczema). 46 non asthmatic, median age 22 years; range 18-73, 50% males, 10.9% current smokers, 19.6% ex-smokers.	Diagnosis was made if reversibility of ≥12% and ≥200 mL in FEV_1, after inhalation of 400 µg salbutamol, or methacholine (PC20) of ≤8 mg/mL in adult patients with respiratory symptoms suggestive of asthma who were thought to require ICS by their physician Measured by (NIOX MINO; Aerocrine, Tolna, Sweden).	The ROC curve to assess the utility of baseline FeNO level as a diagnostic test for asthma had an area under the curve (AUC) of 0.62 (p=0.09). However, ROC curve for baseline FeNO level as predictor of ICS response after 4 weeks had AUC of 0.89 (p<0.0001). Optimal FeNO cut-off point for predicting non-response to ICS was <27 ppb (NPV 93%) & for predicting response was >33 ppb (PPV 92%).
Matsunaga, 2011[23]	Japan, cross sectional study, outpatient setting, high risk of bias.	Reference test; Clinical Diagnosis medical history, N= 366	142 asthmatic patients mean age of 41.5 years, 49% males, 37% current smokers.	Asthma was diagnosed based on presence of significant airway reversibility and/or airway hyper responsiveness during the 6 months follow up period. (cutoffs not	FeNO at 22 ppb cut-off, compared with medical history had sensitivity 90.8%, specificity 83.9% and AUC 0.896.

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			224 healthy controls mean age of 39.4 years, 44% males, 23% current smokers.	specified)	
		FeNO, N= 366		Measured by online electrochemical nitric oxide analyzer (NIOX MINO; Aerocrine AB, Solna, Sweden) at a constant flow rate of 50 mL/sec.	
Menzies, 2007[24]	Scotland, prospective study, high risk of bias.	Reference test; clinical diagnosis, N= 151	101 asthmatic patients, mean age 48.5 years (SD: 1.29), 46.5% males. 50 healthy volunteers, mean age 35.6 years (SD: 1.70), 36% males.	Patients known to have persistent mild-to-moderate asthma from clinical trials database.	In comparison to clinical diagnosis, FeNO (MINO) at 13 ppb had sensitivity 83.2%, specificity 27%, and the AUC was 0.654. In comparison to clinical diagnosis, FeNO (NIOX) at 12.5 ppb had sensitivity 83.2%, specificity 27% and the AUC was 0.619
		FeNO (NIOX device), N= 151		Measured three times at one visi by laboratory-based analyzers (NIOX; Aerocrine AB) at a flow rate of 50 mL/sec. Average was taken for analysis.	
		FeNO (MINO device), N 101		Single measurement at one visit by portable nitric oxide analyzer (MINO; Aerocrine AB; Smidesva¨gen, Sweden) at a flow rate of 50 mL/sec.MINO measurement was always taken after NIOX.	
Miedinger, 2007[25]	Switzerland, longitudinal nonrandomized study, medium risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response) Clinical diagnosis and Airway hyperresponsiveness (AHR), N= 101	14 asthmatics and 87 healthy controls. Mean age 41 years, range 23 to 64, All male firefighters, 33% current smokers.	Asthma was defined as respiratory symptoms and a history of wheezing not restricted to the last 12 months combined with provocative dose of methacholine causing a 20% fall in FEV1 (PD_{20}) and/or provocative dose of mannitol causing a 15% fall in FEV1 (PD_{15})	FeNO at 20 ppb vs. Clinical diagnosis and AHR: sensitivity 60%; specificity 55%. FeNO at 47 ppb vs. Clinical diagnosis and AHR: sensitivity 33%; specificity 94%. FeNO at 20 ppb vs. PD15: sensitivity 64%; specificity 59%. FeNO at 47 ppb vs. PD15: sensitivity 42%; specificity 96%.

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		Reference test; Positive bronchial challenge Mannitol challenge (PD15) , N= 101		If the FEV_1 fell by 10% based on the FEV_1, the dose producing this fall was repeated. The challenge was stopped if the FEV_1 fell by 15%, or when the maximum dose had been administered.	
		FeNO, N= 101		Measured by Nitric oxide analyzer (NIOX; Aerocrine AB; Solna, Sweden) at a flow rate of 0.045 to 0.055 L/sec.	
Miedinger, 2009[26]	Switzerland, cross sectional study, outpatient setting, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Positive bronchial challenge) clinical diagnosis and mannitol bronchial provocation test, N= 235	42 asthmatics. All males, Age range 18-19 years, 38% current smokers. 187 non- asthmatics All males, Age range 18-19 years, 33% current smokers.	Asthma was diagnosed by a military physician not involved in this study per the medical record, results of bronchial provocation test (methacholine and mannitol), current respiratory symptoms and use of asthma medication. All subjects administed the validated German version of a specific respiratory disease questionnaire originally used in the SAPALDIA study. Methacholine challenge was positive if FEV1 >20% decline (PD20)at dose of ≤2mg. Mannitol bronchoprovocation was positive if there was a decline in FEV1 >15% from baseline, or a 10% incremental decline between consecutive doses.	Compared to clinical diagnosis and mannitol bronchial provocation, FeNO 36.5 ppb (N=45) had sensitivity 36%, specificity 84%, PPV 33% and NPV 86%. FeNO 20 ppb: sensitivity 57%, specificity 62%, PPV 25% and NPV 67%.

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		FeNO, N= 235		Performed prior to spirometry, using a device with a built-in biofeedback mechanism (NIOX MINO, Aerocrine AB, Solna, Sweden) at a flow rate of 50 mL/sec.	
Munnik, 2009[27]	Netherlands, cross sectional study, outpatients setting, medium risk of bias.	Reference test; Positive bronchial challenge histamine (PD20) test, N= 362	140 asthmatics Mean age 45 years (SD: 11). 222 non-asthmatic Mean age 51 years (SD: 12).	. Airway hyperresponsiveness was defined as a PC20 of <8 mg/mL.	The AUC ROC for FeNO to diagnose asthma is 0.826 (p value <0.001).
		FeNO, N= 362		FeNO measured prior to other maneuvers that day. Short and long acting bronchodilators held for 8 and 12 hours respectively pre-testing. Measured at one visit by ECO MEDICS CLD 88 in conjunction with DFeNOX 88 (Eco Physics, Durnten, Switzerland) (center# 1) and by Niox Mino device (Aerocrine, New Providence, United States of America) (center# 2), both using an exhalation flow of 50 ml/sec.	
Nayak, 2013[28]	India, cross sectional study, outpatient setting, medium risk of bias.	Reference test; Clinical Diagnosis spirometry, N= 100	55 asthmatic patients, 51% on inhalational steroids, mean age of 45.2 years; range of 12-82 years, 42% males 45 controls, mean age of 48.5 years; ranges 16-76	Asthma diagnosis and categorization based on GINA 2009 guidelines – symptomatology, FEV1 and post bronchodilator reversibility. P. K. Morgan spirometry and pulmonary function tests were done by a trained technician as per ATS standard guidelines.	FeNO at 8 ppb cut-off, compared with spirometry had sensitivity of 72% and specificity of 88%. The mean FeNO levels were significantly higher in both steroid treated cases (15.7 ppb) and steroid naïve cases (41.5 ppb) as compared with controls (14.4 ppb).
		FeNO, N= 100		Three FeNO measurements were recorded for each patient using	

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			years, 49% males	chemiluminescence NO-analyser. Repeat measurements were performed until the three values agreed to 10% of the mean. Mean value of the 3 measurements was recorded as final. FeNO level of < 8.0 ppb was taken as normal.	
Pedrosa, 2010[29]	Spain, cross sectional study, outpatient setting, low risk of bias.	Reference test; Positive bronchial challenge Methacholine challenge (MCH), N= 114	35 asthmatics and 79 healthy controls. mean age 34 years (SD: 13) 62.6% males, 14.8% current smokers, 87% atopic	Asthma was diagnosed on the basis of consistent symptoms and a positive methacholine challenge. A positive methacholine challenge was defined as a decrease in FEV1 from a baseline of 20% or higher obtained after methacholine inhalation.	Compared to MCH, FeNO 40 ppb had sensitivity 74.3% and specificity 72.5% in asthma diagnosis.
		FeNO, N= 114		Measured just before the methacholine challenge. Measured using a portable nitric oxide analyzer (NIOX MINOTM; Aerocrine, Solna, Sweden), at a flow rate of 50 mL/sec.	
Perez Tarazona, 2011[30]	Spain, cross-sectional study, outpatient setting, low risk of bias.	Reference test; Clinical Diagnosis Spirometry, N=144	57 asthmatics mean age 10.4 years (SD: 2.1), 70% males, mean weight 39.4 Kg (SD: 12,7). 87 controls mean age 10.4 years (SD: 2.1), 47% males, mean weight 40.4 Kg (SD: 13,9).	Diagnosis based on clinical history consistent with asthma (history of recurrent cough, wheeze or breathing difficulties with a good response to bronchodilator treatment.) and pulmonary function testing using Portable spirometer Datospir Micro A® (Sibelmed, Barcelona)	Compared to spirometry, the best FeNO cutoff was 19 ppb to diagnose asthma with sensitivity 91.4% and specificity 87.2%. other cutoffs were reported in the analysis.
		FeNO, N=144		Measured for multiple attempts at one visit Using a chemiluminescence analyser (NiOX , Aerocrine AB, Solna, Sweden). Two values of FeNO were obtained and the average was used for the analysis.	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)
Pizzimenti, 2009[31]	Italy, prospective study, outpatient clinic, medium risk of bias.	FeNO, N= 156 Reference test; Combined (Clinical Diagnosis + Positive bronchial challenge) Methacoline challenge test and spirometry, N= 156	14 asthmatics and 142 controls. 41% males, 47.4% atopic, 9% smokers	Bronchial hyperresponsiveness (PD20 FEV-1<800 mu) in asthmatic patients. Measured by portable analyzer NIOX-MINOA (Aerocrine AB, Solna, Sweden).	Compared with methachoine challenge test and spirometry, FeNO cut-off value of 55 ppb had the best combination of sensitivity of 78%, and specificity of 88%, for diagnosis asthma. AUC was 0.85.
Ramser, 2008[32]	Switzerland, cross sectional study, outpatient setting, low risk of bias.	Reference test; Positive bronchial challenge Exercise induced bronchoconstriction (EIB) , N= 169 Reference test; Positive bronchial challenge Methacholine challenge (MCH), N= 169 FeNO, N= 169	84 asthmatics and 50 healthy controls. Age range 6-16 years, 57% males, 61% Atopic.	The protocol was FeNO and exercise bronchoprovocation, if exercise provocation negative or could not exercise they then had methacholine challenge. EIB was defined by a decrease in FEV_1 by ≥15% of baseline. MCH challenge was done according to ARS/ETS guidelines using a panel of incremental dosages of MCH, and a dose of 1.8 mg was defined as threshold of PD20 to differentiate normal airway responsiveness from bronchial hyperresponsiveness. FeNO measured prior to other pulmonary testing. One visit measurement using an online Chemoluminescence analyzer (CLD 77 AM; 191 192 M. RAMSER ET AL. Eco Physics, Durnten, Switzerland) at	FeNO at 10 ppb vs. MCH: sensitivity 83%; specificity 19% FeNO at 20 ppb vs. MCH: sensitivity 61%; specificity 62% FeNO at 30 ppb vs. MCH: sensitivity 41%; specificity 74% FeNO at 40 ppb vs. MCH: sensitivity 29%; specificity 85% FeNO at 50 ppb vs. MCH: sensitivity 26%; specificity 91% FeNO at 10 ppb vs. EIB: sensitivity 86%; specificity 32% FeNO at 20 ppb vs. EIB: sensitivity 64%; specificity 66% FeNO at 30 ppb vs. EIB: sensitivity 50%; specificity 78% FeNO at 40 ppb vs. EIB: sensitivity 36%; specificity 86% FeNO at 50 ppb vs. EIB: sensitivity 32%; specificity 88%

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)
				a flow rate of 50 mL/sec.	
Sachs-Olsen, 2010[33]	Norway, prospective control study, outpatient setting, low risk of bias.	Reference test; clinical diagnosis, N= 227	31 asthmatics (17 with current asthma (mean age 10.7 years (SD: 0.8) and 14 with allergic asthma (mean age 10.8 years (SD: 0.8). 196 healthy patients (mean age 10.9 years (SD: 0.7).	Gold standard was clinicaldiagnosis based on definition below. Asthma diagnosis if 2 out of 3 criteria were met; 1) Dyspnea, chest tightness and/or wheezing. 2) Doctor's diagnosis of asthma. 3) Use of asthma medication. Allergic asthma defined as asthma in the presence of allergic sensitization.	Compared to clinical diagnosis, FeNO 15.6 ppb: sensitivity 35% and specificity 94%. FeNO 16.7 ppb: sensitivity 32% and specificity 96%. FeNO 20.4 ppb: sensitivity 26% and specificity 97%.
		FeNO, N= 227		Measured online by the single breath technique, with a EcoMedics Exhalyzer CLD 88sp with DFeNOX 88 (ECO MEDICS AG, Duernten, Switzerland). NO-free air was inhaled to near total lung capacity, followed immediately by full exhalation at a constant flow of 50 ml/s, expiratory pressure was maintained between 5–20 mmHg to close the soft palate. FeNO was recorded as mean value from three (alternatively two in a few patients) successive reproducible plateaus.	
Sato, 2008[34]	Japan, longitudinal nonrandomized, outpatient setting, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) Clinical diagnosis, airway hyper-	48 asthmatics; 30 bronchial asthmatics had mean age of 55.5 years, range 48.9 to 62.5, 66.6% males and 26.6% smokers. And 18 had cough variant asthma with mean age 48.2 years, range 39.4-57.0, 38.8% males and	Spirometry measured using Chestac-11 Cyber S-type; Chest MI, Inc., Tokyo, Japan). Positive bronchodilator reversibility is defined as an increase in FEV_1 of 200 mL and ≥ 12% from baseline 20 min after inhalation of a short-acting β-2 agonist. Airway hyper-responsiveness (Methacoline challenge test) was defined as a value <12.5 units. The total cumulative dose of methacholine	Compared to clinical diagnosis, airway hyper-responsiveness or bronchodilator reversibility, FeNO 38.8 ppb had sensitivity 79.2% and specificity 91.3% in diagnosing asthma.

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		responsiveness or Bronchodilator reversibility, N= 71	16.7% smokers. 23 Non asthmatics; 8 had eosinophilic bronchitis with mean age of 45.3 years, range 33.3-57.2, 50% males and 12.5% smokers. And 15 had other disorders with mean age of 55.5 years, range 47.5-63.5, 54% males and 33.3% smokers.	at the end of inhaling the highest dose was 50 units.	
		FeNO, N= 71		Measured before other pulmonary testing. Measured three times at a single visit with a chemiluminescence analyzer (Kimoto, Osaka, Japan) wuith exhalation constant flow of 50 mL/sec.	
Schleich, 2012[35]	Belgium, cross section study, medium risk of bias.	Reference test; Positive bronchial challenge Methacholine challenge, N= 174	Overall mean age of 41 years, 42% males, 34% current smokers, 48% atopic.	Methacholine challenges were performed according to a slightly adapted Cockroft's tidal breathing method. Asthma was diagnosed based on airway hyper responsiveness demonstrated by inhaled concentration of Methacholine provoking a 20% fall in FEV_1 of less than 16 mg/m.	FeNO at 34 ppb cut-off, compared with Methacholine challenge test had: sensitivity: 35.4%, specificity: 95.4%, positive predictive value: 88%, negative predictive value: 62%, AUC = 0.62.
		FeNO, N= 174		Measured by chemiluminescence (NIOX, Aerocrine, Sweden), at a flow rate of 50 ml/sec.	
Schneider, 2013 Schneider, 2014[36, 37]	Germany, prospective diagnostic study, outpatient setting, medium risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge)	154 asthmatic patients; mean age 40.5 years, 40.9% males, 48.7% ever smoked. 234 healthy; Mea age 44.6 years, 39.3% males, 42.3% ever smoked.	Spirometry were performed, patients with FEV_1 < 80% predicted received salbutamol with an additional WBP investigation 20 min later. Asthma if FEV_1/VC was $\leq$0.70, clinical symptoms and history fitted and the change in FEV_1 was $\geq$ 12% compared with baseline and $\geq$ 200 mL and lung function returned to the predicted	FeNO at 20 ppb cut-off, compared with WBP and bronchial provocation had sensitivity: 60%, specificity: 63%, PPV: 51%, NPV: 71%. FeNO at 25 ppb cut-off, compared with WBP and bronchial provocation had sensitivity: 49%, specificity: 75%, PPV: 56%, NPV:

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)
		Whole body plethysmography (WBP) and bronchial provocation, N= 388	After 1 year of follow up 81 lost to follow up, 83 had asthma; mean age of 41.9 years, 40% males, 43.3% ever smoked. 219 had no asthma; mean age of 45.5 years, 40.6% males, 48.4% ever smoked.	normal range.	69%. After 1 year of follow up: FeNO at 26 ppb cut-off, compared with bronchial provocation had sensitivity: 47%, specificity: 73.1%, PPV: 39.8%, NPV: 78.4, AUC: 0.603
		FeNO N= 388		FENO measured prior to other pulmonary testing. Measured by (NioxMino, Aerocrine, Solna, Sweden) at a flow rate of 50 mL/s, prior to body plethysmography and bronchial provocation.	
Schneider, 2009[38]	Germany, prospective study, low risk of bias.	Reference test; Combined (Positive bronchial challenge + Bronchodilator response) Bodyplethysmography and Bronchial Provocation, N= 160	160 patients. mean age 43.9 years, 45% males. 75 asthmatics; Mean age 38.7 years (SD:15.1), 41% males, 40% ever smokers. 85 controls as following; 25 COPD, 8 had an overlap of COPD and asthma, and 52 had no Obstructive airway disease; 65.8% ever smokers.	Patients with FEV_1 < 80% of predicted received a bronchodilation test with an additional performance of whole body plethysmography (WBP) 20 minutes after inhaling salbutamol. An incomplete bronchodilator response was stated if the bronchodilation response was ≥ 12% as compared to baseline and at least 200 ml and lung volumes remained below predicted. An asthma diagnosis was made when there was a 20% fall in FEV_1 from the baseline value (PC20) after inhaling methacholine step wise until the maximum concentration (16 mg/mL)	Compared with a 20% fall of FEV_1 after inhaling methacholine concentration ≤ 4 mg/ml, FeNO 12 ppb (N=34): sensitivity 90%, specificity 25%, PPV 40% and NPV 81%. Compared with a 20% fall in FEV_1 from the baseline value (PC20) after inhaling methacholine concentration ≤ 16 mg/ml, FeNO 46 ppb (N=30): sensitivity 32%, specificity 93%, PPV 80% and NPV 61%. FeNO 76 ppb (N= 11): sensitivity 13%, specificity 100% and PPV 100%. In non-smokers (N=110), FeNO 46 ppb had sensitivity 34% and specificity 94%. PPV increased up to 88% and NPV was 52%. FeNO 65 ppb showed specificity of 100% and PPV of 100%.
		FeNO, N= 160		Measured by NioxMino® analyzer at a mouth flow rate of 50 mL/sec over ten seconds and a pressure of 10 cm H2O as per guideline recommendation.	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)
					Other cutoffs results are reported in detailed in the analysis as well.
Sivan, 2009[39]	Israel, prospective study, outpatient clinic, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response) Clinical Diagnosis and bronchodilator response, N= 150	69 Asthmatics mean age 12.6 years, 58% males. 44 healthy controls, mean age 12 years, 55% males.	Asthma was diagnosed by use of conventional clinical criteria and was based on the patient's history of 2 or more clinical exacerbations of wheezing documented by a physician, dyspnea, or cough relieved by bronchodilators, documented variability in FEV_1> 15% in response to bronchodilators at any time during the follow-up period (reversibility), or documented variability in FEV_1> 15% over time with or without controller medications: inhaled corticosteroids (ICS) or montelukast.	In comparison with clinical diagnosis and bronchodilator response, FeNO at 19 ppb was the best cutoff in the diagnosis of asthma with sensitivity 86% specificity 89%, PPV 92% and NPV 80%. Other cutoffs results are reported in the analysis. Eos at 2.7% ppb was the best cutoff in asthma diagnosis with sensitivity 85% and specificity 89%. FeNO at 19 ppb combined with Eos at 3% showed the best asthma diagnosis value with sensitivity 87% and specificity 89%.
		FeNO, N= 150		One visit measurement using Chemiluminescence analyzer (Eco Physics CLD88, NO chemiluminescence analyzer; EcoMedics AG, Duernten, Switzerland) and the Denox 88 NO free supplier module (EcoMedics AG) with online recording, during a single breath exhalation. Test was repeated until 3 reproducible FeNO values were obtained, and the average was recorded.	
Smith 2004[40]	New Zealand, prospective study, outpatient setting, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator	17 asthmatics mean age 41.6 years, range 9–72, 53% males.	Diagnosis of asthma was based on 1/:Relevant symptom history provided using American Thoracic Society criteria.and 2/Positive hypertonic saline was defined as a 15% fall in	Compared with symptom history, bronchodilator reversibility and bronchial hyperresponsiveness, FeNO > 20 ppb had sensitivity 88% and specificity 79% in

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)
		response) relevant symptom history, bronchodilator reversibility and bronchial hyperresponsiveness, N=47	30 healthy controls mean age 31.8 years, range 9–64, 37% males.	FEV1 (PD15) of less than 20 ml. and /or 3/Positive bronchial reversibility defined as an increase in FEV1 of 12% or greater from baseline 15 minutes after inhaled albuterol.	asthma diagnosis.
		FeNO, N=47		FENO was measured before any forced expiratory maneuvers. Measured at three visits at two exhalation flow rates (50 and 250 ml/second). FeNO levels were read at the first NO plateau for the flow rate of 50 ml/second and at the end-of exhalation carbon dioxide plateau for the 250 ml/second.	
Thomas, 2005[41]	Australia, cross-sectional study, high risk of bias.	Reference test; Positive bronchial challenge (Hypertonic Saline Challenge), N= 107	Mean age 14.7 years (SD: 2.3), 57.1% males.	Asthma was defined a priori as an either one symptom of asthma or a PD15 to saline which was defined as a provocative dose of 4% saline to cause a 15% fall in FEV_1 was calculated by linear interpolation (PD15).	FeNO at 7 ppb cut-off, compared with hypertonic saline challenge test at PD15 had a positive predictive value of 54%, and a negative predictive value of 83%. If more than one symptom defined a diagnosis of asthma, FeNO positive predictive value was 63%, negative predictive value was 69%, sensitivity was 47% and specificity was 93%.
		FeNO, N= 107		using a chemiluminescent technique, FeNO was measured off-line by using a 2-L gasimpermeable bag, and the samples were analyzed within 6 hours on a Dasibi oxides of nitrogen analyzer (Model 2107 Dasibi Corporation, Glendale, CA, USA)	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)
Travers, 2007[42]	New Zealand, cross sectional study, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response) clinical diagnosis and bronchodilator response, N= 258	70 asthmatics and 193 healthy subjects. Mean age 56.2 years (SD: 12.9), 52.8% males. 11.9% current smokers, 42.4% Ever smokers.	Physician diagnosis of asthma and symptoms in the previous 12 months or physician diagnosis of asthma and inhaler use in the previous 12 months or an increase in FEV_1> 15% compared with baseline after bronchodilator administration or documented diurnal peak flow variation> 20% in any of the first 7 days of recordings.	Asthma not taking ICS: In comparison with clinical diagnosis and bronchodilator response, FeNO 20 ppb had sensitivity 49% and specificity 61%. FeNO 50 ppb had sensitivity 19% and specificity 96%. Moderate to severe asthma: In comparison with clinical diagnosis and bronchodilator response, FeNO 20 ppb had sensitivity 67% and specificity 61% FeNO 50 ppb had sensitivity 20% and specificity 96%
		FeNO, N= 258		FeNO measured before other pulmonary testing. Withdeld SABA for 6 hours, LABA for 36 hours, and anti-histamine use for 72 hours. FeNO measured using an online Chemoluminescence analyzer nitric oxide monitor (NIOX; Aerocrine AB, Solna, Sweden). Exhalation flow rate 50ml/sec.	
Woo, 2012[43]	South Korea, longitudinal cohort study, outpatient setting, low risk of bias.	Reference test; Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge) Symtotoms , spirometry and methacholine challenge, N=245	167 asthma patients; Mean age 11.7 years, 77% atopic 67% males, 26% passive smokers. 78 healthy controls.	Asthmatic patients diagnosed if they had symptom including cough, wheezing, or shortness of breath with reversible airflow obstruction ($\geq$12% improvement in FEV_1 in response to inhaled b2-agonist) and/or airway hyper responsiveness (methacholine $PC_{20} \leq 8$ mg/mL).	FeNO at 22 ppb cut-off, compared with Spirometry and methacholine challenge test had sensitivity: 57%, specificity: 87%, PPV: 91%, and NPV: 38%. The diagnostic performance of FeNO using cut off of 22 ppb was better in atopic subjects versus non-atopic with a sensitivity 72.1%, Specificity 85%, PPV 91.2% and NPV 58.6%.

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)
		FeNO, N=245		Measured by (NIOX MINO; Aerocrine AB, Solna, Sweden), Exhalation times were 10 s with a 2-min analysis period, at a constant flow rate of 50 mL/sec.	
Yao, 2011[44]	Taiwan, cross sectional study, medium risk of bias.	Reference test; Clinical diagnosis modified ISAAC questionnaire, N=1651	70 asthmatic and 1478 controls mean age 10.3 years, 48.9% males.	Asthma was defined as ever having asthma and either the occurrence of wheeze in the last 12 months or current use of asthma medication.	Compared with modified ISAAC questionnaire, FeNO cut-off of 28 ppb had a sensitivity of 64.3%, a specificity of 69.9%, a PPV of 8.8%, NPV of 97.7% and AUC of 0.67.
		FeNO, N=1651		Using an online chemiluminescence analyzer (CLD 88sp NO analyzers, Eco Medics, Duernten, Switzerland), with a constant flow rate of 50mL/sec.	

AUC: area under the curve; BMI: body mass index; Eos: Eosinophilia count; ERS/ATS recommendation: The European Respiratory Society/ American Thoracic Society recommendation; COPD: chronic obstructive chronic disease; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; ISAAC questionnaire: International Study of Asthma and Allergies in Childhood questionnaire; MCH: Methacholine; NPV: negative predictive value; 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% declaine in FEV_1; PD20: provocation dose causing a 20% decline in FEV_1; PPV: positive predictive value; ROC curve: receiver operating characteristic curve; RCT; randomized clinical trial; SD: standard deviation.

Table C.2. Characteristics of the included studies in KQ 1b

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Disease Activities and Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Agache, 2012 [45]	Romania, longitudinal nonrandomized, outpatient	FeNO, N= 46	**Non- difficult asthma group (N=22)** Mean age 7.36 years (SD: 0.67), 81% male ,	FeNO measurement was done using (NIOX MINO, Aerocrine AB); exhaled NO values were corrected for height, male sex,	Persistently high FeNO in difficult asthma was a significant risk factor comparing to	Baseline: Non- difficult asthma: 15.85 ppb (SD: 2.70)	In children with uncontrolled persistent asthma on ICS,

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Disease Activities and Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
	setting, low risk of bias.		86.36% atopy, 22.73% tobacco exposure, 4.55% Obesity 568.18 mcg (SD:49) beclomethasone **Difficult asthma group (N=24)**	atopy, and infection status. The patients were seen regularly at 1- to 4-month intervals for 12 months, depending on the level of asthma control achieved. ≥ 45ppb was used as cutoff for persistently high FeNO	non-difficult asthma: OR: 0.0297; 95% CI: 0.0010 to 0.8790 Asthma exacerbations, which defines as acute attack requiring oral or systemic corticosteroids, at Baseline (at least 3 moderate or severe asthma exacerbations in the previous year) was 13.64% in non-difficult asthma group and 79.17% Difficult asthma.	Difficult asthma: 26.28 ppb (SD: 4.6).	persistently high FeNO was an independent risk factor for difficult to control asthma (along with obesity and severe rhinitis)
		Spirometry, N= 46	Mean age 7.71 years (SD: 0.61), 66.67% male, 91.67% atopy, 31.82% tobacco exposure 25% Obesity, 572.92 mcg (SD: 87.77) beclomethasone	Lung function testing was done using (spirometry; Microlab MK 8, CareFusion) after a washout period of 12 hours for LABAs and of 4 hours for SABAs; postbronchodilator FEV_1 and magnitude of the bronchodilator response were considered. The patients were seen regularly at 1- to 4-month intervals for 12 months, depending on the level of asthma control achieved.		Baseline: Non- difficult asthma: 103.53 (SD: 2.53) Difficult asthma: 91.13 (SD: 3.04).	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Disease Activities and Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Beerthuizen, 2016 [46]	Netherlands, RCT, outpatient setting, unclear risk of bias.	**Group 1**_ Standard care; ACT every 4 months (N= 89)	Mean age 10.2 years (SD: 3.2), Male 69 %, atopy 100 %.		Cost: Among healthcare cost categories, only the amount of nurse practitioners' consultations differed significantly between the strategies.	Group 1_average €86 annual expenditure (1.20 consultations per patient per year) Group 2_ €129 annual expenditure (1.79 consultations per year per patient) Group 3_ €96 (1.33 consultations per patient per year).	RCT of children with atopic asthma compared standard care vs web-based monthly monitoring ACT vs FeNO and ACT every 4 months. Web-based monitoring was preferred from a healthcare perspective, while the FeNO-based strategy was preferred from a societal perspective.

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Disease Activities and Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Group 2_ Web-based; Monthly ACT (N= 91)	Mean age 10.6 years (SD: 2.8), Male 66 %, atopy 100%.		Quality of Life (QALY) _EuroQoL-5 dimensions (EQ-5D): A 5 domains scale; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. All range from 1 to 3, where 1 represents the most favorable score: Group 2 has a statistically non-significant better utility score.	Group 1: 0.928 Group 2: 0.939 Group 3: 0.932 Group 2 vs 1: 0.011 (−0.005 to 0.027) Group 2 vs 3: 0.006 (−0.008 to 0.021) Group 3 vs 1: 0.004 (−0.018 to 0.026)	QALYs and costs were not statistically significant changes.
		Group 3_ FeNO-based; FeNO and ACT every 4 months (N= 92)	Mean age 10.3 years (SD: 2.9), Male 67 %, atopy 100 %	FeNO was measured online on the NIOX chemiluminescence analyzer or NIOX MINO (Aerocrine, Stockholm, Sweden) according to guidelines, offline,	Cost effectiveness: Assessed by cost-effectiveness acceptability curves (CEACs). From a healthcare perspective (based on healthcare costs only) at willingness-to-pay threshold of €40000/ QALY, Group 2 was the most cost-effective, followed by Group 3 and 1. From a societal perspective (including both healthcare costs and costs due to loss of productivity)	From a healthcare perspective, Group 1: 3%. Group 2: 77% Group 3: 20% From a societal perspective, Group 3: 83%.	

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					at a willingness-to-pay of about €40000/QALY, Group 3 has the highest chance of being most cost-effective.		
Berg, 2008 [47]	Sweden, cost-effectiveness study, unclear risk of bias	NR	NR	NR	Asthma diagnosis based on FeNO measurement results in a cost of £38 per patient compared with £26 for standard diagnostics (defined as one or more of the following: spirometry, reversibility testing, bronchial provocation and sputum eosinophil count) . In mild to severe patients, asthma management with FeNO measurement instead of standard guidelines results in cost-savings of £30 per patient and year. In a more severe population, management with FeNO		Economic evaluation showing that management using FeNO reduced total cost per patient per year compared to standard diagnostic test (spirometry, reversibility testing, bronchial provocation and sputum eosinophil count).

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Disease Activities and Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
					measurement would save costs of £160 per patient		
Bernstein, 2009 [48]	United States & Spain, cross-sectional, medium risk of bias.	FeNO, N=209	Overall N=100 in Uinted States and 109 in Spain. Age: median (IQR): USA: 50 years (40-60), Spain 37 years (25-49). Male: USA 45%, Spain 38%. Caucasians 79% in United States, and 100% in Spain Atopy: USA 83%, Spain 62%.	using a chemiluminescene analyzer (Niox model, Aerocrine, Inc. Solna, Sweden) with a range of detection between less than 1 to 500,000 ppb at the US site and the NioxMino analyzer (MiNo, Aerocrine AB; Smidesvagen, Sweden) at the Spain site.	There were no significant differences among FeNO means across ACT categories for patients from the US site (p=0.31). However, for the Spain site, the FeNO mean for ACT <20 (65.8) was significantly higher than the means for ACT 20–24 (41.0, p<0.01) and ACT 25 (35.2, p<0.01). The FeNO mean value for the Spain site, 45.6, was significantly Higher than the USA site, 24.2 (p<0.001).	FeNO: median (IQR): USA 28.8 (14.5 to 51.9), Spain 42.0 (26.0 to 73.0).	In adult asthmatics, FeNO was correlated negatively with ACT only in patients not on ICS. In other subgroups in the study there was no correlation.

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Disease Activities and Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry, N=209		Forced spirometry at the US site was performed using a Koko spirometer, following the guidelines of the American Thoracic Society. Forced spirometry was performed at the Spanish site using a Jaeger APS pro spirometer (Erich Jaeger, Germany). FEV_1, FVC, and peak expiratory flow rate (PEFR) were recorded for each subject using Crapo spirometric reference values in US and using Castellsague reference values in Spain.	For each site, FEV_1 was positively correlated when patients were dichotomized by ICS usage Correlations was +0.39 ($p<0.05$) at the USA site, and +0.26 ($p> 0.05$) at the Spain site.	FEV_1 %, median (IQR): USA 72 (58 to 87.5), Spain 103 (89 to 116).	
		Asthma Control Test (ACT), N=209		Patients from the US completed the English version of the ACT, whereas those from Spain completed the validated Spanish version.	For each site, ACT was positively correlated when patients were dichotomized by ICS usage Correlations was +0.40 ($p<0.001$) at the USA site, and +0.32 ($p< 0.05$) at the Spain site. Negative correlations were obtained between ACT and FeNO at the Spain site only.	ACT: median (IQR): USA 18 (13 to 22), Spain 22 (19 to 24).	
Bora, 2011 [49]	Turkey, longitudinal	FeNO, N= 83	Mean age 42.3 years (SD: 11.4),	Using a nitric oxide analyzer (NIOX MINO	The proportions of patients with FeNO	Baseline: 15 ppb (11-26).	In adults with asthma on

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	nonrandomized, outpatient setting, high risk of bias.		15.7% male, 9% ever smokers, 23% current smokers.	Airway Inflammation Monitor; Aerocrine AB; Solna, Sweden) at a flow rate of 0.05 liters per second at baseline and 3 months later. FeNO threshold was accepted as 20 ppb.	levels > 20 ppb were 21%, 45% and 38% in current smokers, non-smokers and ex-smokers, respectively (P =0.189)	FeNO > 20 ppb (%) Totally controlled asthma (N=8): 38 Partially controlled asthma (N=36): 53 Uncontrolled asthma (N=39): 25. At 3 months: 14 (11 to 21) FeNO > 20 ppb (%) Totally controlled asthma (N=10): 20 Partially controlled asthma (N=39): 26 Uncontrolled asthma (N=34): 38.	ICS, FeNO did not differentiate those controlled, partially controlled or uncontrolled.
		ACT score, N= 83		A 5 items patient-based questionnaire that investigates the disease control. Patients are questioned about their perception of asthma control in the previous 4 weeks. Totally controlled (ACT = 25), partially		Baseline: 18.98 (SD: 4.59) At 3 months: 19.65 (SD: 4.11).	

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				controlled (ACT = 20-24) and uncontrolled (ACT ≤ 19).			
		Spirometry, N= 83		The test was repeated three times using a spirometer (Jaeger Master Screen Pneumo Spirolab II®). Measurements were according to the ATS criteria and the best values were recorded.		FEV_1 Baseline: 93.9 ± 13.7 At 3 months: 93.0 ± 15.8 (P=0.968) FEV_1/FVC Baseline: 78.2 ± 6.9 At 3 months: 77.7 ± 7.1 (P=0.387).	
		Methacholine bronchial provocation test positivity, N= 83		According to the 2-min breathing protocol as described in ATS guideline. The patients inhaled methacholine at the doses of 0.0625, 0.125, 0.250, 0.500, 1, 4, 8 and 16 mg/mL after three repetitive FEV_1 measurements. Thereafter, the pulmonary function test was repeated. The dose which caused a 20% or more decrease in baseline FEV_1 value was accepted as provocative dose (PD20). A PD20 value of < 8 mg/mL was accepted as an indicator of positive BHR.		Baseline: 59 Totally controlled asthma (N=8): 62 Partially controlled asthma (N=36): 56 Uncontrolled asthma (N=39): 62 At 3 months: 45 Totally controlled asthma (N=10): 30 Partially controlled asthma (N=39):	

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						54 Uncontrolled asthma (N=34): 38	
		sputum eosinophil > 3%, N= 83		After medication with a short-acting β2 agonist, sputum was induced by inhalation of 3% hypertonic saline by a nebulizer (Pari Master, Pari Respiratory Equipment Inc. Richmond, VA, USA) with an output of 0.5 ml/min saline for a maximum period of 20 minutes via a mouthpiece. The patients were encouraged to cough and expectorate sputum in a sterile petri dish 10 minutes after the onset of nebulization and every 5 minutes. Three flow-volume curves were obtained before and after each inhalation for patients with a FEV_1 value < 80%. The sputum induction was terminated when a > 15% FEV_1 decrease was observed in comparison to baseline value or when a symptom occurred.		Baseline: 23 Totally controlled asthma (N=5): 0 Partially controlled asthma (N=21): 23 Uncontrolled asthma (N=21): 29 At 3 months: 30 (P=0.791) Totally controlled asthma (N=4): 50 Partially controlled asthma (N=15): 27 Uncontrolled asthma (N=11): 27	
		sputum neutrophil, , N= 83				Baseline: 32 (11 to 50) Totally controlled asthma: 26 (10 to 44) Partially	

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						controlled asthma: 22 (9 to 45) Uncontrolled asthma: 33 (15 to 57) At 3 months: 34 (18 to 56) (P=0.241) Totally controlled asthma: 42 (29 to 53) Partially controlled asthma: 28 (18 to 56) Uncontrolled asthma: 46 (18 to 64)	
Cano-Garcinuño, 2010 [50]	Spain, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=149	Mean age 10.1 years (SD: 2.1), Males 62.4% Weight 41.2 Kg (SD: 12.7), BMI 19.5 (SD: 3.5)	Using a portable nitric oxide analyzer (NIOX MINO, Aerocrine, Solna, Sweden), which provides FeNO measurements at a flow rate of 50 mL/s.	Lung function was associated with higher FeNO values only in children treated with ICs. Reduced FEV_1/FVC (before or after the	cough in the preceding 4 weeks was associated with a higher FeNO level: median 38.5 ppb (IQR, 19.6-64.0) vs	In children with asthma, FeNO correlated with wheezing and cough the previous 4 weeks. No other

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		Spirometry, N=149		Patients then underwent a spirometry test and a bronchodilator test by inhaling 400µg of salbutamol through a spacer chamber. We performed pulmonary function testing both before and after the salbutamol challenge and obtained the following: FEV_1, the ratio of FEV_1 to forced vital capacity (FVC) and the forced expiratory flow, mid-expiratory phase (FEF).	bronchodilator test) was the spirometric parameter most strongly related to inflammatory measurements. A low FEV_1 (baseline or after salbutamol) was independent of FeNO Level. For the whole sample, FeNO level was not related to asthma control, use of health care resources, limitation of daily activities, or clinical variables. Only cough in the preceding 4 weeks was associated with a higher FeNO.	27.5 ppb (IQR, 11.5-51.3); P=.041. FEV_1, FEF25-75, and FEV_1 values after the challenge with salbutamol were not associated with FeNO level, although patients with reduced FEV_1/FVC had higher FE NO levels, both before and after inhalation: before, median 64.0 ppb (IQR, 33.1-77.8) vs 32.5 (IQR, 16.9 56.6); P=.023; after, median 61.3 ppb (IQR, 48.0- 106.5) vs 32.8 (IQR, 17.0 57.1); P=.021.	associations were demonstrated with symptom frequency, bronchodilator use, asthma crises, hospital admissions, limitation of daily activities, or spirometry results. In patients treated with ICs, FeNO was not related to the clinical expression of asthma except for a reduced ratio of forced expiratory volume in 1 second to force vital capacity.
Ciprandi, 2013 [51]	Italy, cross section, inpatient setting, low risk of bias.	FeNO, N= 180	Median age 13 years, Male 57.2%,	Measured by chemiluminescence analyzer (Model 280 Nitric Oxide Analyzer; Severs Instrument Inc., Boulder, CO, USA) at 50 ml/sec, at one visit, steroid prior to		34 ppb (range 29 to 38).	In children, FeNO was strongly related with the response to reversibility to bronchodilation

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				test was 0%.			testing and could predict bronchial reversibility.
		Spirometry, N= 180		Using a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, UK), with optoelectronic whirl flow meter. It was performed as stated by the ATS and ERS.		FVC, FEV_1, and FEF25–75 were 92%, 81%, and 69% of predicted, respectively.	
		Bronchodilator responsiveness, N= 171		According to international guidelines and using a salbutamol metered dose of 400 mcg. Reversibility (bronchodilator responsiveness, BDR) was considered if an increase of at least 12% of FEV_1 was achieved from baseline, according to ERS/ATS guidelines.		95%	
de Bot, 2013 [52]	Netherlands, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N= 93	Mean age 11.3 years (SD: 3), 65% Male, 100% allergic rhinitis.	A single measurement of FeNO was performed at baseline and after 2 years using a hand-held portable nitric oxide analyser (NIOX MINO, Aerocrine AB, Solna, Sweden) at a mouth flow rate of 50mL/s over 10 seconds.		At baseline (N=91): 36 ppb (18 to 55) At 2 years (N=77): 34 ppb (19 to 59)	In children with allergic rhinitis and asthma, FeNO was elevated and did not correlate with nasal or asthma symptoms

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		House dust mite-specific IgE, N= 93		Serum IgE antibodies to Dermatophagoides pteronyssinus were determined at baseline and after 2 years using the CAP- Phadiatop, according to the manufacturer's instructions. Allergen-specific IgE values of >0.7kU/L (class II) were considered positive.		At baseline (N=93): 55.0 kU/L (SD: 37.2). At 2 years (N=77): 58.4 kU/L (SD: 33.8).	
		Symptoms score, N=93		Symptoms of wheezing/dyspnea and dry cough during the night were subjectively assessed according to a grading scale: 0=no complaints, 1=minor complaints, 2=moderate complaints, 3=serious complaints; the maximum score was 6:		At baseline (N=93): 0.9 (SD: 0.9) At 2 years (N=78): 0.4 (SD: 0.8).	
Delclaux, 2008 [53]	France, longitudinal nonrandomized, inpatient setting, medium risk of bias.	FeNO, N=65	Mean age 34 years (SD: 10), males 40%, weight 68 Kg (SD: 14), atopy (self-reported) 69%, current smokers 30.8%, ever smokers 7.7%.	Offline Exhaled NO Measurement, The fraction of NO, collected at a constant flow rate of 100 mL/s, was measured using a chemiluminescent analyzer (ENDONO 8000; SERES, Aix en Provence, France).	The severity of an asthma attack did not influence exhaled NO values on emergency department admission (p=0.27). When considering the whole group, no	FeNO Baseline: 49 (26 to 78), At 2 Hours: 45 (27 to 69) At 6 hours: 48 (25 to 66).	In adults seen in emergency department, an increase in FeNO is observed in almost all patients with acute asthma. Subsequent

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		Spirometry, N=65			significant modification of FeNO 0.1 was evidenced during emergency department stay (first 6 hours), whereas a highly significant decrease in FeNO 0.1 was observed after 6 to 15 days of treatment (49 [28 to 69] versus 20 [13 to 27], n=38; p<0.0001).	PEF rate (L/min%): Baseline: 295 (SD: 111), At 2 hours: 389 (SD: 104), At 6 hours: 424 (SD: 127).	increase within 6 hours is associated with a better degree of asthma control in the subsequent week.
Fritsch, 2006 [54]	Austria, RCT, outpatient setting, unclear risk of bias.	Rx based on symptoms, beta-agonist use, lung function and FeNO, N=22	Mean age 11.3 years (SD:3.4), 63.6% males	FeNO was measured prior to lung function testing according to ATS recommendations at a flow rate of 50 ml/ sec with the single breath online method using the NIOX1 instrument (Aerocrine AB, Stockholm, Sweden). At each visit repeated exhalations were performed until three NO plateau values agreed at a 10% level.	Significant relationships were found between FeNO and symptoms over the last 4 weeks, as well as with BHR. There was a significant inverse relationship between FeNO and the dose of ICSs (b ¼ 8.67; P < 0.002).	FeNO cutoff of 22.9 ppb, had 80% sensitivity, and 60% specificity, and 53% PPV for predicting exacerbations. FeNO baseline 34.6 ppb (17.5 to 107.5) FEV_1 baseline 101 % pred (91.1 to 107.5)	The cut-off point of 22.9 ppb FeNO best predicted exacerbations (sensitivity of 80% and specificity of 60%) in children with mild to moderate asthma.
		Rx based on symptoms,	Mean age 12.1 years (SD: 2.8), 56% males	Spirometry was performed in a Jaeger Masterlab (Version 4.34, Jaeger,		FeNO baseline 31 ppb (20.8 to 54.8)	

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		beta-agonist use, and lung function only, N=25		Wuerzburg, Germany) according to ATS recommendations. The best of three maneuvers was recorded and reference values of Zapletal were applied. FEV_1 and maximum expiratory flow at 50% of forced vital capacity (MEF50) were used for analyses.		FEV_1 baseline 93.7 % pred (83.8 to 99.6)	
Gelb, 2006 [55]	Canada, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=44	Mean age 51 years (SD: 21), males 45.5%, current smoker 0%.	measured using a chemiluminescence analyzer (Sievers NOA 280; Ionics Instruments; Boulder, CO) at an expiratory flow rate of 100 mL/s with varying expiratory airflow resistors (Ionics; Boulder, CO). Exhaled NO was measured at three separate, constant expiratory flow rates: 100, 150, and 200 mL/s in triplicate; and the mean of three values obtained within 10% of each other was used to calculate bronchial NO maximal flow (large airway NO flux [J'awNO]) and small airway/alveolar NO (CANO) using the technique of Tsoukias and George.	If baseline FeNO was ≥28 ppb, exacerbation occurred in 13 of 17 asthmatics (76%); if baseline FeNO was < 28 ppb, exacerbation occurred only in 9 of 27 asthmatics (33%).	When FeNO ≤22 ppb (N= 19), FEV_1 2.0 L (SD: 0.6) or 69 % pred (SD: 14), FVC 3.1 L (SD: 1.1) or 89 % pred (SD: 15), FVE1/FVC 63% (SD: 10). When FeNO >22 ppb (N= 25), FEV_1 2.2 L (SD: 0.9) or 72 % pred (SD: 25), FVC 3.2 L (SD: 1.1) or 89 % pred (SD: 23), FVE1/FVC 68 % (SD: 11). Baseline FEV_1 2.1 L (SD: 0.71)	In controlled asthmatics on ICS, baseline FeNO with cutoff point of 28 ppb can predict first exacerbation over a follow up of 6 months (area under the curve 0.71; sensitivity, 0.59; specificity, 0.82; positive predictive value, 0.77; negative predictive value, 0.87; LR(+), 3.3; LR(-), 0.5; relative risk for

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		Spirometry, N=44		When clinically stable for at least 6 weeks, asthmatic patients were instructed to continue all their medications, except to withhold inhaled long-acting 2-agonists for 48 h and inhaled albuterol sulfate and ipratropium bromide for 6 h prior to testing. Lung function, including lung volumes, single-breath diffusing capacity, and static lung elastic recoil pressures were measured using a pressure-compensated flow plethysmograph (Model 6200 Autobox; SensorMedics, Viasys; Yorba Linda, CA).	If the baseline FEV_1 in liters was ≤76% of predicted, exacerbation requiring at least one course of tapering oral or parenteral corticosteroids over 18 months occurred in 20 of 31 asthmatics (65%); if FEV_1 was >76% of predicted, exacerbation occurred only in 2 of 13 asthmatics (15%) [p 0.003, 2 8.84]. Using ROC plots for first asthma exacerbation, with cutoff point for FEV_1 at 76% predicted, the area under the curve was 0.67; sensitivity, 0.91; specificity, 0.50; positive predictive value, 0.65; negative predictive value, 0.85; LR(+), 1.8; and LR(-), 0.18.	or 70 % pred (SD: 20) of predicted after 180 microgram of albuterol. Healthy subjects (N= 34), FEV_1 3.0 L (SD: 0.8) or 91 % pred (SD: 12). FVC 0.07 L (SD: 1) and 96 % pred (SD: 12) FEV_1/FVC 81 % (SD: 6).	exacerbation 3.4 (95% CI, 1.3-9.1).
Gill, 2005 [56]	United States,	FeNO, N=46	Mean age 19 years (4–54),	Measured by the manufacturer	Changes in FeNO were not		FeNO measurements

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	longitudinal nonrandomized, outpatient setting, high risk of bias.		35 % males, 100 % atopics, 17% current smoker	(NIOX; Aerocrine AB, Stockholm, Sweden). Baseline FeNO measurements were recorded either before the first bronchodilator treatment was administered or at the first point in care that did not interfere with the treating physician's management and patient stabilization.	associated with NIH class of asthma severity hospitalization, or relapse.		in ED patients with acute asthma exacerbations were poorly reproducible and did not correlate with standard measures of asthma severity.
		Spirometry, N=46		Measured using handheld spirometry (KoKo Peak Pro 6; PDS Healthcare Products, Inc., Louisville, CO) in accordance with ATS standards			
Griese, 2000 [57]	Germany, RCT, outpatient setting, low risk of bias.	FeNO, N=74	Mean age 9.7 years (4-16), 76.1 % males, 100 % atoptics.	FeNO was measured online with a chemiluminescence analyzer (Logon LR 2000, Rochester, Kent, UK) sensitive to ENO at concentrations of 1-5000 parts per billion (ppb, by volume). The response time (10-90%) was <0.65 sec.	FeNO in relation to the recommended change in inhaled therapy.	FeNO > 13ppb = Step up (24) vs No change (8) vs step down (5). FeNO < 13ppb= Step up (12) vs No change (11) vs step down (13).	FeNO values did not correlate with current disease severity in children
		Spirometry, N=74			FEV_1 in relation to the recommended change in inhaled therapy.	FEV_1< 80% pred = Step up (6) vs No change (1) vs step down (1). FEV_1> 80%	

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						pred= Step up (26) vs No change (12) vs step down (17).	
		Symptom score, N=74			Symptom score in relation to the recommended change in inhaled therapy.	Symptoms Yes = Step up (34) vs No change (15) vs step down (11). Symptoms no = Step up (2) vs No change (4) vs step down (8).	
Gruffydd-Jones, 2007 [58]	United Kingdom, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 37	Adults (n=22) median age 56.5 years (37.75-60.5), males 36.4%, ever smokers 36%. Children (n=15), median age 9 years (8-12), males 73%, ever smokers 0%.	Measurements were performed on the Niox chemiluminescence eNO analyzer (Aerocrine Ltd, Sweden) at an expiratory flow of 50ml/sec as per guideline recommendations. It was aimed to obtain three NO values that agreed within 10% of each other (as per ERS guidelines), and repeated exhalations were performed up to a maximum of 10 or when the subject tired.	There was no statistically significant difference in the coefficient of variation (CV) between children and adults (median (IQR) 35.0 (29.6 to 48.4) and 32.4 (20.9 to 51.7) respectively. A significant correlations were observed in adults between changes in lung function and changes in FeNO (a rise in FeNO was moderately correlated with a	Adults: 31.2 ppb (11.5 to 61.9). Children: 55.3 ppb (11.6 to 102.1). FeNO was reduced significantly between the first and the last study visit in children (median change in FeNO =14.5 ppb (-41.5 to -0.2), p= 0.01) but not significantly in	In adults and children seen every 2 weeks for 12 weeks, FeNO values correlated with ACQ, AQLQ and bronchodilator use.

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					fall in % predicted FEV_1, (r= -0.33, p<0.001), and between changes in FeNO and changes in Asthma Quality of Life Questionnaire scores (a rise in FeNO was weakly correlated with worsening asthma related health status, r= -0.22, p=0.02).	adults (-9.1 ppb (-28.7 to 2.7), p=0.14). FeNO was non-significantly lower at baseline in adults than children (median FeNO: 31.2 ppb (11.5 to 61.9) vs. 55.3 ppb (11.6 to 102.1) ppb, p=0.38), but not at the final visit 30.7 (15.7 to 43.2) vs. 24.8 (14.7 to 55.7), p=0.60).	
		Spirometry, N=37		Spirometry: (Vitalograph) performed as per ERS guidelines.		Adults: FEV_1% (median, IQR): 86.5 (57.25 to 101.75), PEF: 435 (400 to 457). Children: FEV_1% (median, IQR): 82 (76 to 94), PEF 310 (280 to 410),	

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		Asthma Control Questionnaire (ACQ), N=37		ACQ: Short-term symptomatic asthma control – the Asthma Control Questionnaire (ACQ) in adults only (this instrument has not been validated in children.)		Adults: 1.1 (0.4-2.3).	
		Asthma Mini Quality of Life Questionnaire (AQLQ), N=37		Health status: in adults – the Asthma Mini Quality of Life Questionnaire (AQLQ); and in children – the Paediatric Caregivers Quality-of-life Questionnaire (PQLQ).		Adults: 5.6 (4.1 to 6.7). Children: 6.1 (5.0 to 6.7).	
Habib, 2014 [59]	Saudi Arabia, cross section study, outpatient setting, high risk of bias.	FeNO, N= 53	Mean age 36.1 years (SD: 14.3), 79.2% male, 43.4% ex-smokers, Weight 28.0 Kg (SD: 5.0) 60% ICS-treated, 64.8% Atopy,	According to the present recommendations of the American Thoracic Society using handheld NIOX MINO Airway Inflammation Monitor (Aerocrine AB, Solna, Sweden). A FeNO level of >47 ppb was used to indicate inflammation and uncontrolled asthma	Mean FeNO values were significantly higher in patients with an ACT score <20 of 65.5 ppb (SD: 35.4) compared with those patients with an ACT score ≥20 of 27.4 ppb (SD: 10.5). Linear regression analysis revealed a significant negative correlation of FeNO with ACT score (r=-0.581, p<0.0001). There was no significant correlation of FeNO	Baseline: 48.9 ppb (SD: 33.3).	In adult asthmatics, there was an inverse relationship between ACT scores and FeNO. At the international cutoff point of 20, the sensitivity was 95.2, and the specificity was 68.8. Maximum sensitivity and specificity were observed at an ACT score cut

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					with age, height, weight, asthma duration, and ventilatory function tests.		off point of 19 (sensitivity: 90.5 and specificity: 81.2).
		Spirometry, N= 53		Ventilatory functions were measured using an electronic spirometer (Vitalograph Co, Clare, Ireland), which was calibrated daily		FEV_1 at baseline: 83.8% pred (SD: 7.7).	
		ACT Score, N= 53		Arabic version of the ACT score questionnaire was used		Baseline: 17.6 (SD: 4.9).	
Hanson, 2013 [60]	United States, retrospective chart review, outpatient setting, high risk of bias.	FeNO, N=75	Age mean (range) 6.4 (4.75-7), 52 % males, BMI 16.9 Kg/m2 (12.2-28.4), 33% atopic dermatitis, 71% allergic rhinitis, 33% ever smokers.	Single-breath FeNO testing was performed using the NIOX MINO device, using a 10-second exhalation time and measured in parts per billion. For subjects unable to perform this maneuver, a 6- second exhalation time was used.	Regression coefficients for assessment of the overall impact of age, asthma severity, allergic rhinitis, atopic dermatitis, use of ICSs, and use of LTRAs on FeNO	Asthma severity had the greatest impact on FeNO (0.32), followed by ICS (-0.27), atopic dermatitis and age (each 0.23), allergic rhinitis (0.20), and LTRAs (-0.16).	In children age 4-7 FeNO values correlated with asthma severity, atopic dermatitis and steroids use; and marginally with allergic rhinitis (p=0.06)
		Spirometry. N=36				Mean FEV_1/FVC 91 % pred (92 to 9.2). Mean FEV_1 102 % pred (SD: 20.1).	
		Childhood Asthma Control Test (C-		Validated Childhood Asthma Control Test (C-ACT) score (ACT score >19 indicating inadequate		Mean C-ACT 17.9 (SD: 5.9) range 4 to 27.	

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		ACT) score, N=43		control).			
Harkins, 2004 [61]	United States, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N=22 Spirometry, N=22	Age range 28-48.years, current smokers 0%.	Using off-line in 10-L Mylar bags after subjects inhaled through an NO-free filter. Content of the bags was measured for NO via chemiluminescnence. Spirometry was obtained following ATS guidelines.	Those with exacerbation within 2 weeks of routine appointment had a higher mean FeNO 29.67 ppb (SD: 14.48) compared with those who did not 12.92 ppb (SD: 5.17).	Patients without exacerbation: FeNO 12.92 ppb (SD: 5.17) FEV_1 1.82 L (SD: 0.99) FEV_1 53.6 % pred (SD: 23.2). Patients with exacerbation: FeNO 29.67 ppb (SD: 14.48). FEV_1 1.81 L (SD: 0.61) FEV_1 62.5 % pred (SD: 15.6).	Adult asthmatics who had an exacerbation in the previous 2 weeks had a higher mean FeNO (29.67 vs 12.92).
Hayata, 2013 [62]	Japan, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N= 297	**Group 1: Low PEF variability (Min% Max ≥80%) (N=245):** Mean age 47.7 years (SD: 15.1), 41.6% male, 75.5% atopy, BMI 22.4 (SD: 3.7), 31.4% Ex-Smokers, 356 ug/day (SD: 133) dose of inhaled steroid.	Online electrochemical nitric oxide analyzer (NIOX MINO; Aerocrine AB, Solna, Sweden) over a week.		At baseline: Group 1: 25.3 ppb (SD: 12.8). Group 2: 51.8 ppb (SD: 22.1. FeNO for predicting Min%Max < 80%: 1.08; (95% CI: 1.05 to 1.11).	In adults asthmatics on ICS, FeNO 40 ppb yielded 75% sensitivity and 90% specificity for identifying the subjects with high variability in PEF.

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		Spirometry, N= 297	**Group 2; High PEF variability (Min% Max < 80%) (N=52):** Mean age 51.7 years (SD: 13.5), 51.9% male, 82.7% atopy, BMI 23.4 (SD: 4.1), 48.1% Ex-Smokers, 433 ug/day (SD: 225) dose of inhaled steroid.	It was measured at baseline and after a week.		FEV_1 at baseline: Group 1: 100.4% pred (SD: 12.8) Group 2: 82.8 % pred (SD: 12.3. FEV_1 for predicting Min%Max < 80%: 1.14; (95% CI: 1.05 to 1.24) FEV_1/FVC at baseline: Group 1: 78.1 % pred (SD: 9.1). Group 2: 70.3 % pred (SD: 10.6) FEV_1/FVC for predicting Min%Max < 80%: 1.03; (95% CI: 0.95 to 1.12)	
		Asthma Control Questionnaire (ACQ), N= 297		The ACQ-5 is a questionnaire that assesses asthma condition according to five items, each of which can be rated on a seven point scale.0 represents excellent asthma control and 6 represents extremely poor control.		At baseline: Group 1: 0.4 ± 0.4 Group 2: 0.9 ± 0.5 (P <0.001) OR for predicting Min%Max < 80%: 11.86; 95% CI: 3.55 to	

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				The overall score was the mean of the five responses. It was measured at baseline and after a week.		39.61	
Hsu, 2013 [63]	Taiwan, cross sectional, outpatient setting, high risk of bias.	FeNO, N=56	Mean age 62.3 years (SD: 16.3), 62.5% male.	Flow of 50mL/sec, using an offline and online chemiluminescence (NOA 280i; Sievers Boulder, CO) in one visit.		Online FeNO groups: Age >65 (N=29): 37.2 ppb (SD: 19.9) Age 20-65 (N=27): 39.8 ppb (SD: 33.8). Online FeNO groups: Controlled/partially: 35.1 ppb (SD: 20.4) Uncontrolled: 45.5 ppb (SD: 38.8). Offline FeNO groups: Age >65 (N=29): 19.2 ppb (SD: 9). Age 20-65 (N=27): 20.5 ppb (SD: 13.5).	In elderly asthmatics, FeNO measurement was feasible and correlated with ACT

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						Offline FeNO Group Controlled/partially: 18.1 ppb (SD: 9) Uncontrolled: 23.2 ppb (SD: 14.4).	
		Spirometry, N=56				FEV_1% pred Age >65 (N=29): 76.3% pred (SD: 21.9). Age 20-65 (N=27): 85.6 % pred (SD: 17.8). FEV_1/FVC Age >65 (N=29): 62.8 % pred (SD: 9.9) Age 20-65 (N=27): 71.4 % pred (SD: 8.6).	
		Asthma Control Test (ACT), N=56		ACT score of ≤19 was defined as poorly controlled asthma		Overall: 20.7 (SD: 4.1). Age >65 (N=29): 19.8 (SD: 4.8). Age 20-65 (N=27): 21.8 (SD: 2.8).	
Kavitha, 2017[64]	India, prospective study,	FeNO, N = 100	Mean age 34.2 years (SD: 11.6), 52.3% males, steroid naïve	FeNO was measured before any other respiratory tests using a	There is significant correlation between change in FeNO	FeNO cutoff ≥48 ppb at baseline and	FeNO may be useful to assess asthma

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	outpatient setting, medium risk of bias		nonsmokers, 34.4% were atopics (allergic rhinitis). 92% received ICS with long acting beta agonists, 82% Leukotriene Antagonists and 6% systemic steroids.	handheld Niox Mino point of care device that measure nitric oxide molecules at very low concentrations.	from baseline to 6-week follow up with the change in FEV1, BDR, ACT score, and PEFR variability, with the strength of association strongest with change in PEFR variability (-0.85), followed by ACT score (-0.73) and FEV1 (-0.72).	FeNO ≥36 ppb At 6 week follow up provide optimal sensitivity (66.6%) and specificity (65.6%) to differentiate patients with controlled and uncontrolled symptoms.	control in both steroid naïve asthmatics and asthmatics on treatment. However, the suboptimal sensitivity and specificity may limit its utility as a point of care single monitoring tool.
		Spirometry, N = 100			FeNO showed significant increased between patients according to both airflow obstruction severity and asthma control according to GINA guidelines.	FEV% predicted: FeNO >70%: 21 ppb 60-69%: 39 ppb 50-59%: 48 ppb 35-49%: 82 ppb <35%: 138 ppb	
		Asthma control test (ACT), N = 100				Controlled: 25.5 ppb Partially controlled: 35 ppb Uncontrolled: 40 ppb.	
Ko, 2011 [65]	China, longitudinal nonrandomized,	FeNO, N= 379	Mean age 46.1 years (SD: 13.2), 31.7% male, 0% current smokers.	using chemiluminescence analyser (NOA280i, Sievers Instruments, Boulder, CO, USA) at a		Baseline: 66.9 ppb (SD: 51.9).	In men with asthma, FeNO level at baseline did

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	outpatient setting, low risk of bias.			flow rate of 50 mL/sec.		Asthma exacerbation at 6 months prediction: AUC 0.45, (P: 0.16). Urgent health-care utilization at 6 months prediction: AUC 0.44, (P: 0.15).	not predict healthcare utilization over 6 months
		Spirometry, N= 379		Spirometry pre- and postbronchodilator was performed using the Vitalograph (Buckingham, UK) spirometer in the sitting position, according to the ATS/ERS standards. The updated predicted spirometry values for the Hong Kong Chinese were adopted.		Baseline: Pre-bronchodilator FEV_1 (N = 339): 85.2% pred (SD: 20.5). Post-bronchodilator (N = 374) FEV_1: 90.4% pred (SD: 20.8). Asthma exacerbation at 6 months prediction: Pre-bronchodilator: AUC 0.54, (P: 0.33) Post-bronchodilator: AUC 0.55, (P: 0.19).	

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						Urgent health-care utilization at 6 months prediction: Pre-bronchodilator: AUC 0.53, (P: 0.50). Post-bronchodilator: AUC 0.53, (P: 0.48).	
		ACT score, N= 379		The ACT is a five-item questionnaire to assess asthma control in the previous 4 weeks. The sum of the scores of the five questions gave the total ACT score (range 5–25). The higher the score, the better the asthma control. The ACT questionnaire was translated into Chinese by a qualified translator and then back-translated into English by another qualified translator, and any inconsistencies found were appropriately corrected		Baseline: 20.0 (SD: 4.1). Asthma exacerbation at 6 months prediction: AUC 0.69, (P: <0.0001). Urgent health-care utilization at 6 months prediction: AUC 0.66, (P: <0.0001).	
Kostikas, 2011	Greece, cross	FeNO, N= 274	Well controlled (N = 99) Mea age 51 years (SD:	using a portable NO analyzer (NIOX	FeNO cutoff >22 ppb provided best	Well controlled: 16 (13 to 20)	FeNO had AUC of 0.790

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[66]	section study, outpatient setting, medium risk of bias.		18), 35% male, 31.3% current Smokers, BMI 28.5 (SD: 4.7), 67.7% ICS-treated. Partly controlled (N = 115) Mean age 51 years (SD: 17), 41% male, 28.7% current smokers, BMI 27.5 (SD: 5.1), 79.1% ICS-treated. Uncontrolled (N = 60) Mean age 46 years (SD: 15), 40% male 31.7% current smoker, BMI 28.0 (SD: 5.0), 60% ICS-treated.	MINO Airway Inflammation Monitor, Aerocrine, Solna, Sweden) at a flow of 50 mL/sec.	predictor of not well-controlled in steroid-naive non-smokers, however, FeNO cutoff >27 ppb provided best predictor of NOT well-controlled in steroid-treated non-smokers.	Partly controlled: 27 (19 to 44) Uncontrolled: 59 (23 to 111) FeNO cutoff >22 ppb provided best predictor of not well-controlled in steroid-naive non-smokers: Sensitivity: 0.87 Specificity: 0.81 PPV: 0.90 NPV: 0.76 AUC: 0.899 (0.778 to 0.967) FeNO cutoff >27 ppb provided best predictor of not well-controlled in steroid-treated non-smokers: Sensitivity: 0.64 Specificity: 0.94 PPV: 0.95 NPV: 0.60 AUC: 0.844 (0.775 to 0.899)	for the identification of not well-controlled asthma (using ACT). FeNO values >30 ppb presented positive predictive values (PPV) > 0.85 with the exception of smokers treated with inhaled corticosteroids.

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		EBC pH, N= 274		EBC was collected using a commercially available device (EcoScreen, Viasys, Germany). Subjects rinsed their mouth with distilled water and performed tidal breathing for 15 min while wearing a nose clip. EBC pH was measured using a commercially available pH meter (Model 3510, Jenway, Essex, UK), immediately after the collection of condensate. Stable pH was achieved after deaeration of the EBC with argon (350 mL/min for 10 min).		Well controlled: 7.44 (7.34 to 7.57) Partly controlled: 7.25 (7.12 to 7.36) Uncontrolled: 7.14 (7.05 to 7.21)	
		Asthma Control Questionnaire (ACQ) , N= 274		Juniper's Asthma Control Questionnaire (ACQ) was used.		Well controlled: 0.57 (0.29 to 0.86) Partly controlled: 1.86 (1.14 to 2.71) Uncontrolled: 3.43 (2.57 to 4.00)	
		Asthma Control Test (ACT) , N= 274				Well controlled: 23 (22 to 24) Partly controlled: 18 (17 to 19) Uncontrolled: 14 (11 to 17)	

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Kwok, 2008 [67]	United States, cross sectional, inpatient setting, high risk of bias.	FeNO, N= 90	Mean age 8.9 years (7.9-9.8), 67% male.	Chemiluminescence analyzer (NIOX MINO) through several visits in 81% of patients. The initial measurement was performed before or after the initial administration of b-adrenergic agonists, but always before the administration of corticosteroids.	There was no difference in the median FeNO concentrations among subjects with mild, moderate, or severe acute asthma exacerbations (P = 0.65)	The mean change in FeNO concentrations from the start to the end of treatment was 0.24 ppb (-1.45 to 1.94).	In children 2–18 years old 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
Leblanc, 2013 [68]	Portugal, longitudinal non randomized, outpatient setting, medium risk of bias.	FeNO, N=185	Mean age 37.48 years (SD: 14.88), 21.6 % males	Measured by chemiluminescence analysis, using NIOX instrument (Aerocrine; Sweden). FeNO evaluation a cut-off value of 35 ppb was used (15) with higher levels reflecting a greater probability of airway eosinophilic inflammation	FeNO change with asthma severity (based on FEV_1)	The mean values of FEV_1 were 85.5% (SD of 21.6%) for patients with low probability of inflammation (FeN0<35) and 84.8% (SD of 16.0%) for those with FeN0≥35. Among patients with FeNO < 35 ppb, 66% had FEV_1 > 89% and 52% had asthma control	Among patients with partially and controlled asthma, 60% had FeNO less than 35.
		Spirometry, N=232		Spirometry values, FEV_1 and FEF25-75%, were expressed as 3-level variables: percent predicted less than 60%, between 60 and 80% and greater than 80%			

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		Score registration of the Asthma Control Test, N=232		Divided into 3 different groups: less or equal to 19 (uncontrolled asthma), 20 to 24 (partially controlled) and equal to 25 (well controlled asthma). A second ana lysis was performed dividing ACT™ score in 2 groups (score ≤19 and >19)		test score > 19.	
Lex, 2007 [69]	Germany, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N=85	Mean age 11 years (5-16) male 52%.	Measured by online chemiluminescence analyzer (NOA280, Sievers Instruments, Boulder, CO), at 50 ml/sec, Steroid prior to test was 49.4%, bronchodilators withheld prior to test was 9.4%.	FeNO was significantly elevated in those with exercise induced bronchoconstriction (EIB) defined as reduction of FeV1 > 15% vs those without. The cut off level of FeNO 25 ppb resulted in the best combination of sensitivity and specificity to predict exercise c induced bronchoconstriction .	With EIB (N=12) 51.3 ppb (31.1 to 67.3) vs Without EIB (N= 73) 20.2 ppb (10.9 to 42.3). Sensitivity 100% Specificity 58% PPV 28% NPV 100% AUC 0.796	In children with atopic asthma, FeNO was significantly elevated in those with exercise induced reduction of FeV1 (> 15%) with NPP 100% and PPV 28%. NPV and PPV for reported asthma symptoms within 2 weeks preceding the

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		Spirometry, N= 85		Patients were asked to withhold ß2-agonists for at least 12 hr; inhaled steroids were not withdrawn prior to testing. After measuring specific airway resistance (sRaw,tot) by body plethysmography, baseline spirometry was performed.	FEV_1 and FVC were significantly elevated in those with exercise induced bronchoconstriction (EIB) vs those without EIB, however, FEV_1/FVC ratio was lower in patients with EIB vs without EIB.	With EIB (N=12) FEV_1% pred 95.2 (88 to 105.3) FVC % pred 86.1 (78.1 to 98.1) FEV_1/FVC % pred 116.2 (111.1 to 123) Without EIB (N= 73) FEV_1% pred 101.9 (95 to 114) FVC % pred 94.7 (85 to 105.6) FEV_1/FVC % pred 114.9 (108.1 to 263.2).	study were 96% and 26%. Thus, FeNO can be used to exclude EIB in atopic child
		Asthma symptoms in 2 weeks preceding exercise challenge, N= 38			Asthma symptoms in 2 weeks preceding exercise challenge has a higher specificity but lower sensitivity, NPV and PPV to predict exercise induced bronchoconstriction (reduction of FEV_1 >15%) than FeNO.	sensitivity 83% specificity 62% PPV 26% NPV 96%	

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Mahut, 2010 [70]	France, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=200	Mean age 16 years (12-38), male 52.5% current smoker 0%, atopy 82%	Measured by online chemiluminescence analyser (ENDONO 8000; SERES, at 50-250 ml/sec, Steroid use prior to test was 82.5%	FeNO did not correlate with ACQ /short-ACQ nor was influenced by severity classes.		In adults and children stable and on treatment (mostly ICS), FeNO did not correlate with ACQ or short ACQ.
		Asthma Control Diary (ACD) and Asthma Control Questionnaire (ACQ), N= 200			There was a good agreement between ACD and the weekly telephonic ACQs questionnaires when considering weekly assessments separately as well as the multiple assessments per patient.		
Martins, 2008 [71]	Portugal, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N=54	mean age 7.8 years (SD: 1.1), Males 57.4%, atopy; 38.9% sensitized to at least one aeroallergen, 22.2% had positive skins prick tests for grass and/or olive tree pollen and 35.2% positive for house-dust mites.	FeNO measurement was read after the spirometry was performed, using a portable analyzer, Niox® Mino (Aerocrine, Sweden), in which the expiratory flow rate is maintained at 50 mL/s.	The correlation between FeNO and FEV_1, FEV_1/FVC and ΔFEV_1 was weak and not statistically significant (rho -0.189, -12.8 and 0.038 respectively). Comparing the	The mean FEV_1 value (a percentage of the theoretical value) was 100% (SD:14), the ΔFEV_1 (a variation percentage in relation to the base value) was	In children, FeNO levels could differentiate those who had exacerbations and needed bronchodilators in the previous 6 months.

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		Spirometry, N=54		The spirometer used was a Vitalograph® Compact (Buckingham, UK). 200µg of salbutamol were administered for the bronchodilation challenge.	children who had at least one wheezing and/or respiratory difficulty episode in the six months prior to the evaluation with those who were complaint-free during the same period, we find statistically significant differences for the ΔFEV_1 (8% median [p25-75%: 3.25-16.5%] versus 4.5% median [p25-75%: 3-7%] respectively; p=0.04). We also find statistically significant differences for the FeNO (23 ppb median [p25-75%: 12-31.75 ppb] versus12 ppb median [p25-75%: 9-21.25 ppb] respectively; p=0.02).	8.1% (SD: 7.3) and the con-centration of nitric oxide in exhaled air (FeNO) in parts per billion (ppb) was 20.8 ppb (SD: 14.7). Comparing the children who needed to use a bronchodilator in the six months prior to the evaluation with those who had no need of this medication, we find statistically significant differences for the FeNO: 27 ppb median [p25-75%: 19.75-34.25 ppb] versus 11 ppb median [p25-75%: 9-18.75 ppb] respectively; p<0.0001.	
McCormack, 2013 [72]	United States, longitudinal	FeNO, N= 150	Mean age 11 years (5-17), 57% Male,	FeNO level was measured at baseline, 3, 6, 9, and 12 months using the online	FeNO level was not a strong predictor of asthma-related	Baseline: 32 ppb (16-61)	In high risk children (minorities in

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	nonrandomized, outpatient setting, low risk of bias.		91% Black, 43.3% ex-smokers Weight 28.0 Kg (SD: 5.0), 60% ICS-treated, 90% Atopy.	Niox MINO (Aerocrine Inc) according to the ATS guidelines.	health-care use in the subsequent 3 months; however, lung function was a better predictor than FeNO. ED visit in the past 12 months n: 111 patients. Acute visit in the 12 months follow period: 237 in 78 patients. ED visit in the 12 months follow period: 125 in 58 patients. Hospitalizations: 7 in 5 patients.		urban areas with persistent asthma and atopy) on controller medication, FeNO every 3 months was not a significant predictor of acute visits, ED visits, unscheduled doctor visits, or hospitalization in adjusted analysis.
		Spirometry, N= 150		Spirometry was performed at baseline, 3, 6, 9, and 12 months according to ATS guidelines using a KoKo spirometer (nSpire Health Inc) and National Health and Nutrition Examination Survey reference equations for calculating % predicted values.		FEV_1 Baseline: 94.4% pred (SD: 17.7) FEV/FVC Baseline: 80.7 % pred (SD: 9.6).	
Menzies, 2008 [73]	United Kingdom, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=267	Mean age 51.6 years (SD: 1.1), 46% male, 0% ever smokers, 0% current smokers.	Online chemiluminescence analyzer (NIOX MINO) through one time visit during 3 months period.	Exacerbations experience at 3 months: 14 patients Exacerbations experience in the 12 months before the visit: 72 patients Royal College of Physicians symptom score of 0 was identified as a significant negative predictor for exacerbations in the 12 months (P = 0.008) and 3	Exacerbation group: 31.3 ppb (SD: 8.3). No exacerbation group: 28.0 ppb (SD: 1.7) (P: 0.66)	In adults with asthma, FeNO was measured and correlated with exacerbations 12 months before and 3 months after. Levels of FeNO were significantly lower in frequently exacerbating patients receiving
		Spirometry, N= 267.		Was performed in accordance with American Thoracic Society/European Respiratory Society guidelines to determine forced expiratory volume in 1 second (FEV_1), forced		Exacerbation group: 85 % pred (SD: 5.9). No exacerbation group: 86.7% pred (SD: 1.3) (P: 0.75).	

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				vital capacity (FVC), and FEV_1/FVC.	months (P = 0.005) before the clinic visit but not for the 3 months after the visit (P = 0.45)		higher doses of maintenance ICS compared with patients with mild disease who were corticosteroid naive. Measurement of FeNO was an insensitive method (sensitivity, 66.7%; specificity, 51.9% at a cutoff value of 20 ppb) for identifying patients who subsequently exacerbated.
Meyts, 2003 [74]	Belgium, cross-sectional, outpatient setting, high risk of bias.	FeNO, N=73	Good asthma control (defined if both day- and night-time symptoms were absent, if the frequency of short-acting beta2-agonist use was less than four times during the past 2 weeks, and if the FEV1 of a well-per) (N= 21) median age 10.9 years, atopy 76%.	Exhaled air was led via a Teflon tubing system to the chemiluminiscence analyzer (Ecophysics CLD 700 AL MED, Durnten, Switzerland). Air was continuously sampled at a sampling rate of 0.700 ml/min. Response time of the analyzer was 1 sec; detection limit for NO was 1 part per billion (ppb).	Percentages of change in FEV 1 (median (quartiles)) After salbutamol administration were 2% (0-7) for group 1, 2% (2–8%) for group 2, and 8% (6–14%) for group 3. These percentages differed significantly	Good asthma control: baseline FEV_1% 101 (SD: 15), FVC% 105 (SD: 11). FeNO median 11 ppb (quartiles 9-21). Acceptable asthma control: baseline FEV_1% 94 (SD: 15),	In children with asthma seen in outpatient settings, FeNO differentiates those with insufficient, acceptable and good control (defined if both day- and night-time symptoms were absent, if

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		Spirometry, N= 73	Acceptable asthma control (N= 31) median age 10.9 years, atopy 83.9%. Insufficient asthma control (N= 21) median age 10.7 years, atopy 85.7%.	All subjects underwent baseline and postbronchodilator (20 min after 400 micro.g salbutamol administration with pMDI and Volumatic 1 spacer) flow-volume measurements, using the IOS digital (Jaeger, Germany).	between all three groups (P¼ 0.005), between groups 1 and 3 (P¼ 0.002), and between groups 2 and 3 (P¼ 0.006).	FVC% 103 (SD: 14). FeNO median 15 ppb (quartiles 11-26). Insufficient asthma control: baseline FEV_1% 91 (SD: 15), FVC% 103 (SD: 14). FeNO median 28 ppb (quartiles 19-33).	the frequency of short-acting beta2-agonist use was less than four times during the past 2 weeks, and if the FEV1 of a well-per) (28 ppb, 15 ppb, 11ppb; p<0.01).
Michils, 2008 [75]	Belgium, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=341		FeNO was measured before any forced expiratory maneuvers using a daily calibrated LR 2000 chemoluminescence analyzer (Logan Research Ltd, Rochester, UK) with on-line measurement of a single exhalation at flow rate of 50 mL.s-1 (ATS/European Respiratory Society standard).	In non-severe asthma, an optimal control was documented at the first visit in 164 pairs (out of 415). Loss of optimal control at visit two is considered as a positive event. This occurred in 39 occasions. In the whole population, an	ICS naïve patients: 49.8 ppb (24 to 103.5). ICS dose ≤500 microg: 27 ppb (11.7 to 62.1), ICS >500 microg: 20.5 ppb (9 to 46.7),	In unselected population of adults with persistent asthma, FeNO correlated with ACT and need for control optimization. This correlation was reduced in those of high dose ICS.

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		Spirometry, N= 341		Spirometry was performed using a Zan 300 spirometer (Zan1, Oberthulba, Germany). Pre-bronchodilator FEV_1 was used as an index of airway caliber.	FeNO increase, 30% makes a loss of optimal control unlikely (NPV 82%). In steroid naïve patients, an initial FeNO level. 35 ppb predicts asthma control optimization in two out of three cases (PPV 68%). In ICS-treated patients, asthma control is unlikely to become optimal after treatment increase if FeNO was 35 ppb at the first visit (NPV 88%). FEV_1 never predicted optimization.	ICS naïve patients: FEV_1%: 88.9 (SD:18.5) ICS dose ≤500 microg: FEV_1%: 90.1+/-15.1, ICS >500 microg: FEV_1%: 84.1 (SD: 19)	
		Asthma Control Questionaire (ACQ), N= 341				ICS naïve patients: 2 (0 to 5.2). ICS dose ≤500 microg: 0.8 (0 to 4.8). ICS >500 microg: 1.3 (0 to 5.2).	

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Michils, 2009 [76]	Belgium, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N= 470	Nonsmokers (n= 411) Mean Age 41 years (SD: 16), male 47.4%, atopic 85.1%. Smokers (n=59); mean age 38 years (SD: 11), male57.6%, atopic 91.5%.	Measured by online chemoluminescence analyzer (Logan Research Ltd, Rochester, UK) at a flow rate of 50 mL/sec (American Thoracic Society (ATS)/European Respiratory Society (ERS) standard).	FeNO exhibits high operating characteristics in both nonsmoking and smoking groups. The cut-off values for decreases in FeNO which had the highest NPVs for establishing control were 30% in nonsmokers and 20% in smokers. When considering the subgroup of smoking patients treated with >500 mg equivalents BDP.day-1, FeNO was no longer significant in assessing an improvement of asthma control. As for improvement assessment, FeNO exhibited analogous operating characteristics in nonsmoking and smoking patients.	Baseline FeNO: Nonsmokers: 33.7 (14.3 to 79.2), smokers: 18.1 (6.9 to 47.5).	Correlation between FeNO and ACQ were noted in smokers and nonsmokers on ICS.
		Asthma control questionnaire (ACQ), N= 470		Asthma control was assessed using a French translation of the short version of the ACQ of Juniper et al.		ACQ score: Nonsmokers: 1.5 (0 to 5), smokers: 1.7 (0 to 5.3).	

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		Spirometry, N= 470			With a cut-off value at 30% change, a high NPV was observed in both groups. When considering the subgroup of smoking patients treated with >500 mg equivalents BDP.day-1, FeNO operating characteristics in assessing asthma control worsening are less significant.	FEV_1: Nonsmokers: 85.6 (SD: 15.7), smokers: 86.2 (SD:17.9).	
Nayak, 2013 [28]	India, cross section study, inpatient setting, medium risk of bias.	FeNO, N= 100	Asthmatics (N=55): Mean age 45.2 years (12-82), 41.8% male, 51% On inhalational steroids. Controls (N=45): Mean age 48.5 years	Three FeNO measurements were recorded for each subject using chemiluminescence NO-analyser and the procedure was performed as per standard recommendation. FeNO level of < 8.0 ppb was	The FeNO levels were not significantly lower in steroid treated cases as compared with steroid naïve cases.	asthmatics: 16.5 ppb (SD: 10.3) Controls: 5.5 ppb (SD: 2.7). Steroid-treated cases (N=28):	In patients with bronchial asthma, FeNO levels significantly correlate with the severity of asthma and the levels

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			(16-76), 48.9% Male.	taken as normal.		15.7 ppb (SD: 9.8). Steroid-naive cases (N=27): 17.3 ppb (SD: 10.9). Correlation of FeNO with severity of asthma in steroid-treated cases: Mild asthma: 6.3 ± 2.6 Moderate asthma: 15.1 ± 9.7 Severe asthma: 18.8 ± 9.7. Correlation of FeNO with severity of asthma in steroid-naïve cases: Mild asthma: 11.9 ± 8.3 Moderate asthma: 20.7 ± 8.2 Severe asthma: 28.9 ± 11.3	reduce with steroid therapy.
Nittner-Marszalsk	Poland, longitudinal nonrandomi	FeNO, N=72	Pregnant asthmatics with a median age 29 years (18-38),	Flow of 50mL/sec, using an online chemoluminescence	No asthma exacerbation experience. It is	31.6 ppb (7.3 to 129.8).	Pregnant asthmatics women

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a, 2013 [77]	zed, outpatient setting, low risk of bias.		0% male, 0% current smokers, 73.6% atopy.	analyzer (NIOX, Aerocrine, Stockholm, Sweden), in a fasting status every month for 6 months.	defined as an episode of increasing asthma symptoms requiring a change of corticosteroids treatment.		underwent monthly FeNO and there was a weak correlation between FeNO and ACT and wide variation in FeNO values. Results were the same in atopic and non-atopic women. Levels did not significantly differ in women who lost control from values during control.
		Spirometry, N=72		Spirometry (Master Scope, Jeager, Germany) was performed according to the recommendations of the American Thoracic Society and the European Respiratory Society		FEV_1 97.1% pred (55 to 135).	
Ozier, 2011 [78]	France. longitudinal cohort study, medium risk of bias.	FeNO (EndoNO), N= 90	controlled asthma (N= 62) mean age of 38.5, 32% males, 77.4% atopic, 23% ever smoked. uncontrolled asthma (n=28): mean age of 44.8 years, 46% males, 82.1 atopic, 32% ever smoked.	chemiluminescence device EndoNO (SERES, France) on-line at a flow rate of 50 ml/s and a pressure of 10 cm H2O		FeNO (EndoNO) cutoff of 22 ppb (n=89) can predict the persistence of asthma control with: Sensitivity 77.7%, specificity 62.9%, PPV 47.7%, NPV 86.7%.	In Adults, FeNO can predict the persistence of asthma control in controlled patients and may can be used in asthma management since it can accurately be measured by means of hand-held

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		FeNO (MINO) , N= 90		Electrochemical device NIOX MINO (Aerocrine AB, Sweden).		FeNO (MINO) cutoff of 31 ppb (n=78) can predict the persistence of asthma control with: Sensitivity 60%, specificity 66%, PPV 45.4%, NPV 77.8%.	devices.
		Asthma control questionnaire (ACQ) , N= 90		All clinical and the functional items were equally weighted and averaged (each quoted from 0-6).		Well controlled: 0.62 Non-well controlled 2.48	
Papakosta , 2011 [79]	Greece, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N= 160	Adults with newly diagnosed asthma Mean age 39.7 years (SD: 16.6), 35% male.	FeNO was measured at an expiratory flow rate of 50 ml/s by a chemiluminescence analyzer (CLD 88sp; ECO MEDICS AG, Duernten, Switzerland) according to the latest American Thoracic Society / European Respiratory Society (ATS/ERS) recommendations.		Baseline: 25.97 ppb (SD: 25.68) At 4–12 weeks after initiation of treatment: 17.0 ppb (SD: 14.77). Completely Controlled group (N=37) Baseline: 20.52 ppb (SD:24.97) At 4–12 weeks after initiation of treatment (N = 48):	In adults with newly diagnosed asthma, patients with uncontrolled asthma had statistically higher FeNO values than patients with partly controlled (p = .038) and completely controlled asthma (p = .016). ACT score was

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						19.23 ppb (SD: 18.18). Partly controlled (N=85) Baseline: 24.39 ppb (SD: 20.58) At 4–12 weeks after initiation of treatment: 15.39 ppb (SD: 12.72) Uncontrolled (N= 38) Baseline: 34.78 ppb (SD: 33.92). At 4–12 weeks after initiation of treatment (N = 13): 21.04 ppb (SD: 14.66)	found to have a negative correlation with FeNO.
		Spirometry, N= 160		FEV_1 was measured by an electronic spirometer (Wright Ventilometer, Clement Clarke International, London England).		Baseline: FEV_1 88.18% pred (SD: 14.17) At 4–12 weeks after initiation of treatment: FEV_1 92.63 % pred (SD: 12.34) Completely controlled	

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						(n = 37): Baseline: FEV_1 0.28 % pred (SD: 14.60) At 4–12 weeks after initiation of treatment (N = 48): FEV_1 95.07 % pred (SD: 13.01) Partly controlled (N= 85): Baseline FEV_1 88.74 % pred (SD: 13.19) At 4–12 weeks after initiation of treatment (N = 99): FEV_1 92.23 % pred (SD: 11.79) Uncontrolled (N = 38): Baseline FEV_1 84.89 % pred (SD: 15.62) At 4–12 weeks after initiation of treatment (N = 13):	

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						FEV_1 86.71 % pred (SD: 12.57).	
		Asthma Control Test (ACT) score, N= 160		The ACT questionnaires administered to the patients of this study had been formally translated into Greek. Patients were classified into three groups based on ACT scores (9): completely controlled (ACT score = 25), partly controlled (ACT score range = 20–24), and uncontrolled (ACT score range = 5–19).		Baseline: 21.27 ± 3.74 At 4–12 weeks after initiation of treatment: 23.00 ± 2.19 (P < 0.001)	
Plaza, 2013 [80]	Spain, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 381	Mean age 44.3 years (SD: 14.86), 43% male, 66.4% atopy.	Flow of 50mL/sec, using a NioxMino® portable equipment (Aerocrine, Sweden)	The combination of FeNO and ACQ-7, showed 75% specificity and a 85.2% positive predictive value to identify patients with not well controlled asthma. The area under the ROC curve was 0.8754 for FeNO and ACQ-7 combined, and 0.544 for sole FeNO.	Baseline: 44.18 ppb (SD: 29.82) At 1 month: 26.8 ppb (SD: 20.82).	In adults with not well controlled persistent asthma and a positive bronchodilator test, adding FeNO to ACQ-7 increased the detection of not well controlled asthma following maintenance therapy adjustment by 14.8%.
		Spirometry, N= 381		Spirometry was performed according to the European Respiratory Society/American Thoracic Society guidelines using the predicted values for Mediterranean populations.		FEV_1 Baseline: 79% pred (SD: 18.8) At 1 month: 85.3% pred (SD: 16.6).	
		ACQ-7 score, N= 381		The questionnaire contains 7 items comprising 6 multiple choice test questions on		Baseline: 2.21 (SD: 0.81) At 1 month: 1.10 (SD: 0.78).	

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				the frequency of asthma symptoms and the use of rescue medication within the prior 7 days, and the FEV_1 percent of predicted value. The total ACQ-7 score, computed from its 7 items, ranges from 0 (maximum control) to 6 (minimum control), and a 0.75 point threshold was chosen to consider controlled asthma			
Quaedvlieg, 2009 [81]	Belgium, cross section, outpatient setting, low risk of bias.	FeNO, N= 134	Well controlled group (N=31): mean age 40 years (SD: 13), Male 52%, Ever smokers 32%, current smokers 3%, atopy 90%. Borderline group (N=32): mean age 47 years (SD: 12), Male 50%, Ever smokers 0%, current smokers 25%, atopy 69%. Uncontrolled group (N=71): mean age 42 years (SD: 12),	measured by an online chemoluminescence analyser (NIOX, Aerocrine, Stockholm, Sweden), at one visit, at a flow rate of 50 mL/s, in accordance with the recommendations of the ATS/ERS task force. Corticosteroid use and bronchodialtors withhold prior to test in each group were 64%, 62%, 65% and 100%, 100%,100%, prospectively.	There is no FeNO significant difference between the three groups.	Controlled mean 47.9 ppb (11.4 to 130), borderline mean 30.6 ppb (2.8 to 222), uncontrolled mean 50.2 ppb (4.1 to 244).	In adults with asthma mostly on ICS, FeNO did not differentiate well controlled/borderline controlled/well-controlled based on ACQ.
		A bronchial responsiveness (methacholine challenge test), N=		Measured by a modified Cockroft's method. Inhaled tidal breathing for 2 min fourfold increasing concentrations of methacholine chloride from 0.06 to 16 mg/mL.	Uncontrolled asthmatics had a greater BHR to methacholine than controlled asthma.	PC20 in controlled mean 6.3 mg/ml (0.17 to 16), borderline mean 3.9 mg/ml (0.05 to 16),	

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		134	Male 49%, Ever smokers 20%, current smokers 20%, atopy 69%.	The aerosol was generated by a jet nebulizer (Hudson, Temecula, CA, USA).		uncontrolled mean 1.6 mg/ml (0.06 to 16).	
		Sputum eosinophilia, N= 134		induced by inhalation of a hypertonic saline (NaCl 4.5%) combined with additional salbutamol delivered by an ultrasonic nebulizer (Ultra-Neb 2000, De Vilbiss, Somerset, PA, USA) with an output set at 0.9 mL/min. Sputum was weighed and homogenized by adding three volumes of PBS, vortexed for 30 s and centrifuged at 800 g for 10 min at 41C.	Uncontrolled asthmatics had a greater sputum eosinophilia than controlled and borderline asthma.	Controlled mean 0.4% (0 to 31.2), borderline mean 1.4% (0 to 26), uncontrolled 5.6% (0 to 93.4).	
		Spirometry, N= 134		Electronic spirometer connected in real time to a computer (Spirobank, MIR, Rome, Italy). All manoeuvres were repeated three times and the best FEV_1 value was selected by the software program (Winspiro, MIR).		FEV_1 (% pred); controlled mean 101 (SD: 11), borderline mean 88 (SD: 13), uncontrolled mean 81 (SD: 27). FEV_1/FVC (%); controlled mean 80.6 (SD: 4.5), borderline mean 76.5 (SD: 6.5), uncontrolled mean 79 (SD:	

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						21).	
		Asthma Control Questionnaire (ACQ), N= 134		The ACQ score from the six-item Juniper ACQ questionnaire deleting the FEV_1 from the original questionnaire (0 = totally controlled and 6 = severely uncontrolled).		Controlled ACQ < 0.75, uncontrolled ACQ > 1.5, borderline ACQ 0.75-1.5.	
Raj, 2014 [82]	India, longitudinal cohort study, outpatient setting, medium risk of bias.	FeNO, N= 243	mean age of 8.3 years, 76% males, 100% atopic (positive to at least one allergen).	measurement was done using NIOX MINO (Aerocrine AB, Solna, Sweden), 81% were on inhaled steroids,	Pulmonary score did not correlate with acute exacerbation FeNO (r=0.1, Spearman correlation, P=0.29). FeNO cutoff = 20 ppb during exacerbation had a sensitivity of 44%, specificity of 68.7%, AUC of 0.59.	Baseline (n=185) Median 15 ppb (9-26) Personal best (n=218) Median 8 ppb (5-12) During exacerbation (n=143) Median 17.7 ppb (12-25.3).	In children with acute exacerbation of asthma, FeNO during exacerbation was not higher than that during follow up but was significantly higher than personal best. FeNO during acute exacerbation did not correlate with the severity of acute exacerbation and could not diagnose or predict exacerbation.
		Spirometry, N= 243		Spirometry was done using portable spirometer (Superspiro MK2, Micro Medical Ltd, UK)			
		Pulmonary score, N= 243		Each parameter is rated on a 0-3 scale, with a maximum total score of 9. Mild, moderate, and severe acute exacerbations were defined as pulmonary score of 0-3, 4- 6, and 7-9,			

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				respectively.			
Ricciardolo, 2016 [83]	Italy, cross sectional, outpatient setting, high risk of bias.	FeNO, N=363	Mean age 46.28 years (SD: 17.11), 41.3 % males, BMI 25.31 kg/m^2 (SD: 5.18), 81.3% atopic (allergy).	Measured with a chemiluminescence analyser(Eco Medics CLD88 sp, Duernten, Switzerland) beforespirometry; the detection limit of the apparatus was 1-5parts per billion (ppb), as required by ATS guidelines	Compared to controlled and partly controlled asthmatic, poorly controlled asthmatics showed the highest FeNO values ($p < 0.001$), with a probability almost four times greater to have pathological values compared to controlled asthmatic patients ($p = 0.002$).	Poorly controlled asthmatic median: 42.90 ppb, 25th-75th:19.63 to 77.15). (OR: 3.71, 95%CI: (1.74 to 7.89); p = 0.002)	FeNO assessment in clinical practice may be a useful tool for monitoring asthmatics as it is associated with several clinical factors, including asthma control.
		Spirometry, N=363		Spirometry was performed using a computer-assisted spirometer (Pulmolab 435-spiro 235, Morgan, England, ---predictive values ECCS 1993), with optoelectronic whirl flowmeter.			
Robroeks, 2007 [84]	Netherlands, cross sectional study, outpatient clinic, high risk of bias.	FeNO, N= 64	mean age 10.7 years (SD: 0.4), mean weight 38 Kg (SD: 2).	Measured at one visit using offline chemoluminescence analyzer nitric oxide monitor (NIOX; Aerocrine AB, Solna, Sweden) at an exhalation flow rate of 50 ml/sec.	Compared to FEV_1, FeNO, IFN-g and IL-4 were significant indicators of an asthma diagnosis, with odds ratios ranging from 1.03	FeNO at 30ppb: OR: 3.32; 95% CI: 1.05 to 10.5. FeNO at 20 ppb: OR: 2.26;	FeNO, 8-isoprostane, IFN-gamma and IL-4 were significant indicators of asthma control with a

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		exhaled breath condensate (EBC), N= 64		The acidity of EBC was immediately measured in non-deaerated samples (Radiometer, type PHM201, Zoetermeer, the Netherlands) and EBC was rapidly frozen at 80 1C using dry ice, and was stored at 80 1C until analysis. Then, cytokines (IFN-g, TNF-a, IL-2, -4, -5, -10) were assayed with flow cytometry (CBA, BD Biosciences, San Diego, CA, USA).	for FeNO to 5.21 for IL-4 in EBC.	95%CI: 0.92 to 5.55.	sensitivity of 82%, specificity of 80%, and area under the curve was 0.761.
Rosias, 2004 [85]	Netherlands, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N=23	Mean age 10.6 years (SD: 2.8), weight 35.4 Kg (SD: 12.3).	FeNO was measured by means of NIOX (Aerocrine, Solna, Sweden) according to the criteria of the American Thoracic Society. At a constant flow rate at 50 ml/sec, guided by a balloon meter. The mean FeNO value of three consecutive measurements was used for analysis.	The correlate ons found between FeNO and preFEV$_1$ (r ¼ 0.59, P< 0.05), and FeNO and ACQ score (r¼ 0.48, P¼ 0.06).	FeNO median 23.1 (SD: 5). FEV$_1$% pred; Pre-FEV$_1$: 96.4% (SD:16.2), Post-FEV$_1$: 103.2% (SD: 16.7).	In children with mild to moderate persistent asthma on ICS, FeNO weakly correlated with asthma control questionnaire (p=0.06).
		Spirometry, N= 23					

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Sato, 2009 [86]	Japan, cross sectional, inpatient setting, medium risk of bias.	FeNO, N=78	Non-exacerbation group (N=62): mean age 60.4 years (SD: 14.1), male 43.5%, atopic% 54.8, BMI 21.7 (SD: 8.6), current smoker 12.9%, ever smoker 19.4%. Exacerbation group (N=16): mean age 64.6 years (SD: 7.2), male 37.5%, atopic% 56.3, BMI 21.9 (SD: 7.8), current smoker 6.3%, ever smoker 18.8%.	Using an online collection apparatus using chemiluminescence (280A Sievers Nitric Oxide Analyzer, Boulder, CO, USA) according to the ATS (American Thoracic Society) guidelines.	The area under the curve (AUC) of the cut-off points of the second node, as the combination of the ACT score ≤23 and the percentage of predicted FEV_1 ≤91.8% (AUC 0.678, 95% CI 0.513 to 0.833) are the most predictive factors in comparison with those of the first node, as the ACT score ≤23 (AUC 0.613, 95% CI 0.453 to 0.773), or those of the third node, as the combination of the ACT score ≤23, and the percentage of predicted ≤91.8% and FeNO≥36.7 ppb (AUC 0.625, 95% CI 0.453 to 0.797).	FeNO: non-exacerbation group: 42.8 (SD: 30.6), exacerbation group: 47.1 (SD: 40.2).	In adults with mild to moderate asthma, clinically stable for 3 months on ICS, FeNO did not accurately predict future exacerbations over a year (AUC 0.501 (0.341–0.661), sensitivity 0.44, specificity 0.57.
		Spirometry, N=78		When clinically stable for at least 2 months, asthmatic patients were instructed to continue all their medications, except to withhold inhaled long-acting ß2-agonists for 24 hours and inhaled albuterol sulfate for 6 hours before testing. Spirometry was performed		Baseline FEV_1% Non-exacerbation group: 92.7 (SD: 15.8), exacerbation group: 83.3 (SD: 17).	
		ACT, N=78		using a CHESTAC-8800 (CHEST, Tokyo, Japan).		ACT score: non-exacerbation group: 23.6 (SD: 2.2), exacerbation group: 23.4 (SD: 1.8).	

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Shirai, 2008 [87]	Japan, cross sectional, outpatient setting, high risk of bias.	FeNO, N= 105 Classified by 5-item ACT questionnaire score. (Totally controlled =25, well controlled = 20-24, uncontrolled= 5-19).	Total controlled (N=45) Median age 54 years (35-62), male 42.2%, ever smoker 24.4%, current smoker 8.9%. Well controlled (N=28) Median age 57 years (43-67), male 32.1%, ever smoker 23.1%, current smoker 14.3%. Uncontrolled (N=32) Median age 49 years (36-62), male 32%, ever smoker 37.5%, current smoker 12.5%.	Measured by online nitric oxide analyzer (Sievers NOA 280i; Sievers, Boulder, Colorado) at 50 ml/sec.	FeNO were significantly lower in the totally controlled asthma group than in the uncontrolled asthma group. ACT score was negatively correlated with FeNO, however, it was a weak correlation (r= -0.310).	Total controlled Median 53 (44.5 to 64.5). Well controlled Median 61.9 (33.5 to 105.6). Uncontrolled Median 72.1 (45.9 to 142.8).	In adults with asthma on ICS for 3 months, ACT ability to differentiate controlled from uncontrolled was improved with FeNO
		Spirometry, N= 105			No significant differences were seen in %FEV_1 and FEV_1/ FVC between three groups. ACT score was positively correlated with %FEV_1 but not with FEV_1/FVC, however, it was a weak correlation FEV_1% pred (r 0.219).	FEV_1 % pred Total controlled median 93.4 (84.5 to 105.4). Well controlled median 87.9 (76.0 to 94.3). Uncontrolled median 86.4 (71.8 to 95.9). FEV_1/FVC Total controlled median 78.0 (66.9 to 84.9). Well controlled median 73.4 (66.4 to 80.6).	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Disease Activities and Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
						Uncontrolled median 73.2 (62.9 to 84.5).	
Szefler, 2008 [88]	United States, RCT, outpatient setting, low risk of bias.	FeNO monitoring, N= 276. (guideline-based care and FeNO)	Mean age 14.4 years (SD: 2.1), 52.9% males, Race: Black 66%, Hispanic 22%, other or mixed 11%.	Measured by a rapid-response chemiluminescent analyzer (flow rate 50 mL/s; NIOX System, Aerocrine, Sweden) according to the guidelines of the American Thoracic Society.	Maximum days with symptoms, which was our primary endpoint, did not differ between treatment groups over the study period (p=0·78). Control levels did not differ between groups. lung function, fraction of exhaled NO, and adherence did not differ between groups during the study; however, despite the level of control achieved, fraction of exhaled NO was less than 20 ppb in only 190 (35·6%) of 534 participants on at least 80% of visits during the treatment period.	306/534 patients (57·3%) had their asthma under good control (control level=1) for at least 80% of visits. In 122/534 patients (22·8%), asthma control was at level 3 or 4 for at least 20% of visits. (22·1% of FeNO monitoring Group and 23·6% of control group).	Patients aged 12–20 years with persistent asthma randomized to guideline based treatment vs treatment modified by FeNO (for 46weeks). Both groups had similar days with symptoms, and exacerbation rate. FeNO group had higher ICS doses.
		Control (guideline based care only), N=270	Mean age 14.4 years (SD: 2.1), 52.6% males, Race: Black 61%, Hispanic 23%, other or mixed 16%.				
van der Valk, 2012 [89]	Netherlands, Switzerland and Italy, longitudinal	FeNO, N=27	Moderate exacerbations (N=18): Mean age 11.7 years (SD: 2.5), 44.4% male,	Fractional exhaled nitric oxide was measured daily using a handheld airway inflammation monitor (NIOX MINO, Aerocrine,		Moderate exacerbations (N=18): 21 ppb (14 to 32).	In Children with asthma receiving daily measurements of FeNO,

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	nonrandomized, outpatient setting, medium risk of bias.		Weight 43.8 Kg (SD: 11.8). Severe exacerbations (N=9): Mean age 10.1 years (SD: 2.1), 22.2% male, Weight 37.6 Kg (SD: 11.1).	Solna, Sweden), along with daily symptom scores for 30 weeks at home		Severe exacerbations (N=9): 19 ppb (10 to 40).	slope and trends can predict exacerbations
		Spirometry N=27				Moderate exacerbations (N=18): FEV_1 86.7% pred (SD: 16.6) Severe exacerbations (N=9): FEV_1 78.7% pred (SD: 24.3).	
van Vliet, 2015 [90]	The Netherlands, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N =96	Age mean (range) 10 (6-17), 52 % males, 76 % atoptic asthma	FeNO was measured online using a NIOX analyzer (Aerocrine, Solna, Sweden) according to American Thoracic Society/European Respiratory Society (ATS/ERS) criteria. A standard flow rate of 50 ± 5 ml/sec was required for a correct maneuver.	Performance of, FeNO in prediction of asthma exacerbation	Estimate (95% CI) -0.011 (−0.029 to 0.007)	In asthmatic children on ICS, FeNO measured every 2 months did not predict exacerbations even when combined with inflammatory markers and clinical characteristics.
		ACQ Questionnaire, N=96		The ACQ was used to assess asthma control at the clinical visits. The cut-off points used for level of asthma control were: ACQ ≥ 0.75 (controlled asthma); 0.75< ACQ ≤1.5 (partly controlled); and ACQ >1.5 (uncontrolled	Performance of asthma clinical characteristics (ACQ score) in prediction of asthma exacerbation	Estimate (95% CI) 0.082 (- 0.424 to 0.589)	

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				asthma).			
		spirometry, N=96		Performed by means of the ZAN 100 spirometer, according to ATS/ERS standards (nSpire Health GmbH, Oberthulba, Germany). Recorded parameters included: FEV_1, forced vital capacity (FVC) and maximum expiratory flow at 50% of FVC (MEF50)	Performance of (Bronchodilator response, delta FEV_1 % predicted value) in prediction of asthma exacerbation	Estimate (95% CI) −0.047 (−0.104 to 0.011)	
Visitsunthorn, 2014 [91]	Thailand, cross-sectional study, outpatient setting, high risk of bias.	FeNO, N=114	Mean age 12.3 years (SD: 3.5), 61.4% males, BMI 20.21 (SD: 4.65), atopy 100%.	Measured by means of an electrochemical technique (ECO medics, CLD 88 sp, chemiluminescence NO-analyzer with optional ultrasonic flow meter). Carried out according to the manufacturer's and American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations, requires a single-breath on-line measurement with the mouthpiece in place.	The FeNO levels and log FeNO in patients with different asthma control status	uncontrolled group FeNO 39.15 ppb (2.40 to 192.30), partly controlled group FeNO 24.90 ppb (2.20 to 85.70) controlled group FeNO 19.20 ppb (5.10 to 108.90). The mean+ SD of Log FeNO in controlled group 1.295+0.31, partly controlled group 1.298+0.41 uncontrolled group 1.417+0.49	In children with asthma (mostly mild persistent), FeNO levels differentiated controlled, partly controlled and uncontrolled in those not on ICS (trend was not statistically significant in those on ICS)
		Spirometry, N= 114		Spirometry was performed using the standard method.			

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Visitsunthorn, 2017[92]	Thailand, prospoctive study, inpatient setting, low risk of bias.	FeNO, N = 70 Spirometry, N= 70	Overall Median age 12.6 year, 65.7% males, 100% atopics (allergic rhinitis). 18.6% develop asthma exacerbation (AE) vs 81.4%. * AE episode had to include at least one of the following: PEFR <20% of predicted; use of a beta-2 agonist for ≥2 days; use of systemic corticosteroids or an increase from a stable maintenance dose for ≥ 3 days; hospitalization or emergency-room visit that necessitated administration of systemic corticosteroids.	A single breath FeNO measured every 3 month using a CLD 88 Chemiluminescence Nitric Oxide Analyser with optional ultrasonic flow meter (ECO Medics, Dürnten, Switzerland) according to the (ATS/ERS). Spirometry was performed at first visit and every 3 months by standard method. FEV1 and FEV1/FVC ratio were expressed as absolute values and percentage of predicted values.	Baseline FeNO levels, FEV1 bronchodilator reversibility and FEF25–75% bronchodilator reversibility were significantly higher in 18.6% patients with AE within the next 12 months than in 81.4% those without AE. FeNO of 31 ppb provided optimal sensitivity and specificity for AE prediction than FEV1 reversibility and FEF25–75%.	Baseline level in AE vs without AE: FeNO (ppb): 35.6 vs 16.5. FEV1:7 vs 4 FEF25–75%: 34 vs 14 FeNO of 31 ppb for AE prediction: Sen 92.3% Spe 75.4% PPV 46.2% NPV 97.7%	Baseline FeNO level was significantly higher in asthmatic patients who experienced an asthma excaerbation within the next 12 months. The optimal cutoff point of FeNO level for the prediction of an AE is 31 ppb.
Voorend-van Bergen, 2015 [93]	The Netherlands, RCT, outpatient setting, high risk of bias.	FeNO, N= 266	FeNO Group (n=92) Mean age 10.3 years (SD: 2.9), 67 % males, 100 % atoptic. Web based mointoringgroup (n =91) Mean age 10.6 years (SD: 2.8), 66 % males,	FeNO was measured online on the NIOX chemiluminescence analyzer or NIOX MINO (Aerocrine, Stockholm, Sweden) according to guidelines, offline, Assessed using an electronic spirometer (Masterscreen, Jaeger, Würzburg, Germany) and	Mean difference was higher in web group than other groups.	FeNO change from baseline over time expressed as ratio of geometric means; FeNO group 1.40 Web group 1.64 Standard care	RCT of children with atopic asthma compared web-based monthly monitoring ACT vs FeNO and ACT every 4 months vs standard care.

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			100 % atoptic. Standard care Group (n=89) Mean age 10.2 years (SD: 3.2), 69 % males, 100 % atoptic.	expressed as percentage predicted or z-score according to= GLI2012		group 1.18	There was no statistically significant difference in terms of ACT or asthma free days. Lower ICS use was in the web based approach. QALYs and costs were not statistically significant
		Spirometry, N= 229			FEV_1 % pred mean difference was higher in standard care group than other groups.	FeNO group 0.16 Web group -0.10 Standard care group 0.26	
		Asthma Control Test, N= 269		Used the Dutch, translated and linguistically validated version of the ACT (MAPI-research institute, Lyon, France) in children from the age of 12 years, and the C-ACT for children aged 4–11 years	Mean difference was higher in web group than other groups.	FeNO group 0.12 Web group 1.73 Standard care group 0.37	
Warke, 2004 [94]	Ireland, cross sectional, outpatient setting, high risk of bias.	FeNO, N=133	Median age 9.9 years (range 5-14), 53.3% male.	Measured by online chemiluminescence analyzer (NOATM 280, Sievers Instruments Inc., Boulder, Colorado). The flow rate was 50 ml/s and this corresponded to a mouth pressure of 17 cm H2O.	FeNO levels (median [IQR] ppb) were significantly elevated in children who had recent symptoms compared with those without recent symptoms.	Recent symptoms (n = 101) 14.6 ppb [6.5 to 45.3]) vs those without recent symptoms (n=32) 6.0 ppb [3.2 to 17.4].	In children, FeNO levels differed significantly between the controlled and uncontrolled asthmatics and between the

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		Spirometry, N=133		Performing a forced expiratory maneuver (MicroLab 3300 spirometer, Micro Medical Ltd., Gillingham, UK).	The difference between medians was 8.6 ppb (95% CI for the difference 1.8 to 13.9, p = 0.004). However, there was a significant difference in FeNO levels between the controlled and uncontrolled group (difference between medians 17.9 ppb [95% CI for difference 0.1 to 22.8], p=0.03).		three treatment decision subgroups (up, down, or unchanged).
Yamashita, 2015 [95]	Japan. longitudinal cohort study, outpatient setting, high risk of bias.	FeNO, N=37	uncontrolled asthma (N= 18) mean age of 49.2, 33.4% males, 16.6% current smokers. controlled asthma (N= 19) mean age of 52.2, 23.3% males, 5.3% current smokers.	NIOX MINO© (Aerocrine AB, Solna, Sweden), at a constant flow rate of 50 mL/s.	Using a FeNO cut-off level of 34 ppb yielded a sensitivity of 76.5% and specificity of 73.7% for the achievement of full asthma control. AUC = 0.86.	uncontrolled 60.7ppb (SD35). controlled: 24.9 ppb (SD 14.5)	Using a FeNO cut-off level of 34 ppb yielded a sensitivity of 76.5% and specificity of 73.7% for the achievement of full asthma control.
		Gold standard, N=37		A positive indication of airway reversibility after inhalation of a short-acting β2 agonist, response to a provocative concentration of methacholine, or sputum eosinophil counts >3% or FeNO levels >22 parts per billion (ppb). Mild asthma was defined as a forced expiratory volume within 1 s (FEV_1.0			

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				predicted) of >80% at the first diagnosis of asthma.			
Yang, 2015 [96]	Korea, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N=145	Mean age 10.58 years (SD: 2.60), males 71%, BMI 19.15 (SD: 3.75), atopy 100%	FeNO was measured by an NO analyzer with electrochemical sensors (NIOX MINO; Aerocrine AB, Solna, Sweden), according to the ERS/ATS guidelines. Constant flow rate of 50 mL/s. FeNO was measured twice and a third measurement was performed if there is a more than 10% difference between first 2 measurements.	H-FeNO (mean (95% CI, ppb) (No loss of asthma control vs loss of asthma control) R21FeNO (%) mean (95% CI) (No loss of asthma control vs loss of asthma control)	32.98 (29.70 to 36.63) vs 59.82 (55.60 to 64.35) 22.80 (16.41 to 29.19) vs 58.10 (53.45 to 62.75)	In patients aged 8-16 years with atopic asthma serially monitored over 2 years, loss of asthma control was predicted by the highest FeNO of serial measurements and the rate of FeNO > 21 ppb.
		Spirometry, N=145		Lung function tests were performed with spirometer (Vmax SensorMedics, Yorba Linda, CA, USA) in accordance with ERS/ATS recommendations	L-%FEV_1 mean (95% CI) (No loss of asthma control vs loss of asthma control) L-FEV_1/FVC (%) mean (95% CI) (No loss of asthma control vs loss of asthma control)	84.40 (80.34 to 88.46) vs 78.03 (75.41 to 80.64) 79.63 (77.12 to 82.13) vs 74.16 (72.32 to 76.00)	

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Yavuz, 2012 [97]	Turkey, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 76	Mean age 8.7 years (SD: 1.4), 61.8% male.	Using an online NIOX-MINO; Aerocrine, Stockholm, Sweden at a flow of 50mL/sec. The mean value of three consecutive measurements was used for analysis. Bronchodilators withheld prior to FeNO test in 39.5 %.	A C-ACT score of 22 or less had 69% sensitivity and 77% specificity in determining not well-controlled asthma, whereas a FeNO value of 19 ppb or higher had 61% sensitivity and 59% specificity in patients who completed 3 visits.	**Baseline:** Well controlled asthma (N=40): 16 ppb (13–22) Not well controlled asthma (N=36): 20 ppb (13–28). **At 1 month:** Well controlled asthma (N=45): 18 ppb (12 to 26.5). Not well controlled asthma (N=19): 23 ppb (16 to 31). **At 2 months:** Well controlled asthma (N=39): 16 ppb (13 to 26) Not well controlled asthma (N=12): 21.5 ppb (14 to 69).	In children, multivariate analysis revealed that a C-ACT score of 22 or less (odds ratio, 8.75; 95% CI, 4.35–17.59) and a FeNO of 19 ppb or greater (odds ratio, 2.60; 95% CI, 1.07–6.29; P .03) were significant indicators for not well-controlled asthma.
		Spirometry, N= 76		Spirometry tests used ZAN100 spirometry system (nSpire Health, Longmont, Colorado)		**Baseline:** Well controlled asthma (N=40): FEV_1 96% pred (89 to 103) FEV_1/FVC 90% pred (84 to 94)	

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						Not well controlled asthma (N=36): FEV_1 84% pred (75 to 94) FEV_1/FVC 85% pred (80 to 94). **At 1 month:** Well controlled asthma (N=45): FEV_1 97% pred (89 to 102) FEV_1/FVC 91% pred (85 to 95). Not well controlled asthma (N=19): FEV_1 84% pred (74 to 94). FEV_1/FVC 87% pred (80 to 94). **At 2 months:** Well controlled asthma (N=39): FEV_1 93% pred (86 to 105) FEV_1/FVC 89% pred (83 to 94). Not well controlled asthma (N=12): FEV_1 78% pred	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Disease Activities and Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
						(76 to 85). FEV_1/FVC 83% pred (78 to 86).	
		Childhood Asthma Control Test (C-ACT), N= 76		The official Turkish version of the C-ACT questionnaire was administered. Children and parents answered their respective parts of the test separately, and the sum of their scores was used for analysis. Absolute values for the C-ACT scores are demonstrated, and changes in C-ACT scores are expressed as a percentage of the initial value.		**Baseline:** Well controlled asthma (N=40): 24 (21 to 26) Not well controlled asthma (N=36): 19 (17 to 21) **At 1 month:** Well controlled asthma (N=45): 25 (23 to 26) Not well controlled asthma (N=19): 20 (16 to 23) **At 2 months:** Well controlled asthma (N=39): 24 (22 to 26) Not well controlled asthma (N=12): 23 (21 to 25).	

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Zeiger, 2006 [98]	United States, RCT with cross-over, outpatient setting, unclear risk of bias.	FeNO, N= 99	Range age (6-13) years, Male 59%.	Measured by (78% online) NIOX Aerocrine AB – chemiluminescence,	FeNO decreased after 16 weeks of fluticasone propionate (FB) 100 mg BID, and montelukast (MT) 5-10 mg once a day but the decrease was greater after fluticasone. Change in FeNO correlated with improvements in asthma control days (ASDs) in fluticasone but not with montelukast.	Baseline 39.5 ppb (34.2 to 44.7) FP 20.6 ppb (15.0 to 26.2) MT 30.9 ppb (25.5 to 36.2) FP-MT mean difference -10.3 ppb (-16.9 to -3.7). FeNO vs ACDs FP -0.21 (-0.33 to -0.08) MT -0.04 (0.17 to 0.09)	Change in FeNO level significantly predicted asthma control days in children treated with fluticasone (but not montelukast)
		Spirometry, N= 126			Fluticasone (FB) led to significant improvements in prebronchodilator FEV/FVC while montelukast (MT) associated with a significant but small decrease. However, greater improvements in prebronchodilator FEV_1/FVC occurred after fluticasone (FB) than after montelukast (MT).	FEV_1/FVC % baseline 126 80.1 (79.1 to 81.1) FP 82.2 (80.9 to 83.6) MT 79.0 (77.6 to 80.5) FP-MT mean difference 3.2 (2.3 to 4.1)	

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		Asthma control questionnaire , N= 127			Compared with baseline, both fluticasone (FB) and montelukast (MT) treatments were associated with significant improvements in ACQ scores, but better control was achieved with fluticasone.	Baseline 0.96 (0.89 to 1.03) FP mean 0.59 (0.50 to 0.69) MT mean 0.76(0.66 to 0.87) FP- MT mean difference -0.17(-0.27 to -0.07)	
Zeiger, 2011 [99]	United States, cross section study, outpatient setting, medium	FeNO, N= 325	Group 1; 1st quartile of FeNO (7-19 ppb): (N=88) Mean age 37.2 years (SD: 14.5), 25% Male, 59.1% Allergic rhinitis 30.7% Atopic dermatitis	FeNO measurements were done using the NIOX MINO® handheld device (Aerocrine AB, Solna, Sweden)		Group 1: 15 ppb (7 to 19) Group 2: 25 ppb (20 to 28) Group 3: 37 ppb (29 to 47) Group 4: 72 ppb (48 to 215)	In atopic 12- to 56-year-old persistent asthmatics on ICS, higher FeNO levels significantly correlated with

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	risk of bias.	Spirometry, , N= 325	BMI 28.6 (SD: 7.9). Group 2; 2nd quartile of FeNO (20- 28 ppb): (N=77) Mean age 37.7 years (SD: 14.4), 41.6% male, 55.8% Allergic rhinitis, 27.3% Atopic dermatitis, BMI 28.2 (SD: 6.6). Group 3; 3rd quartile of FeNO (29- 47 ppb): (N=79) Mean age 36.4 years (SD: 14.8), 51.6% male, 60.8% Allergic rhinitis, 26.6% Atopic dermatitis, BMI 28.6 (SD: 6.5). Group 4; 4th quartile of FeNO (48- 215 ppb): (N=81) Mean age 31.4 years (SD: 14.8), 42% male 59.3% Allergic rhinitis, 32.1% Atopic dermatitis, BMI 27.6 (SD: 6.5).	Spirometry captured FEV_1, FEV_1% predicted, and FEV_1/FVC using the KOKO electronic Pneumotach spirometer (Ferraris Respiratory, Louisville, CO, USA) by ATS standards and over-reading for quality assurance. Age, gender, and ethnicity appropriate prediction equations were used to calculate the percent of predicted FEV_1.		FEV_1 Group 1: 89.4% pred (SD: 14.0) Group 2: 87.1 % pred (SD:14.1) Group 3: 84.8 % pred (SD:13.9) Group 4: 83.8 % pred (SD:16.8) FEV_1/FVC Group 1: 0.80 % pred (SD:0.08) Group 2: 0.77 % pred (SD:0.09) Group 3: 0.77 % pred (SD:0.08) Group 4: 0.74 % pred (SD:0.09)	more SABA dispensing and oral steroids courses in the past year, lower FEV (1) % predicted levels, but not ACT score.
		Asthma Control Test (ACT) score, N= 325		>19 controlled, 16–19 not well controlled, and <16 very poorly controlled		Asthma control test: 3-level categories (%) **Group 1:** controlled: 61.4 not well controlled: 18.2 very poorly controlled: 20.5 **Group 2:** controlled: 57.1 not well controlled: 20.8 very poorly controlled: 22.1	

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						Group 3: controlled: 75.9 not well controlled: 15.2 very poorly controlled: 8.9 **Group 4**: controlled: 48.1 not well controlled: 28.4 very poorly controlled: 23.5 Emergency department/urgent care (%) Group 1: 33 Group 2: 28.6 Group 3: 22.8 Group 4: 38.3 Hospitalization (%) Group 1: 2.3 Group 2: 7.8 Group 3: 0 Group 4: 11.1	

ACT: asthma control test; ACQ: Asthma control questionnaire; AUC: area under the curve; BHR: Bronchial Hyperreactivity; BMI: body mass index; CI: confidence interval; COPD: chronic obstructive pulmonary disease; EBC: Exhaled breath condensate; ED: emergency department; ERS/ATS recommendation: The European Respiratory Society/ American Thoracic Society recommendation; FEF: forced expiratory flow; FEF25–75: forced expiratory flow at 25–75% of forced vital capacity; Eos: Eosinophilia count; FeNO: fraction exhaled nitric oxide; FEV1: forced expiratory volume in the first second; FEV1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; IFN: Interferon; IgE: Immunoglobulin E; IL: Interleukin; IQR: interquartile range; LR: likelihood ratio; LTRA: Leukotriene receptor antagonist; NPV: negative predictive value; NR: Non-Reported; OR: odds ratio; PC15: provocation concentration causing a 15% fall in FEV1; PC20: provocation concentration causing a 20% fall in FEV1; PD15: provocation dose causing a 15% decline in FEV1; PD20: provocation dose causing a 20% decline in FEV1; PEF: he peak expiratory flow; PH: potential hydrogen; pMDI: pressurized Metered-Dose Inhaler; PPV: positive predictive value; R: correlation coeffieient; RCT: randomized clinical trial; ROC curve: receiver operating characteristic curve; SD: standard deviation; QALYs: Quality-Adjusted Life-Year.

Table C.3. Characteristics of the included studies in KQ 1b (Adherence)

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Disease Activities and Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Beck-Ripp, 2002 [100]	Germany, RCT, outpatient setting, high risk of bias.	FeNO, N= 31	Mean age 10.5 years (SD: 0.5), 51% male	Measured by on-line chemiluminescence analysis in the LR 2000 NO analyser (Logan Research, Rochester, Kent, UK).	Correlation between the reduction of FeNO and the compliance, with inhaled budesonide during the 4-week run-in period. Compliance calculated as (Pulmicort Turbohaler doses taken for each steroid treatment course / doses prescribed) x 100 (%).	A positive correlation was established between the patients' compliance to take their prescribed inhaled steroid medication and the reduction of FeNO. With a better compliance with budesonide a greater reduction of FeNO during the run-in period was observed ($p<0.01$, $r=0.59$).	FeNO values were associated with compliance to therapy in children.
		Spirometry, N= 31		Spirometry was performed in a Jager MasterLab (Jager, Wurzburg, Germany) and the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and mean maximal expiratory flow (MMEF) were measured according to the recommendations of the American Thoracic Society (ATS).			
Vijverberg, 2012 [101]	Netherlands, cross sectional, inpatient setting, medium risk of bias.	FeNO, N= 601	Mean age 9 years (SD: 2.2), 62.9% male, 80.1% atopy, 12.9% tobacco exposure, 88.5% were on ICS.	Online hand-held electrochemical analyzer (NIOX Mino; Aerocrine, Solna, Sweden) with an expiration time of 6 s. FeNO was dichotomized using a cutoff value of 25 ppb.	There was a very weak correlation between FeNO levels and total ACQ score (R= 0.13, p< 0.01). FeNO >25 ppb was associated with lower medication adherence rates (OR: 0.4; 95% CI 0.3 to 0.6), fewer antibiotic courses in the past year (OR:	FeNO median 13 ppb (7-27), >25 ppb in 26.8% and <5 ppb in 6% patients.	In children with asthma (mostly on ICS), high FeNO was associated with low adherence based on parental reported Medication Adherence Report Scale (OR: 0.4; 95%
		Asthma Control Questionnaire (ACQ), N=601		Asthma control was assessed using the 6-item version of the ACQ (symptoms plus rescue medication use). An ACQ score < 0.75 was considered 'well-controlled		Well controlled in 56.2% patients.	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Disease Activities and Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
				asthma', a score ≥0.75 was considered 'not well-controlled asthma'	0.6; 95% CI: 0.4 to 0.9), fewer leukotriene antagonists use in the past year (OR: 0.4; 95% CI: 0.2 to 0.9), and fewer visits to a Pulmonary pediatrician (OR: 0.6; 95% CI: 0.4 to 0.9).		CI: 0.3–0.6)

ACQ: Asthma control questionnaire; CI: confidence interval; ERS/ATS recommendation: The European Respiratory Society/ American Thoracic Society recommendation; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; ICS: inhaled corticosteroid; OR: odds ratio; R= correlation; SD: standard deviation.

Table C.4. Characteristics of the included studies in KQ 1c (Algorithm using FeNO to guide drug therapy for RCTs)

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Calhoun, 2012 [102]	United States, RCT with cross-over, outpatient setting, unclear risk of bias.	FeNO, N =324	Group 1: Physician Assessment based adjustment (PABA), (N=114) Mean age 34.2 years (SD: 11.9), 36.8% male, BMI 28.2 Kg/m2 (SD: 7.9), 85.1% atopic. Group 2: Biomarker - based adjustment (BBA), (N = 115) Mean age 34.8 years (SD: 11.3), 28.7% male, BMI 29 Kg/m2 (SD: 7.3), 86.1% atopic. Group 3: Symptom based adjustment (SBA), (N = 113) Mean age 36 years (SD: 12.2), 26.5% male, BMI 27.1 Kg/m2 (SD: 6.2), 82.3% atopic.	Every 6 weeks for 9 months.	Inhaled corticosteroid therapy adjusted based on FeNO or day-to-day symptoms.	Asthma exacerbation (including multiple episodes) rates did not differ among the treatment groups 0.23 (97.5% CI, 0.10 to 0.37) events/person-year for PABA vs 0.21 (97.5% CI, 0.10 to 0.32) for BBA and 0.12 (97.5% CI, 0.03 to 0.21) for SBA. The hazard ratio was PABA vs BBA 1.1 (97.5% CI, 0.4 to 2.8), PABA vs SBA 2.0 (97.5% CI, 0.8 to 5.4), BBA vs SBA 1.9 (97.5% CI, 0.7 to 4.9).	At 12 weeks: Group 1 (N=108): 21.38 (0.62) Group 2 (N=114): 18.88 (0.66) Group 3 (N=110): 20.78 (0.54)	In adults with mild to moderate asthma controlled by low-dose ICS, FeNO based or symptom-based or physician assessment-based adjustment of ICS had similar treatment failure.
		Sputum eosinophils, N =324					At 6 weeks: Group 1 (N=79): 0.40 (0 to 1.20) Group 2 (N=67): 0.20 (0 to 0.80) Group 3 (N=76): 0.40 (0 to 1.40)	
		Blood eosinophils /mm3, N =324					At 4 weeks: Group 1 (N=111): 132.0 (100.0 to 222.0) Group 2 (N=108): 178.5 (100.0 to 300.0) Group 3 (N=108): 169.0 (100.0 to 224.0)	
		Asthma Control Questionnaire, N =324		Scores on the Asthma Control Questionnaire range from 0 to 6, with a higher score indicating worse asthma control; the			At 12 weeks: Group 1: 0.72 (SD: 0.50) Group 2: 0.79 (SD: 0.54) Group 3: 0.73 (SD: 0.49)	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
				minimal clinically important difference (MID) is 0.5				
		Asthma Quality of Life Questionnaire , N =324		Scores on the Asthma Quality of Life Questionnaire range from 1 to 7, with a higher score indicating a better quality of life; the MID is 0.5			At 6 weeks: Group 1 (N=112): 6.27 (SD: 0.76) Group 2 (N=115): 6.16 (SD: 0.77) Group 3 (N=113): 6.25 (SD: 0.72)	
		Asthma Symptom Utility Index , N =324		Scores on the Asthma Symptom Utility Index range from 0 to 1, with a higher score indicating better asthma control; the MID is Unclear, but a difference of 0.3 is suggested to distinguish between mild to moderate and moderate to severe asthma.			At 12 weeks: Group 1: 0.90 (SD: 0.10) Group 2: 0.88 (SD: 0.12) Group 3: 0.90 (SD: 0.10)	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
De Jongste, 2009 [103]	Europe, RCT, outpatient setting, high risk of bias.	FeNO, N=151	FeNO group (adjust for FeNO and symptoms) (N= 77): Mean age 11.6 years (SD: 2.6), 59.7% 46 males, weight 43.4 Kg (SD: 12.5), Race 91% were white, 100% atopic.	Measured by (NIOX MINO; Aerocrine, Solna, Sweden). Measurements were performed daily. Measurement time was recorded by the device for later review.	30 weeks of ICS which doses were adjusted every 3 weeks on the basis of either FeNO and symptom	There were 372 ICS dose changes in the FeNO group, as compared with 174 in the symptom group. At the end of the study, the	Baseline FeNO: FeNO group: 27.5 ppb (15 to 54), symptom group: 32 ppb (15 to 59).	Children with atopic asthma were monitored daily for symptoms (vs symptoms and FeNO) over 30 weeks and ICS doses

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry, N=151	Symptom group (adjusted only for symptoms) (N=74): age 11.8 years (SD: 4.3), 73% males, weight 42.2 Kg (SD: 14.5), race 88% were white, 100% atopic.	All children recorded asthma symptoms in a palmtop electronic diary (PalmOne Tungsten W PDA equipped with TrialMax software; CRF Inc., Helsinki, Finland).	scores, or symptom scores alone.	FeNO group used 200 (0 to 500) mg, and the symptom group 200 (100 to 500) mg, of budesonide equivalent per day (P<0.0001 for both changes from baseline). The time course of ICS dose changes, and the change from baseline, did not differ significantly between groups (P = 0.76 at the end of the study for the changes from baseline). The ICS dose distribution at the end was similar in both groups. ICS could be stopped in 16 children in the FeNO group, and in 12 in the symptom group (P = 0.98).	Baseline FEV_1%: FeNO group: 55% pred (SD: 15) Symptom group: 55% pred (SD: 12). Baseline reversibility of FEV_1%: FeNO group: +7 % pred (SD: 11), symptom group: +6 % pred (SD: 7).	were adjusted by phone every 3 weeks. Both groups had similar outcomes in terms of symptoms and exacerbations.

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Hashimoto, 2011 [104]	Netherlands, RCT, outpatient setting, high risk of bias.	FeNO, N= 51	Group 1: Internet-based management group (N=51) Mean age 48.5 years (SD: 12.4), 45% male, 41.2% current smokers BMI 28.3 Kg/m2 (SD: 5.4), 45% atopic Group 2: Conventional management group (N=38) mean age 52.4 years (SD: 11.7), 47% male, 44.7% current smokers, BMI 30 Kg/m2 (SD: 8.8), 50% atopic.	Online hand-held NO analyser (Niox Mino; Aerocrine AB, Solna, Sweden) before medicine intake on a daily basis for 6 months. In group 2 the test was done on a monthly basis	36 months of daily oral prednison 10 mg/day (5-15).	ACQ and FeNO contributed to the decisions of the computer algorithm in 84% and 16% cases, respectively.	Baseline: Group 1: 38 ppb (18 to 81) Group 2: 34 ppb (13 to 75)	In adults with prednisone-dependent asthma, an internet-based management tool including home monitoring of symptoms, lung function and FeNO in severe asthma is superior to conventional treatment in reducing total corticosteroid consumption without compromising asthma control or asthma-related quality of life.
		Spirometry, N= 51		Lung function was done hand-held spirometer (Piko-1; Ferraris Respiratory, Hertford, UK). In group 2 the test was done on a monthly basis			FEV_1 baseline Group 1: 76.3 % (SD: 24.7) Group 2: 71.3 % (SD:21) FVC baseline Group 1: 113 % (SD:11.1) Group 2: 94 % (SD:15.5) FEV_1/FVC baseline Group 1: 0.63 % (SD:0.18) Group 2: 0.69 % (SD:0.49)	
		Juniper Asthma control questionnaires (ACQ) score, N= 51		Asthma control questionnaires (ACQ) were completed weekly. In group 2 the test was done on a monthly basis			Mean difference Group 1: 0.26 (SD: 0.09) Group 2: 0.12 (SD:0.12)	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Juniper Asthma-related quality of life questionnaires (AQLQ) score, N= 51		Asthma-related quality of life questionnaires (AQLQ) were completed at baseline and every 3 months thereafter. In group 2 the test was done on a monthly basis			Mean difference Group 1: -0.03 (SD:0.10) Group 2: 0.14 (SD:0.13)	
Honkoop, 2015 [105]	Netherlands, RCT, outpatient setting, high risk of bias.	FeNO, N=611	Partly Controlled group (PCa) (N= 219): Mean age 38.9 years (SD: 9.3), 31.6 % males, BMI 26.8 Kg/m2 (SD: 5.9), 13% current smoker. Controlled group (Ca) (N= 203) Mean age 39.9 years (SD: 9.8), 34.2 % males, BMI 26.0 kg/m^2 (SD: 4.9), 16% current smoker. FeNO controlled group (FCa) (N= 189) Mean age 39.5 years (SD: 9), 27.7 % males, BMI 26.1 kg/m^2 (SD: 5.1),	Measured by NIOX MINO (Electro-chemical), at an exhalation flow rate 50 ml/sec.	Treatment decisions were based on a dedicated algorithm for each strategy. Medication classified as an asthma treatment step ranging from 0 (only short-acting b-agonists) to 5 (oral prednisone) based on the US National Asthma Education	Quality of life using EuroQol classification system (EQ-5D) (95% CI)	PCa group 0.89 (0.88 to 0.90) Ca group 0.91 (0.90 to 0.91) FCa group 0.90 (0.89 to 0.90)	Adults randomized to an algorithm that uses FeNO + asthma controlled questionnaire to adjust treatment had better symptom control, lower medication use and was cost-effective, compared with strategies using only the questionnaire. Quality of life and exacerbations were similar.
						Intervention costs (dollars)	PCa group $ 0. Ca group $ 0. FCa group $ 105.	
						Asthma-related visits (dollars, 95% CI)	PCa group $ 269 (234 to 304) Ca group $ 281 (257 to 308) FCa group $ 224 (205 to 242)	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
			14% current smoker		and Prevention Program guideline.			
						Asthma medication (dollars, 95% CI)	PCa group $ 452 (427 to 479) Ca group $ 551 (526 to 588) FCa group $ 456 (429 to 482)	
Malerba, 2015 [106]	Italy, RCT, outpatient setting, unclear risk of bias.	FeNO, N= 28	Group A: treatment according to FeNO and sputum eosinophils (N= 14) mean age age 45.2 years (SD: 31.2), 36 % males, 21% ever smoker. Group B: treatment according to clinical score (N= 14) Mean age 46.7 years (SD: 30.1), 43 % males, 29% ever smoker.	measured with a high-resolution chemiluminescence NO analyzer (Ecomedics AG CLD88; Ecomedics; Durnten, Switzerland). Measurements were carried out according to the ATS guidelines using a standardized method for the single-breath online measurement of FeNO in adults.	24 months of adjusted inhaled corticosteroids (ICS) treatment.	Compared with baseline, mean FeNO at 24 months were reduced in both groups but were lower in the group A.	Group A At baseline 56.2 (SD: 33.8) At 12 month 22.6 (SD: 10.5) At 24 month 18.2 (SD: 5.3) Group B At baseline 48.3 (SD: 19.7) At 12 month 51.6 (SD: 41) At 24 month 39.8 (SD: 29.4)	Adults with eosinophilic asthma randomized to treatment based on FeNO and sputum eosinophils had lower mean symptom score and exacerbations without increase in ICS treatment.
		Symptom				Compared	Group A	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		score, N= 28				with baseline, mean symptom scores at 24 months were reduced in both groups but were lower in the group A.	At baseline 28.7 (SD: 7.3) At 12 month 9.1 (SD: 1.8) At 24 month 8.1 (SD: 1) Group B At baseline 27.8 (SD: 6.7) At 12 month) 13.4 (SD: 3.4) At 24 month) 11 (SD: 2.6)	
		Spirometry, N= 28				Compared with baseline, mean FEV_1 % pred at 24 months were increased in both groups but were higher in the group A.	Group A FEV_1 at baseline 99.3% (SD: 19.7). FEV_1 at 12 month 104.4% (SD: 11.8) FEV_1 at 24 month 107.6% (SD: 12.1) Group B FEV_1 at baseline 96.2% (SD: 10.6). FEV_1 at 12 month 102% (SD: 12.4). FEV_1 at 24 month 100.5% (SD:	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
							11.6)	
Peirsman, 2014 [107]	Belgium, RCT, outpatient setting, high risk of bias.	FeNO, N= 99	Clinical group (N=50) Mean age 10.7 years (SD: 2.1), 66 % males, 19.5% tobacco exposure. FeNO group (N=49) Mean age 10.6 years (SD: 2.2), 67 % males, 11.6% tobacco exposure.	Measured by NIOX MINO (Electro-chemical), at an exhalation flow rate of 50 ml/sec.	In the clinical group, asthma control and treatment adjustments during each visit were determined by the reporting of symptoms. In the FeNO group, FeNO measurements were primarily used to adjust the treatment.	Number of asthma exacerbations over 1 year, count	Clinical group 35/ 1 year FeNO group 18/ 1 year	Children randomized to a FeNO based algorithm (lowering FeNO below 20 ppb) had fewer exacerbations than a comparison group in which treatment was adjusted based on clinical and spirometry parameters based on the GINA guidelines. FeNO did not improve symptom free days and was associated with an increased leukotriene receptor antagonist use and higher inhaled corticosteroid
						Percentage of Symptom-free days, median (interquartile range)	Clinical group 79.6% (51.7 to 94.0) FeNO group 83.7% (27.1 to 91.9)	
						Number of children with >1 hospital admission, count/total (%)	Clinical group 2.3% FeNO group 2.3%	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
								doses.
Petsky, 2015 [108]	Australia, RCT, outpatient setting, low risk of bias.	FeNO, N= 63	Group 1: Treatment strategy based on FeNO levels, adjusted for atopy (N=31): Median age 10.17 years (range 6.56 to12.69), 58.1% male, 74% atopic. Group 2; The symptoms-based management (N=32): Median age 10.08 years (range 6.25 to 12.44), 40.6% male, 87.1% atopic.	Measured with a chemiluminescence analyser (Sievers NOA 280i, Colorado, USA) with children exhaling at 0.05 L/sec for >4 sec in order to obtain a stable NO value for >2 sec. Patients were followed up for 12-months, with monthly visits for the first 4 months and every 2 months thereafter. At each visit patients assessed with FeNO first, then spirometry before and after 400 mg inhaled salbutamol.	Fluticasone and Budesonide (different doses based on specific hierarchy). The difference between final and baseline dose: Group 1: 0 (-175, 100) Group 2: -200 (-300, 100) (P= 0.139). The cumulative dose per child-year: Group 1:	FeNO values not significantly different between the groups at the end of, or at any time point of the study.	Baseline: Group 1: 24.00 (10.92 to 48.45) Group 2: 25.60 (13.40 to 53.70) ≥1 exacerbation over the study period Group 1: 6 Group 2: 15 ≥2 exacerbations per year: Group 1: 3 Group 2: 5	Taking atopy into account when using FeNO to tailor asthma medications is likely beneficial in reducing the number of children with severe exacerbations at the expense of increased ICS use. The strategy is unlikely beneficial for improving asthma control.
		Spirometry, N= 63		Spirometry was performed using		FEV_1 % predicted	FEV_1 Baseline: Pre-	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
				ATS criteria and % predicted based on local age and sex matched reference values in Hong Kong and Eigen from Australian data (Hibbert (children ≥8 years) in Brisbane.	168,000 (93000, 210000) Group 2: 105000 (73500, 156000) (P= 0.016).	values not significantly different between the groups at the end of, or at any time point of the study.	bronchodilation: Group 1: 92.10 (85.20 to 102.90) Group 2: 88.00 (83.65 to 104.15) Post-bronchodilation Group 1: 97.30 (88.90 to 101.35) Group 2: 91.50 (82.30 to 105.4)	
		Asthma symptom score, N= 63		The asthma scores were quantified by entering the numerical answer into a spreadsheet and average obtained for the previous month.			Baseline: Group 1: 3.0 (0 to 13.38) Group 2: 6.75 (1.13 to 23.0) At 12 months: Group 1: 0 (0 to 8.75) Group 2: 0 (0 to 17.25)	
Pijnenburg, 2005[109]	Netherlands, RCT, outpatient setting, high risk of bias.	FeNO, N=85	FeNO Group (treatment were made on both FeNO and symptoms) (N= 39) mean age 11.9 years (SD: 2.9), 64.1% males, Weight 43.2 kg (SD: 15.0)	FeNO was measured online according to guidelines from the European Respiratory.	Inhaled corticosteroids (≥400 or ≤400 mg budesonide or equivalent daily dose).	No FeNO significant change was found Within the FeNO group adjusted for baseline, whereas in the symptom group, there	FeNO group Ratio of geometric means 1.32 (95% CI, 1.04 to 1.68). Symptom group From 30.8 to 36.7 ppb.	In children with asthma, 1 year of steroid titration based on FeNO did not result in higher steroid doses but did improve
		Spirometry, N= 85		Measured by Masterscreen				

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
			Symptom Group (treatment were made only on symptoms) (n=46) Mean age 11.9 years (SD: 2.9) 65.2% males, Weight 48.5 kg (SD: 18.8).	electronic spirometer (Jaeger, Wurzburg, Germany).		was a significant increase in FeNO. However, at all-time points, FeNO correlated strongly with later FeNO values in the same subjects (all p< 0.001).		airway hyper-responsiveness and inflammation
Pike, 2013 [110]	United Kingdom, RCT with cross-over, outpatient setting, low risk of bias.	FeNO, N= 90	Group 1: FeNO-driven therapy (N=44) Mean age 10.51 years (SD: 2.62), 47.7% male, 9.1% tobacco exposure 81.1% atopic. Group 2: Standard management (N=46) Mean age 11.42 years (SD: 2.69), 65.2% male, 13% tobacco exposure, 88.4% atopic.	Using an online chemiluminescence portable monitor (NIOX MINO; Aerocrine, Solna, Sweden) through several visits (two times monthly) during 12 months period.	Inhaled corticosteroid dose (400–800 mcg/day or >800 mcg/day beclomethasone equivalent) according to symptoms control. Median initial corticosteroid	Neither group experienced a significant change in FeNO during follow-up.	FeNO changes Group1 3.1 ppb (-5.5 to 11.6) Group2 3.3 ppb (-8.5 to 15.1) Median number of exacerbations: Group 1: 3 (range 1–5). Group 2: 2 (range 1–4). Percentage of patients with exacerbation: Group 1: 84.1%.	Children with moderate to severe asthma randomized to FeNO-driven therapy (adjustment of ICS and LABA) or to a standard management group (driven by conventional markers of asthma control). No difference

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry, N= 90			dose: Group 1: 750 ug (400 to 1000) Group 2: 800 ug (400 to 1000) Median final corticosteroid dose: Group 1: 800 ug (400 to 1000) Group 2: 500 ug (400 to 1000)	There is no significant change different in FEV_1, FVC or FEF 25–75% during follow-up between groups.	Group 2: 82.6%. Of these, severe exacerbation ≥ 8 hours admission: Group 1: 11.4%. Group 2: 6.5%.	was found between the two groups in either change in corticosteroid dose or exacerbation frequency. Results were similar in atopic asthmatics.

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Powell, 2011 [111]	Australia RCT, outpatient setting, low risk of bias.	FeNO, N= 220	Group 1; FeNO-guided asthma management (N=111) All pregnant women, mean age 28.1 years (range 27.12–29.09), 37.9% ex-smoker, BMI 27.9 Kg/m2 (range 24.1–32.4), 41.4% were on ICS, 75.2% atopic Group 2; Clinical guideline algorithm (N=109) All pregnant women, mean age 28.8 years (range 27.72–29.84), 40.2% ex-smoker, BMI 28.7 Kg/m2 (range 24.1–32.8), 43.1% were on ICS, 76.2% atopic,	using an online chemiluminescence ECOMEDICS, Duernten, Switzerland at a flow rate of 50 mL/sec, monthly visit for 5 months.	Inhaled corticosteroid titrate based on FeNO levels. Median Beclomethasone dipropionate equivalent ICS dose (µg per day) Baseline: Group 1: 800 (400–1600) Group 2: 800 (400–1600) At 23 weeks: Group 1: 200 (0 to 400) Group 2: 0	ER/labor ward visit: Group 1: 0.04 (0.001 to 0.07) Group 2: 0.02 (-0.01 to 0.04) Hospital admission: Group 1: 0 (0 to 0) Group 2: 0.03 (-0.004 to 0.06) Unplanned or unscheduled doctors visit: Group 1: 0.26 (0.16 to 0.36) Group 2: 0.56 (0.40 to 0.72)	FeNO at baseline: Group 1: 13.9 (6.6 to 32.0) Group 2: 13.1 (7.5 to 24.0) FeNO at the end of the study: Group 1: 10.55 (5.95 to 19.3) Group 2: 11(5.9 to 21.4)	Pregnant, non-smoking women with asthma were randomly assigned before 22 weeks' gestation to treatment adjustment at monthly visits by an algorithm using clinical symptoms or FeNO to uptitrated (FeNO >29 ppb) or down titrate (FeNO <16 ppb) ICS. The exacerbation rate was lower in the FeNO group (incidence rate ratio
		Spirometry, N= 220					FEV_1% at baseline Group 1: 95.10 % (92.76 to 97.44) Group 2: 96.12 % (93.49 to 98.73) FEV_1 at the end of the study: Group 1: 96.4 % (94.31 to 98.46) Group 2: 94.4 % (91.84 to 96.96)	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Asthma Quality of Life Questionnai (AQLQ-M), N= 220		Asthma Quality of Life Questionnaire_ Marks; Good=0, poor=10.	(0 to 800)		AQLQ Group 1: 0.75 (0.38 to 1.25) AQLQ Group 2: 0.81 (0.38 to 1.63)	0.496, 95% CI 0.325-0.755, NNT=6). Quality of life and neonatal hospitalizations were also better with FeNO approach.
Shaw, 2007 [112]	United Kingdom, RCT, outpatient setting, low risk of bias.	FeNO, N= 118	FeNO group: therapy based on FeNO (N=58) Median age 50 years (20-75), 69% male, BMI 27.5 Kg/m2 (SD: 5.02), 22% ever smokers, Oral steroid courses in last yr/patient (mean ± SD): 1.2 ± 2.0 62% atopic Symptom group: therapy based on British Thoracic Society guidelines (N=60) Median age 52 years (24-81), 67% male, BMI 28.1 Kg/m2 (SD: 5.43), 25% ever smokers, 70% atopic	using a Niox chemiluminescence analyser (Aerocrine, Stockholm, Sweden), at a flow of 50 mL/sec, through several visits (every 2-4 weeks) during 12 months period.	Corticosteroid therapy in stepwise reduction fashion.	The total amount of inhaled corticosteroid used during the study was 11% greater (95% CI, 15 to 37%; p 0.40) in the FeNO group compared with the control group.	Exacerbations Group 1: 12 patients Group 2: 19 patients	Adults with a primary care diagnosis of asthma were randomized to corticosteroid therapy based on either FeNO measurements or British Thoracic Society guidelines. There was no significant difference in exacerbations. The final daily dose of ICS was lower in the FeNO group (557 vs. 895 g; mean difference, 338 g; 95%

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
								CI, 640 to 37; p 0.028).
Smith, 2005[113]	New Zealand, RCT, unclear risk of bias.	FeNO, N= 94	Overall mean age 45 years (12 to 73). FeNO group (N=46) and Control group (N= 48).	Measured with 15 ppb used as the cutoff point for controlled vs uncontrolled, at 250 ml/sec.	12 months of upward adjusted daily dose of Fluticasone 292 to 370 µg (FeNO group) and 567 to 641 µg (control group).	No significant differences between groups.	FeNO group Baseline 8.2 (7 to 9.5) 12 months 8.6 (7.5 to 9.9). Control group Baseline 6.5 (5.2 to 1.8) 12 months 7.6 (6.4 to 9.1).	In adults, With the use of FeNO measurements, maintenance doses of inhaled corticosteroids may be significantly reduced without compromising asthma control.
		Clinical outcomes, (exacerbation), N= 94				A non-significant reduction in the FeNO group compared with control.	FeNO group 0.49 episode per patient per year (0.20 to 0.78). Control group 0.90 episode per patient per year (0.31 to 1.49).	
		spirometry, N= 94		According to the American Thoracic Society criteria.		No significant differences in FEV_1% pred in the two groups.	FeNO group FEV_1% pred Baseline 85.2 (79.4 to 91). 12 months 86.1 (80.6 to 91.6). Control group Fev1% pred	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
							Baseline 83.8 (77.5 to 90.1). 12 months 82.3 (75.8 to 88.8).	
		Sputum eosinophilia, N= 94				No significant differences in sputum eosinophils. At 12 months, 65.8% in the FeNO group and 65.9 % in the control group had sputum eosinophil counts of < 3%.	FeNO group Baseline 2.5 (1.7 to 3.7). 12 months 1.1 (0.7 to 1.8). Control group Baseline 1.7 (1 to 2.8). 12 months 1.2 (0.7 to 2).	
Syk, 2013 [114]	Sweden, RCT, outpatient setting, high risk of bias.	FeNO, N= 181	Group 1: FeNO guided treatment (N= 93) Mean age 40.9 years (SD: 11.8), 51.6% male, 0% current smoker, BMI 27.0 Kg/m2 (SD: 5.08), 100% atopic. Group 2: Usual care (N=88) Mean age 41.1 years (SD: 12.9), 52.3% male, 0% current smoker,	using an online Chemiluminescence NIOX MINO; Aerocrine AB, Solna, Sweden) at a flow rate of 50 mL/sec, Cutoff levels were based on data that showed that most healthy subjects had FeNO levels below 20 ppb and on the suggestion that levels above	Median Budesonide equivalent ICS dose (ug/d) Baseline: Group 1: 400 (400-800) Group 2: 400 (400-800) At 1 year: Group 1: 0 (-400 to	Exacerbations after 1 year: Moderate (≥1 event) Group1: 8.6% Group2: 22.7% Severe (≥1 event) Group 1: 8.6% Group 2: 6.8% Any (≥1	FeNO Change after 1 year Group 1 (N=87): -2.57 (SD: 20.94) Group 2 (N=78): -1.46 (SD: 23.86)	Primary care adult patients randomized to an algorithm that adjusts ICS and leukotriene receptor antagonists based on FeNO had lower exacerbation rate and improved symptom

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
			BMI 26.1 Kg/m2 (SD: 4.79), 100% atopic.	approximately 25 ppb are associated with eosinophilic inflammation.	400) Group 2: 0 (-200 to 200)	event) Group1: 16.1% Group2: 28.4% No. of exacerbations / patient/y (95% CI): Group 1: 0.22 (0.14 to 0.34) Group 2: 0.41 (0.29 to 0.58)		control without increasing overall inhaled corticosteroid use (compared with control group)
		Spirometry, N= 181					FEV_1 % pred change after 1 year: Group 1 (N=88): -0.034 (SD: 0.28) Group 2 (N=78): -0.006 (SD: 0.28) FVC % pred change after 1 year: Group 1 (N=88): -0.084 (SD: 0.35) Group 2 (N=78): -0.019 (SD: 0.29) FEV_1/FVC % Change after 1 year: Group 1 (N=88): 0.009 (SD: 0.057) Group 2 (N=78): 0.002 (SD: 0.054)	
		Asthma Control Questionnaire score, N= 181		Juniper 6-item Asthma Control Questionnaire			Change after 1 year: Group 1 (N=81): -0.17 (-0.67 to 0.17) Group 2 (N=74):	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
							0 (-0.33 to 0.50)	
		Mini Asthma Quality of Life Questionnaire, N= 181		Juniper Mini Asthma Quality of Life Questionnaire			Change after 1 year: Group 1 (N=80): 0.23 (0.07 to 0.73) Group 2 (N=77): 0.07 (-0.20 to 0.80).	
		Gothenburg Quality of Life Instrument, N=181		Generic quality of life.			Change after 1 year: Group 1 (N=85): 0.06 (-0.22 to 0.28) Group 2 (N=78): 0 (-0.39 to 0.39).	
Verini, 2010 [115]	Italy, RCT, high risk of bias.	FeNO, N= 32 (therapy was assessed by FeNO measurements and GINA guidelines)	Mean age 10.7 years (SD: 2.4), 56.2% male.	Measeured by online chemiluminescence assay (Ecomedics CLD 88), according to ATS-ERS, at 50 ml/sec.	12 months of inhaled corticosteroid (N= 20), antileukotrienes (N= 8) or none (N= 5).	Asthma Severity score (ASS) and Asthma Exacerbation Frequency (AEF) significantly decreased at 6 months, however, there was no increase in Asthma therapy score (ATS) over time.	**ASS mean** baseline 1.09 (SD: 0.81) 6 month 0.56 (SD: 75) 12 months 0.75 (SD: 0.95) **AFE mean** baseline 1.96 (SD: 1.18) 6 month 1 .01 (SD: 0.96) 12 months 0.83 (SD: 0.98) **AST mean** baseline 1.5 (SD: 0.7) 6 month	In children with allergic asthma, a strategy of FeNO monitoring (vs GINA based management) reduced asthma severity score and asthma exacerbation score.

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
							1.43 (SD: 0.7) 12 months 1 .53 (SD: 0.6).	
		GINA, N= 32 (therapy was assessed based on symptoms, short acting β2-agonist use, and lung function, according to GINA guidelines).	Mean age 11.3 years (SD: 2.1), 56.2% male		12 months of inhaled corticosteroid (N= 15), antileukotrienes (N= 3) or none (N= 4).	No difference was detected in ASS and AFE in the corresponding times. However, asthma therapy score (ATS) was significantly step up at 6 month.	**ASS mean** Baseline 1.09 (SD: 0.77) 6 month 0.93 (SD: 0.61) 12 month 0.92 (SD:0.82) **AFE mean** baseline 2.01 (SD: 1.17) 6 month 1.78 (SD: 1.29) 12 months 1.85 (SD: 1.34) **AST mean** baseline 1.03 (SD: 0.9) 6 month 1.62 (SD: 0.6) 12 months 1.4 (SD: 0.7).	

ACQ: Asthma control quiestionaire; BMI: body mass index; CI: confidence interval; 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; FEV_1% pred: forced expiratory volume in the first second percentage predicted, FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: Long acting Beta-agonist; PEF: peak expiratory flow; RCT: randomized clinical trial; SD: standard deviation.

Table C.5. Characteristics of the included studies in KQ 1c (Algorithm using FeNO to guide drug therapy NON-RCTs)

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Griese, 2000 [57]	Germany, prospective nonrandomized, outpatient setting, low risk of bias.	FeNO, N=74	Mean age 9.7 years (range 4-16), 76.1 % males, 100 % atoptic.	FeNO was measured online with a chemiluminescence analyzer (Logon LR 2000, Rochester, Kent, UK) sensitive to ENO at concentrations of 1-5000 parts per billion (ppb, by volume). The response time (10-90%) was <0.65 sec.	Step wise approach system.	FeNO in relation to the recommended change in inhaled therapy.	FeNO > 13ppb = Step up (24) vs No change (8) vs step down (5). FeNO < 13ppb= Step up (12) vs No change (11) vs step down (13).	In children, FeNO values above 13 ppb weakly correlated with the changes in asthma therapy and had modest sensitivity of 0.67 and a specificity of 0.65 to predict a step up in therapy.
		Spirometry, N=74				FEV_1 in relation to the recommended change in inhaled therapy.	FEV_1< 80% pred = Step up (6) vs No change (1) vs step down (1). FEV_1> 80% pred= Step up (26) vs No change (12) vs step down (17).	
		Symptom score, N=74				Symptom score in relation to the recommended change in inhaled therapy.	Symptoms Yes = Step up (34) vs No change (15) vs step down (11). Symptoms no = Step up (2) vs No change (4) vs	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
							step down (8).	
Laforce, 2014 [116]	United States, observational, outpatient setting, high risk of bias.	FeNO, N =50	Mean age 35.1 years (SD: 15.81), 40 % male, BMI 27.4 kg/m^2 (SD: 6.2), 30% ex-smoker,	Measurement was obtained (NIOX MINO, Aerocrine AB, Solna, Sweden)	94% were on short acting B-agonists, 40% on long acting B-agonists combined with anti-inflammatory medication, and 16% on leukotriene receptor antagonists.	Asthma medication changes based on FeNO results.	No medication change (64%), added medication or increased medication dose (20%), and Subtracted medication or decreased medication dose (16%).	Treatment decisions made in a single office visit based on a single FeNO test in 50 asthmatics led to change in therapy (augmentation in 20% and reduction in 16%) and were estimated to reduce cost by $629 per patient per year.
		Asthma control test (ACT) scores, N =50				FeNO values by ACT scores	ACT scores ≤19= FeNO 40.3 ppb (SD: 50.84). ACT scores ≥19= FeNO 26.1 ppb (SD: 21.96).	
		Spirometry, N = 50				FeNO values by FEV_1	≤80% Predicted= FeNO 41.1 ppb (SD: 46.92). >80% Predicted= FeNO 41.1 ppb (SD: 46.92).	
Malerba, 2008 [117]	Italy, longitudinal nonrandomized study, medium risk of bias.	FeNO, N= 14	Mean age 43.9 years (SD: 10.1), 43% male, Weight 67.2 Kg (SD: 10.8), 43% ever smokers, 0% current smokers 100% Eosinophilic phenotype.	Online chemiluminescence nitric oxide analyzer (Ecomedics AG CLD88; Ecomedics. Durnten, Switzerland), at a flow of 50 mL/sec, through several	12 months of Inhaled corticosteroids in a stepwise fashion according to FeNO and sputum eosinophilia values.	There is a significant positive correlation between FeNO and sputum Eosinophilia (r= 0.49, P < 0.01 at baseline; r=	Baseline: 57 ppb (SD: 33) At 3 months: 26 ppb (SD: 16) At 6 months: 17 ppb (SD: 8) At 12 months: 22 ppb (SD: 10)	Adults with mild-moderate persistent asthma treated based on FeNO and sputum eosinophils had fewer symptoms and

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
				visits during 12 months period, 4 weeks washout.		0.53, P < 0.01 at 3 months; r= 0.28, P < 0.01 at 6 months). Also, there is a significant positive correlation between FeNO and sputum eosinophilia mean difference at 6 months (r = 0.41, P < 0.01) but not at 3 months (r = 0.06, P = 0.39). Mean number of exacerbations was significantly lower		exacerbations compared with the previous year in which they were treated conventionally
		Spirometry, N= 14		Spirometry and maximal fill flow-volume curve were obtained using a pneumotachograph with volume integrator (CAD/ Net system 1070; Medical Graphics Corporation; St. Paul, MN). Static lung volumes were measured by means of the multibreath nitrogen washout method.			FEV_1 baseline: 99% pred (SD: 20) At 3 months: 101% pred (SD:17) At 6 months: 103 % pred (SD:15) At 12 months: 105 % pred (SD:12) FEV_1/FVC Baseline: 91 % pred (SD:11) At 3 months: 91 % pred (SD:10) At 6 months: 93 % pred (SD:10) At 12 months: 95 % pred (SD:7)	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Sputum eosinophilia (sEOS), N =14		Subjects were pretreated with inhaled salbutamol (200 ug by metered-dose inhaler), and 10 min later hypertonic (4.5%) sterile saline nebulized solution was inhaled for three periods of 5 min at most by means of an ultrasonic nebulizer (Ultraneb 2000; DeVilbiss; Somerset, PA). The subjects were instructed to cough sputum into containers. If any symptom occurred, nebulization was discontinued. The cutoff for an abnormal result was defined when sEos count was > 3% as percentage cells.		compared to baseline (3 vs 9 exacerbations, P < 0.001).	Count at Baseline: 27% (SD: 27) At 3 months: 13% (SD: 15) At 6 months: 4% (SD: 3) At 12 months: 3% (SD: 3)	
Malerba, 2012 [118]	Italy, longitudinal nonrandomized,	FeNO, N= 14	Mean age 44.9 years, 42.9% male 42.9% ex-smokers, Mean weight 67.2 Kg,	Using an online high-resolution chemiluminescence nitric oxide	Median beclomethasone equivalent:	No changes were observed in the frequency	FeNO (ppb) at Baseline: 20.7 At 6 months: 26.1	Titration of ICS based on FeNO and sputum

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
	inpatient setting		64.3% atopic	analyzer (Ecomedics AG CLD88; Ecomedics; Dumten, Switzerland). Values of FeNO included from 4 to 20 ppb were considered within normal limits.	At baseline: 500 ug At 6 months: 750 ug At 12 months: 500 ug.	of clinical asthma exacerbations (3, 4 and 3 exacerbations at baseline, 6 month, and 12 month visit, respectively).	At 12 months: 19.8	eosinophils in adults with mild-to-moderate persistent asthma was associated with reduction in symptom scores and ICS dosage.
		Spirometry, N= 14		Spirometry and maximal full flow-volume curve were obtained using a pneumotachograph with volume integrator (CAD/ Net system 1070; Medical Graphics Corporation, St. Paul, MN, USA).			FEV_1 % pred at baseline: 99.5 At 6 months: 98 At 12 months: 100 FEV_1/FVC % pred at baseline: 94 At 6 months: 92 At 12 months: 93	
		Methacholine challenge test (PD20), N= 14		The methacholine challenge was performed as a dose-response curve by increasing (doubling) doses of methacholine chlorohydrate (starting with 12.5 ug) every 3 min. The test was stopped when the			PD20 (ug) at baseline: 714.5 At 6 months: 995.8 At 12 months: 877	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
				highest dose (1.600 ug) was tolerated, or if a fall> 20% in forced expiratory volume in the first second FEV_1 from baseline (saline solution) was induced after methacholine inhalation. A methacholine challenge result was considered positive if the PD20 was < 1.600 ug.				
		Sputum Eosinophilia count (sEos), N= 14		After baseline spirometry measurements, subjects were pretreated with inhaled salbutamol (200 ug by metered-dose inhaler), and 10 min later hypertonic (4.5%) sterile saline nebulized solution was inhaled for three periods for a maximum of 5 min by means of an ultrasonic nebulizer			sEos count (%) at baseline: 2.7 At 6 months: 3.6 At 12 months: 1.9	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
				(Ultraneb 2000; DeVilbiss; Somerset, PA, USA). The cut-off for an abnormal result was defined when sEos count was> 3% as percentage cells.				
		symptom score, N =14		Obtained from diary cards. Mean daily symptom scores (dyspnea, wheezing, cough, daytime and nighttime awakenings, each scored 0 to 3.			Mean score at baseline: 10 At 6 months: 8.5 At 12 months: 8	
Wan, 2014 [119]	Taiwan, Cross section study, high risk of bias.	FeNO, N= 140	mean age 6 years, 56.6% males, 100% were on ICS.	Measured by (MINO device) once every three months for one year.	ICS (Flixotide 50 g; 2 puffs) with or without Singulair (5 mg orally per day).	FeNO levels decreased in 86.4% patients and increased in 13.6% patients, which were correlated with the changing of C-CAT (≥20 ppb, ≤19 ppb).	Baseline 32.31 ppb (SD: 13)	In Children with Asthma who received ICS, FeNO can be used to detect response to treatment.
		International Study of Asthma and Allergies in Childhood questionnaire (ISAAC) , N= 140					Baseline 18.13 (SD: 2.10).	

ACT: Asthma control test; 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; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; PD20: provocation dose causing a 20% decline in FEV_1; PEF: he peak expiratory flow; R: correlation coefficient; SD: standard deviation.

Table C.6. Characteristics of the included studies in KQ 1c (Drug selection)

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Ciolkowski, 2016 [120]	Poland, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N=86	Mean age 14 years (SD: 5), 73.3% male, 4 % Eosinophilic phenotype, 97.6% atopic.	Three measurement by online electrochemical-based Medisoft HypAir FE (NO) device (Medisoft SA, Belgium), at 50 ml/sec, steroid prior to test was 100%.	12 months of montelukast switched form patients daily low-dose ICS.	FeNO increased significantly more in patients last visit prior to exacerbation (N= 22) than final values of patients who completed the study (N= 64). However, an increased risk of exacerbations was noted among patients with FeNO> 20 ppb.	26 ppb (SD: 15) to 39 ppb (SD: 31) vs 18.5 (SD: 12) to 24.5 ppb (SD: 15). FeNO > 20 ppb (RR 3.7, 95% CI: 1.3 to 10.7, p=0.01).	In children with mild asthma on low dose ICS who were switched to montelukast, FeNO >20 ppb predicts exacerbations, however, the strongest factors that predict exacerbation was Eosinophilia.
		Spirometry, N= 86		Using (Easy One - Medizin Technik Schweiz) according to the ATS/ERS guidelines, with at least three correct forced exhalations. The dose-response slope (DRS) was calculated as the ratio of reduction		DRS increased in patients last visit prior to exacerbation (N= 22) and decreased in patients who completed the study (N= 64). An increased risk of	0.55 (SD: 53) to 2.06 (SD: 3.46) vs 0.22 (SD: 0.29) to 0.29 (SD: 0.38). DRS > 0.25 (RR 9.5, 95% CI: 2.8 to 31.6, p <0.01.	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
				of FEV_1 (% of initial value) by volume of the sodium chloride inhaled (mL)		exacerbations was noted among patients with DRS > 0.25.		
		Asthma control test (version for adults and older children), N= 86				The median ACT score at the last visit prior to exacerbation (n= 22) remained in the range of good asthma control but was slightly lower than final values of patients who completed the study (N= 64).	23.5 (SD: 3) vs 25 (SD: 1).	
		Sputum eosinophilia, N= 72		An 8 cycles of inhalation of 4.5% sodium chloride: 30 s, 30 s, 1 min, 2 min, and then four times for 4 min. Then, sputum was assessed macroscopically for plugs at the time of collection. An adequate specimen was defined as one		Sputum eosinophilia increased significantly more in patients last visit prior to exacerbation (N= 22) than final values of patients who completed the study (N= 64).	5.8% (SD: 4.6) to 7.3 (SD: 5) vs 0.7% (SD: 2) to 2% (SD: 3.5). Eos> 2.5%; RR 36.6, 95% CI: 7.1 to 189.3, p < 0.001.	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
				producing countable cytospin slides for an estimation via differential cell count, with minimal squamous contamination <50% and pulmonary macrophages present. A differential cell count was obtained from 200 cells on May-Grunwald-Giemsa stained slides.		An increased risk of exacerbations was noted among patients with initial Eos% > 2.5%.		
Cowan, 2015 [121]	New Zealand and United States, non-randomized trial, outpatient setting, low risk of bias.	FeNO, N=46	Mean age 39.8 years (SD: 2), 63 % males, Weight 78.5 Kg (SD: 2.5), 80.4% atopic.	Measured with a chemiluminescence analyzer (NiOX MINO; Aerocrine, Stockholm, Sweden) before any forced expiratory maneuvers according to current guidelines at an exhaled flow rate of 50 mL/sec.	500 mg of fluticasone (Flixotide; GlaxoSmith Kline, Greenford, United Kingdom) twice daily by means of inhalation through a spacer for a period of 28 or more days.	Asthmatic patients with baseline FeNO values of 35 ppm or greater had 10.5-fold greater likelihood of response to inhaled steroids, as measured by improvement in clinical outcomes,	By 2 clinical outcomes improvements: OR, 3.43; 95% CI, 0.93 to 413.54; P 0.004. By 3 clinical outcomes improvement: OR, 10.50; 95% CI, 1.73 to 203.7; P 0.014.	In steroid-naive adults with asthma FeNO predicted clinical responsiveness to ICS. The combination of FeNO values and urinary BrTyr levels had the best prediction power

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Urinary bromotyrosine test (BrTyr), N = 46		BrTyr levels were assayed by using stable isotope dilution HPLC with online electrospray ionization tandem mass spectrometry.		Asthmatic patients with baseline urinary BrTyr level of 0.45 ng/mg of creatinine or greater were 6.22	By 2 clinical outcomes improvement: OR 6.22; 95% CI, 1.22 to 47.94; P 0.31. By 3 clinical outcomes improvement: OR 1.5; 95% CI, 0.3 to 7.3; P 0.619.	
Mahut, 2011 [122]	France, Cross section study, outpatient setting, medium risk of bias.	FeNO, N= 169	Mean age 10.5 years (SD: 2.6), 61% male, 21 paternal and maternal tobacco exposure, BMI 18.0 Kg/m2 (SD: 3.5), 84% Atopic. 48% were on Beta-	Exhaled NO was measured online, using the Nitric Oxide Analyzer (NIOX; Aerocrine AB; Solna, Sweden: measurement at a constant 50 mL/sec expiratory flow rate: FeNO.	Bronchodilator (salbutamol) 400 µg and ICS dose > 200 µg/day.	The multivariate analysis demonstrated that log FeNO correlated with bronchodilator response and ICS dose > 200 ug/day.	Correlation with bronchodilator response: r = 0.26, p = 0.011. with ICS dose > 200 µg/d response: r = -0.17, p =0.019.	In children, FeNO identified ICS dependent asthma phenotype

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry, N= 169	agonist on demand, 52% were on ICS different doses, and 43% on LABA.	Spirometry and plethysmographic measurement of specific airway resistance and thoracic gas volume were performed according to international guidelines.			FEV_1 Pre-bronchodilator: 97 % pred (SD: 13). Post-bronchodilator: 107 % pred (SD: 12). FVC Pre-bronchodilator: 105 % pred (SD: 13). Post-bronchodilator: 108 % pred (SD: 12). FEV_1/FVC Pre-bronchodilator: 78 % pred (SD: 8). Post-bronchodilator: 84 % pred (SD: 6).	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Martin, 2016 [22]	United Kingdom, longitudinal nonrandomized study, low risk of bias.	FeNO, N=28	Mean age 29 years (range18-70), 39%, 17.9% current smoker, 14.3% ex-smoker, 14.3% atopic (eczema).	Measured by (NIOX MINO; Aerocrine, Tolna, Sweden)	12 week beclomethasone dipropionate (200 µg PID) via a metered dose inhaler.	FeNO ROC curve as a predictor of ICS response after 4 and 12 weeks had an AUC= 0.89 (p<0.0001) and AUC=0.86 (p<0.0001), respectively. FeNO < 27 ppb predicts non-responce.	AUC= 0.89 (p<0.0001) at 4 weeks and AUC=0.86 (p<0.0001) at 12 weeks.	In adult asthmatics, FeNO reliably predicts those who responds to ICS (Auc 0.89 and 0.86 at 4 and 12 weeks; respectively; level <27ppb predicts non-response).
		Blood eosinophilia, N=28				Blood eosinophil count did not perform as well as predictors of ICS response.	AUC= 0.67.	
		spirometry, N=28				FeV1 did not perform as well as predictors of ICS response.	AUC= 0.85.	
		Methacholine challenge test, N=28				PC20 did not perform as well as predictors of ICS response.	AUC= 0.32.	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Smith, 2005 [123]	New Zealand, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 52	Mean age 40.5 years (14-71), Male 24%, current smokers 6%, ever smokers 19%.	measured using a chemiluminescence analyzer (NiOX; Aerocrine, Stockholm, Sweden) at an exhaled flow rate of 50 ml/ sec.	4 weeks of inhaled fluticasone (250 g/ puff, 1 puff twice daily via matching inhaler).	FeNO >47 ppb predicted treatment response in the two response endpoint (increase in FEV_1 and increase in mean morning peak flows) better than lung function (FEV_1 < 80% predicted) and methacholine challenge test (PD20 < 8 u/mol).	FeNO >47 ppb predicted treatment response When endpoint is increase in FEV_1 >12%: Sensitivity: 67% Specificity: 78% PPV: 47% NPV: 89% When endpoint is increase in mean morning peak flow >15%: Sensitivity: 82% Specificity: 81% PPV: 53% NPV: 94%	FeNO > 47 ppb predicted steroid response in patients with undiagnosed respiratory symptoms. Response defined as an increase in FEV_1 of 12% or greater or an increase in mean morning peak flow of 15% or greater after fluticasone, 500 g/day for 4 weeks.
		Spirometry, N= 52					FEV_1 < 80% predicted treatment response When endpoint is increase in FEV_1 >12%: Sensitivity: 17% Specificity: 88% PPV: 29% NPV: 78% When endpoint is increase in mean morning peak flow >15%: Sensitivity: 36%	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
							Specificity: 93% PPV: 57% NPV: 84%	
		Methacholine challenge test (PD20), N= 52		Measured using standard protocols.			PD20 < 8 u/mol predicted when endpoint is increase in FEV_1 >12%: Sensitivity: 58% Specificity: 69% PPV: 37% NPV: 84% When endpoint is increase in mean morning peak flow >15%) Sensitivity: 55% Specificity: 68% PPV: 32% NPV: 84%	

AUC: area under the curve; CI: confidence interval; Eos: Eosinophilia count; ERS/ATS recommendation: The European Respiratory Society/ American Thoracic Society recommendation; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: long acting beta agonist; NPV: negative predictive value; OR: odds ratio; PC20: provocation concentration causing a 20% fall in FEV_1; PD20: provocation dose causing a 20% decline in FEV_1; PPV: positive predictive value; R= correlation; RCT: randomized clinical trial; SD: standard deviation.

Table C.7. Characteristics of the included studies in KQ 1d FeNO response to administration of Leukotriene receptor antagonists (LTRA)

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Bisgaard, 1999 [124]	Denmark, RCT with cross-over, outpatient setting, unclear risk of bias.	FeNO, N= 26	Mean age 12 years (6-15).	Measured by online Aerocrine NO system, at 110 ml/sec, two times per visit, steroid use prior to test was 42.3%	2 weeks of 5 mg montelukast once daily or placebo, then cross over for 2 weeks additional of 200 mg budesonide.	FeNO was significantly reduced with montelukast and budesonide Compared with placebo. This effect was independent of concurrent steroid treatment.	Montelukast mean difference from placebo 7.3 ppb (1.4 to 13.1). Budesonide mean difference from placebo 15.7 ppb (9.5 to 22.0).	FeNO was significantly reduced by 20% after 2-wk treatment with montelukast and budesonide. This effect was independent of concurrent steroid treatment.
		Spirometry, N= 24				Spirometry exhibited a tendency to improve after montelukast and after budesonide as compared with the placebo treatment period, but this was not statistically significant	FEV_1 Montelukast mean difference from placebo 0.132 L (-0.022 to 0.286) FEV_1 Budesonide mean difference from placebo 0.116 L (-0.045 to 0.277).	
Bratton, 1999 [125]	United States, longitudinal nonrandomized, outpatient	FeNO, N=24	Mean age 9.3 years (SD: 1.6), 67 % males.	using a chemiluminescent analyzer (Model 280 NOA, Sievers Instruments, Inc., Boulder CO).	Montelukast sodium (5 mg chewable tablet) administered once daily at bedtime, and	Change of FeNO after montelukast sodium treatment	Mean difference from baseline 24 ppb ($P < 0.01$)	In 12 children with chronic asthma, FeNO concentrations decreased

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
	setting, high risk of bias.	Spirometery, N=24			after a 2-week posttreatment washout period.	Change of FEV_1 (% predicted) after montelukast sodium treatment.	FEV_1 at baseline 81 % pred (SD: 4) After Montelukast 85 % pred (SD: 4).	after 4 week treatment with montelukast sodium, which again rose after treatment was withdrawn.
Montuschi, 2007 [126]	Italy, RCT, outpatient setting, low risk of bias.	FeNO, N= 26	Montelukast group (N= 14) Mean age 10.8 years (SD: 0.5), 78.5% male Placebo group (N= 12) Mean age 10.5 years (SD: 0.6), 83% male	Measured by online NIOX system (Aerocrine; Stockholm, Sweden), at 50 ml/sec.	1 month of montelukast 5mg/day or placebo then 2 weeks treatment withdrawal.	Montelukast showed a significant reduce in FeNO, however, it was increased 2 weeks after withdrawal. No changes were seen in placebo group.	Montelukast group Week 1: 45.5 ppb Week 5: 37.9 ppb Week 7: 52.2 ppb Placebo group Week 1: 37.5 ppb Week 5: 46.3 ppb Week 7: 40.6 ppb	Montelukast reduced FeNO concentrations in children with asthma, and withdrawal can result in increased FeNO values and worsening of Spirometry.
		Spirometry, N= 26		Spirometry (Pony FX; Cosmed; Rome, Italy), and the best of three consecutive maneuvers were chosen.		Montelukast had no effect on Spirometry test results in asthmatic children, however, test results were	Montelukast group FEV_1 % pred Week 1: 93.1 (SD: 3.1) Week 5: 92.9 (SD: 3.0)	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
						lower than baseline after the 2 week treatment withdrawal. Placebo treatment and its withdrawal had no effect on Spirometry tests.	Week 7: 90.7 (SD: 2.8) FEV_1/FVC Week 1: 96.7 (SD: 2.2) Week 5: 95.9 (SD: 3.0) Week 7: 94.7 (SD: 3.0) Placebo group FEV_1 % pred Week 1: 94.3 (SD: 2.4) Week 5: 95.7 (SD: 2.9) Week 7: 90.6 (SD: 3.1). FEV_1/FVC Week 1: 99.2 (SD: 2.4) Week 5: 99.8 (SD: 2.8) Week 7: 96.4 (SD: 2.8).	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Ohkura, 2009 [127]	Japan, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 20	Mean age 68.1 years (SD: 12), 75% male.	Measured by online chemiluminescence at a flow rate of 0.05 L/sec. Steroid prior to test was 100%.	1 month of Pranlukast 450 mg/day added to ICS+LABA (salmeterol 100 µg/day), then 1 month of washout period (only ICS+LABA (salmeterol 100 µg/day).	FeNO decreased significantly after adding pranlukast. FeNO after wash-out period was also lower than baseline.	Baseline 26.6 ppb (SD: 1.1). Pranlukast + ICS+ LABA 18.3 ppb (SD: 1.9). ICS+LABA 21.1 ppb (SD: 1.1).	Pranlukast added to ICS and inhaled LABA reduced FeNO.
		Spirometry, N= 20				FEV_1 increased significantly after pranlukast was added and decreased significantly after wash-out period.	Baseline 2.08 L (SD: 0.12). Pranlukast + ICS+ LABA 2.14 L (SD: 0.56). ICS+LABA 2.08 L (SD: 0.58).	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Sandrini, 2003 [128]	Canada, RCT with crossover, outpatient setting, unclear risk of bias.	FeNO, N=20	mean age 34.8 years (SD: 12.6), 25% males, 5% smoker. 12 received placebo and 8 received Montelukast.	Performed according to ATS recommendations, using an expiratory flow rate of 0.046 L/s.20The exhaled breath condensate was collected using a commercial apparatus (Cryocond; Boehringer Ingelheim; Burlington, ON, Canada) that cools and freezes the exhaled air to −30°C while patients breathe at tidal volume, wearing nose clips, for 5 min. Frozen samples were stored at −70°C. H2O2 was measured as described previously.	Two 2-week treatment periods with Montelukast (10 mg daily) or matching placebo, with each treatment being followed by 1 week of washout. The tablets were taken in the evening, and visit 2 was considered to be the initial day of the first treatment arm.	Montelukast resulted in a significant reduction of FeNO from day 1 of treatment to day 14, however, FeNO remained lower in comparison to baseline during the washout period. The maximal effect was observed on day 7. Montelukast median difference from baseline at day 7 was −11.3 ppb (25th to 75th percentile, −16.8 to −4.6), and the median difference for placebo was 1.5 (25th to 75th percentile, −1 to 9.9).	FeNO in Montelukast group (N= 8): 52.5 (38 to 102). Placebo group (N=12): 44 (28 to 95).	Montelukast r educed FeNO in adults with mild asthma in an RCT, reduction was noted as early as day 1 with a maximum effect on day 7.

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry, N=20		Spirometry was performed after ENO measurement and breath condensate collection using ATS standards.			FEV_1 % in Montelukast(N=8) : 88% (range 83 to 95) Placebo group (N=12): 91% (range 83 to 98)	

ATS standards: American Thorcic Society standards; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: long acting beta agonist; RCT: randomized clinical trial; SD: standard deviation.

Table C.8. Characteristics of the included studies in KQ 1d FeNO response to administration of Omalizumab

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Silkoff, 2004 [129]	United States, RCT, outpatient setting, low risk of bias.	FeNO, N=29	Mean age 9.6 years (SD: 1.4), 70 % males, Weight 37.9 Kg (SD: 13.8).	Measured by using a standardized single breath method, which conformed to American Thoracic Society recommendations for FeNO measurement	52 weeks Omalizumab (N= 18) vs placebo (N= 11). The dose of omalizumab was based on each patient's serum total IgE level and body weight at baseline to provide a dose of at least 0.016 mg/kg per IU/mL of IgE per 4-week period.	During the first 12 week of the study where steroid doses were reduced, the variability of adjusted FeNO in the placebo group was greater than that of the omalizumab group at most visits, with a significant difference between groups for AUC of adjusted FeNO. However, Omalizumab reduced FeNO after 52 weeks as reported.	AUC for adjusted FeNO Omalizumab 0.88 (SD: 0.69) vs placebo 1.65 (SD: 1.06). Omalizumab Baseline 41.9 (SD: 29.0) At 52 weeks 18.0 (SD: 21.8)	Omalizumab reduced FeNO in children
Tajiri, 2014 [130]	Japan, prospective observational study, outpatient setting, medium risk of bias.	FeNO, N =31	Mean age 55 years (SD: 16), 32.3% males, BMI 25.0 kg/m^2 (SD: 5.3), 42% ever smoker.	Using a chemiluminescence analyzer (NOA 280; Sievers, Boulder, Colorado). Fractional eNO (FeNO) levels were determined at 3 expiratory flows of 50 (FeNO50), 100, and 200 mL/sec.	48 weeks Omalizumab treatment.	FeNO changes from baseline to 48 weeks of treatment	Baseline 50.2 (SD: 60.1) At 48 weeks 31.4 (SD:28.4)	Omalizumab reduced exacerbations and symptoms and FeNO in 31 adults asthmatics.
		Spirometry, N =31		Chestac-8800 (Chest, Tokyo, Japan).		FEV_1 (L) changes from baseline to	Baseline 2.17 (SD: 0.53	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
						48 weeks of treatment	At 48 weeks 2.24 (SD:0.55	
		Asthma Quality of Life Questionnaire (AQLQ), N =31				AQLQ Changes from baseline vs 48 weeks	1.36	
		Asthma Control Questionnaire (ACQ), N =31				ACQ Changes from baseline vs 48 weeks	-1.11	

AUC: area under the curve; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; RCT: randomized controlled trial; SD: standard deviation

Table C.9. Characteristics of the included studies in KQ 1d FeNO response to administration of Cortisone

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Baraldi, 1997 [131]	Italy, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N=16	Mean age 9.3 years, range 6-13, 50 males, Weight 37.1 Kg (SD: 2.9).	measured with a chemilumescence analyzer (CLD 700 AJ-Med, Ecophysics, CH, Switzerland) sensitive to NO concentrations from 1 to 1000 ppb. Flow used was 0.7 L/min. NO reached a steady plateau during oral breathing after 1-2 min without further fluctuations.	5 days of oral corticosteroid therapy (prednisone 1 mg/kg per day orally).	5 days oral corticosteroid resulted in FeNO mean decrease by 46% (SD: 4%) $p < 0.001$) accompanied by a significant improvement in FEV_1 ($p < 0.001$).	Baseline: 31.3 ppb (SD: 4.2) After prednisone: 16.5 (SD: 2.3)	FeNO values significantly decrease after 5 days of oral prednisone given for acute exacerbation of asthma
		Spirometry, N =16		Pulmonary function parameters were measured by means of a 10 L bell spirometer Biomedin, Padua, Italy), and the best of three maneuvers was expressed as a percentage of predicted values according to Polgar and Promadhat.			FEV_1 at baseline: 62.4 % (SD: 4.4). After prednisone: 90.7 % (SD: 4.3).	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Beck-Ripp, 2002 [100]	Germany, RCT, outpatient setting, high risk of bias.	FeNO, N=31	Mean age 10.5 years (SD: 0.5), 51% males.	Measured by on-line chemiluminescence analysis in the LR 2000 NO analyser (Logan Research, Rochester, Kent, UK), however, FeNO measurement was done before spirometry.	4 weeks of two doses of inhaled budesonide, twice daily with additional inhaled b2-agonists (salbutamol 200 mg or terbutaline 500 mg) as needed vs treatment with only inhaled b2-agonists as needed	FeNO was significantly reduced after 4 weeks of combined inhaled budesonide and beta-agonist, however, FeNO was significantly increased again back to initial values when inhaled beta-agonits was used alone.	Baseline 14.8 ppb (SD: 1.9) budesonide and beta- agonist 7.6 ppb (SD: 0.8) inhaled b2-agonits 14 ppb (SD: 1.2)	FeNO values were lower in ICS users among asthmatic children
		Spirometery, N=31		Spirometry was performed in a Jager MasterLab (Jager, Wurzburg, Germany) and the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and mean maximal expiratory flow (MMEF) were measured according to the recommendations of the American Thoracic Society (ATS).		The initial 4-week inhaled budesonide treatment resulted in an increase in the FEV_1. When inhaled beta-agonits used alone, mean FEV_1 was reduced, but only changes in the later were significant.	Baseline FEV_1 83.1% (SD: 2.0) budesonide and beta- agonist 93.4% (SD: 2.4) inhaled b2-agonits 88.2 % (SD: 3.3)	
Bulac, 2015 [132]	Turkey, longitudinal nonrando	FeNO, N=95	Mean age 42.6 years (SD: 12.3), 15.8 % males, Weight 72.5 K	Performed with a NIOX MINO device according to the suggested method.	Group 1 (N=30) Budesonide/ formoterol	Changes observed in FeNO (ppb) values (pre vs post).	Group 1 14.17 (SD: 4.78) vs 13.97 (SD:4.53)	3-weeks of beclometasone dipropionate/formoterol-HFA added

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
	mized, outpatient setting, low risk of bias.		(SD: 11.8), 8.4% ex-smoker.		320/9 ug dry powder inhaler (DPI). <u>Group 2 (N=30)</u> Fluticasone/ salmeterol 500/50 ug DPI according to The combination they used. <u>Group 3 (N=35)</u> Random selection from previous two groups, and beclometasone dipropionate/ formoterol hydrofluoroalkane (HFA) 100/6 ug pMDI was prescribed.		Group 2 15.57 (SD:5.08) vs 15.11 (SD:5.62) Group 3 15.17 (SD:4.83) vs 12.93 (SD:5.05)	to patients with previously controlled asthma reduced FeNO
		Spirometry, N= 95				Changes observed in FEV_1 (% pred) values (pre vs post).	Group 1 86.63 (SD:11.51) vs 89.97 (SD:12.63) Group 2 86.94 (SD:11.38) vs 87.43 (SD:10.9) Group 3 85.7 (SD:9.17) vs 90.2 (SD:12.2)	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Byrnes, 1997 [133]	United Kingdom, cross sectional and longitudinal, outpatients setting, medium risk of bias.	FeNO, N=31	Mean age 11 years, range 7-16. 45.2% male, 48.4% were on bronchodilators, and 51.6% on inhaled corticosteroids.	Measured by the chemiluminescence method sensitive to 2,000 4,000 ppb, per volume of NO, using an analyzer (Dasibi Environmental Corp.) with a 95% response time of 6.4 seconds. One set of measurements was performed by direct exhalation into the NO analyzer with a total flow of 440 ml/min with continuous recordings of NO in ppb, carbon dioxide in volume percent, and mouth pressure standardized to 4 mmHg.	6 months cross-sectional study subgrouped to bronchodilators alone (N=15), and inhaled corticosteroids regularly (N=16). Then, 2 weeks longitudinal study of patients never treated with steroids before (N=6), they were studies before and after starting inhaled corticosteroids.	Cross section FeNO was significantly higher in bronchodilator therapy group than in inhaled corticosteroids group. Longitudinal In asthmatics who never been treated with steroid, mean FeNO fell after 2 weeks of inhaled corticosteroid treatment.	Cross section Bronchodilators group: 126.1 (77.1), range (14.4-361.1). Inhaled corticosteroids group: 48.7 ppb (SD 43.3) Longitudinal FeNO median from 124.5 ppb to 48.6 ppb.	FeNO values were lower in ICS users.
		Spirometry, N=31				FEV_1 and FVC were significantly higher in Inhaled corticosteroids therapy group than in Bronchodilators group.	Cross section Bronchodilators group: FVC 92% (SD 14.5). FEV_1 78% (SD 10.4). Inhaled corticosteroids group: FVC 98% (SD 18.5)	

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							FEV_1 86% (SD 17.5).	
Dupont, 1998 [134]	Belgium Cross-section study, outpatient setting, high risk of bias.	FeNO, N=99	Asthmatics subdivided according to their PC20 histamine and current steroid treatment. Group 1; (No steroids for 3 month and negative histamine test) (N=56): Mean age 40 years (SD: 17), 0% smoker 60.7% atopic. Group 2; (No steroids and positive histamine test) (N=18): Mean age 42 years (SD: 18), 0% smoker, 5.6% atopic. Group 3; (Steroids and negative histamine test) (N=25): Mean age 39	Flow of 20 mL/sec, using an online Ecophysics CLD 700 AL MED (Dürnten, Switzerland) chemiluminescence analyzer adapted for online recording. Three reproducible recordings (15% variation) were made in one visit at 2-min intervals, and the highest of three readings was used for analysis.	Inhaled steroids (between 500 and 1000 mg beclomethasone dipropionate or equivalent for at least 6 weeks) (%): Group 1: 0 Group 2: 0 Group 3: 100 Group 4: 0		Group 1: 21 ppb (SD: 11). Group 2: 11 ppb (SD: 3). Group 3: 13 ppb (SD: 5).	FeNO correlated with airway hyperresponsiveness in steroid-naïve mild asthmatics, but not in steroid using asthmatics
		Spirometry, N=99		Spirometry was done according to American Thoracic Society (ATS) guidelines.			FEV_1 % pred Group 1: 102 (SD: 12). Group 2: 107 (SD: 12). Group 3: 108 (SD: 13). FVC % pred Group 1: 107 (SD: 12). Group 2: 107 (SD: 13). Group 3: 109 (SD: 13).	

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		Airway hyperresponsiveness, N=99	years (SD: 18), 0% smoker, 60% atopic	Measured as the dose of histamine that produced a 20% decrease in FEV_1 (PC20histamine). Normal bronchial responsiveness (positive test) was considered when (PC20 histamine ≥ 8 mg/ml).			Group 1: 1.8 (SD: 2.2) Group 2: > 8 Group 3: 2.0 (SD:2.2)	
Ehrs, 2010 [135]	Sweden, RCT, outpatient setting, low risk of bias.	FeNO, N=70	Corticosteroid group (N=36); mean age 38 years (18-61), 36% male, 61% ever-smoker, 33% current smokers, 67.6% atopic. Placebo group (N=34); mean age 39 years (20-63), 35% male, 44% ever-smoker, 18% current smokers, 67.6% atopic.	Measured by online chemiluminescence (NIOX®, Aerocrine, Stockholm, Sweden), at 50 ml/sec, at several visits.	A three month of Inhaled fluticasone (250 mg twice daily) or placebo.	A 3 months Fluticasone significantly reduced FeNO, as opposed to placebo.	Fluticasone; 19.3 ppb (13.3 to 39.5) vs 13.9 ppb (8.1 to 18.7). Placebo; 20.7 ppb (12.8 to 36.5) vs 23.0 ppb (10.5 to 35.7).	In steroid free mild asthmatic adults, ICS reduced FeNO and altered bronchial responsiveness but did not change quality of life.
		Spirometry, N=70		measured using a MicroLab 3300 Spirometer (Micro Medical Ltd, Rochester, Kent, UK) according to the standards of the American Thoracic Society. Spirometry was measured before and 20 min after inhalation of the bronchodilators. Significant reversibility was defined as an FEV_1 increase 10% of the pre-inhalation value.		Fluticasone slightly increased FEV_1 while placebo decreased it. However, fluticasone increased FVC but less than placebo does. Alongside, salbutamol and ipratropium bromide further increased FEV_1 and FVC in both groups before and after 3 month fluticasone and	FEV_1 after Fluticasone (2.8%) vs placebo (-0.8%). FVC after Fluticasone (0.8%) vs placebo (1.1%).	

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						placebo.		
		Asthma Quality of Life Questionnaire, N=70		A 32 items questionnaire has four domains: activity limitations, symptoms, emotional functions and influence of environmental stimuli. The minimal important difference (MID) indicates the smallest difference in the score of a domain that the patient perceives as beneficial. In the AQLQ, the definition of MID is 0.5.		The mean overall score was increased in both groups. However, there were no significant differences between the fluticasone and placebo group with regard to change in quality of life.	Fluticasone; from 5.62 to 6.0 vs Placebo from 5.74 to 6.0.	
		A bronchial responsiveness (methacholine challenge test), N=70		Inhalation of the diluent followed by doubling concentrations of methacholine starting at 0.5 mg/mL. The challenge was stopped at an FEV_1 decrease (measured with a wedge spirometer; Vitalograph®, Maids Moreton, Buckingham, UK) of 20% compared with the value obtained after inhalation of the diluent or after inhalation of the highest methacholine		Fluticasone increased median methacholine responsiveness (PD20) more than placebo does.	Fluticasone; from 0.18 mg (0.07 to 0.57) to 0.42 mg (0.16 to 0.80) Vs Placebo; from 0.22 mg (0.10 to 0.50) to 0.25 mg (0.14 to 0.52).	

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				concentration (32 mg/mL).				
Erin, 2008 [136]	United Kingdom, RCT with cross-over, high risk of bias.	FeNO, N= 21	Mean age 26 years (19-39), 48% male, 38% ever smoker.	Measured by chemiluminescence analyzer (Logan Research Limited; Rochester, UK) at 50 ml/sec	A 7-day of ciclesonide 320 ug in the morning and placebo in the evening, ciclesonide 640 ug bid, and placebo.	Compared with placebo, ciclesonide 320 ILg qd improved median exhaled NO levels after 3 and 7 days. Similarly, ciclesonide 640 ILg bid improved median exhaled NO levels after 3 and 7 days. No Significant differences in FeNO were detected between patients treated with ciclesonide 320 ILg qd and 640 ILg bid.	ciclesonide 320 ug qd median difference Day 3: -17.7 ppb. Day 7: -22.6 ppb. ciclesonide 640 ug bid Day 3: -15.4 ppb. Day 7: -20.7 ppb.	FeNO values were lower in ICS users.
		Airway responsiveness (measured as the provocative concentration of adenosine monophosphate (AMP) producing a				Ciclesonide 320 ug qd and 640 ug bid produced Significantly greater improvements in PC20 compared with placebo on days 1, 3, and 7. There were no	Ciclesonide 320 ug qd mean difference Day 1: 1.59. Day 3: 1.78. Day 7: 2.13. Ciclesonide 640	

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		20% reduction in FEV_1 (PC20), N= 21				significant differences between ciclesonide doses for PC20 on days 1, 3, or 7.	ug bid mean difference Day 1: 1.23. Day 3: 1.51. Day 7: 2.20.	
		Spirometry, N= 21				Ciclesonide 640 ug bid achieved Significantly greater improvements in FEV_1 compared with placebo after 3 and 7 days. Ciclesonide 320ug qd produced significantly greater improvements in FEV_1 compared with placebo after 7 days.		
		Sputum eosinophils, N= 21				Sputum eosinophils decreased after 7 days of ciclesonide treatment. Although not statistically Significant, this decrease was more pronounced with ciclesonide 640 ILg bid.		

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Gelb, 2008 [137]	United States, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N=30	Mean age 43 years (SD: 9) 20 % males, 0% smokers.	Measured using a Sievers NOAi 280 chemiluminescene analyzer (Ionics Instruments, USA) at three separate constant expiratory flow rates: 100 mL/s, 150 mL/s and 200 mL/s, in triplicate. The mean of three values (that were required to be within 10% of each other to be acceptable) was reported.	12 weeks as following; Visit 1: Patients were on fluticasone 250 µg/salmeterol 50 µg (F/S) twice a day for longer than a year. visit 2: After four weeks of F/S plus montelukast 10 mg (M). visit 3: After four weeks of S plus M. visit 4: After Four weeks of S only.	FeNO were significantly higher when taking S alone compared with the three other regimens.	visit1: 16 (9 to 21). visit2: 14 (9 to 21) visit3: 15 (9 to 27) visit4: 19 (10 to 32).	In nonsmoking with mild to moderate asthma on ICS, addition of montelukast did not further reduce FeNO
		Spirometry, N=30				There were no statistical differences for spirometry in asthmatic patients during visits 1 to 4.	FEV_1 (% pred) visit1: 86 (SD:17) visit2: 86 (SD:19) visit3: 83 (SD:17) visit4 : 84 (SD:19) FEV_1/FVC (%) visit1: 77 (SD:10) visit2: 78 (SD:9) visit3: 77 (SD:10) visit4: 77 (SD:10)	
Hozawa, 2014 [138]	Japan, RCT, outpatient setting, high risk of bias.	FeNO, N=30	SMART group (N= 15) (budesonide/formoterol (BUD/FM; Symbicort) for maintenance and reliever therapy): Mean age 41.9 years (SD: 8.7),	Measured using a NIOX MINO® (Aerocrine, Stockholm, Sweden) before any forced expiratory maneuvers. Two readings were obtained and the mean value was used for the analysis.	SMART group (N= 15) 8 weeks of twice-daily budesonide/formoterol (BUD/FM) 160/4.5 mg plus as-	FeNO values decreased significantly from baseline at 8 weeks in SMART group more than FP/SM group.	FeNO mean difference SMART group -13.13 ppb. FP/SM group -8.20 ppb.	When stepping up from ICS therapy, budesonide/formoterol for maintenance and reliever therapy (SMART) reduced FeNO compared with a fixed dose

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			40 % males, BMI 21.2 kg/m^2 (SD: 1.8). <u>FP/SM group</u> (N= 15) (fluticasone propionate/salmeterol): mean age 41.3 years (SD: 9.9), 40% males, BMI 21.1 kg/m^2 (SD: 2).		needed BUD/FM. <u>FP/SM group</u> (N= 15) 8 weeks of one inhalation twice daily fluticasone propionate/salmeterol (FP/SM) 250/50 mg plus as-needed procaterol.			of maintenance therapy with fluticasone propionate/salmeterol.
		Asthma Control Questionnaire (ACQ), N=30		Asthma Control Questionnaire (ACQ5; five-item Japanese version)		ACQ5 mean score reduced in SMART group more than FP/SM group.	SMART group Baseline 1.25 (SD:0.28) At 4 weeks 0.76 (SD: 0.23) At 8 week 0.33 (SD: 0.18). FP/SM group, baseline 1.24 (SD:0.24) At 4 weeks 1.07 (SD: 0.28) At 8 week 0.69 (SD: 0.36)	

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		spirometry, N=30		measured by Spiro Sift SP370HYPER (Fukuda Denshi Co., Ltd., Tokyo, Japan).		FEV_1 improved in SMART group more than FP/SM group.	SMART group FEV_1% pred Baseline 92.4 (SD:7.2) At 4 weeks 94.2 (SD: 6.7) At 8 week 100 (SD: 7.5). FP/SM group FEV_1% pred Baseline 91.9 (SD:8.9) At 4 weeks 95.9 (SD: 9.8) At 8 week 97.6 (SD: 9.2)	
Kermode, 2011[139]	Australia, longitudinal nonrandomized, medium risk of bias.	FeNO, N= 19	Mean age 36.4 years (range 20-62), 47.4% male, 0% current smokers.	Measured by an offline technique at 200 ml/s according to American Thoracic Society guidelines, at one visit, steroid prior to test was 0%.	12 weeks of treatment with fluticasone proprionate/salmeterol xinafoate 250/25 ug MDI 2 puffs bd via spacer.	The treatment reduced FeNO by 46%.	From 13.1 ppb (10.3 to 16.6) to 7.1 ppb (6.2 to 8.1).	In adults with asthma taking ICS for 12 weeks, FeNO significantly was reduced.
		Asthma Control Questionnaire (ACQ), N=19				There was a significant improvement in ACQ after treatment.	From 1.3 (1.0 to 1.6) to 0.7 (0.4 to 1.0).	
		Spirometry, N=19		Calculated by referencing the maximal inhalations to plethysmographic TLC using a Medisoft BodyBox 5500 (Medisoft		The treatment showed a significant improvement in FEV_1, FVC and the FEV_1/FVC	FEV_1: from 74.9% pred (67.2 to 82.6) to 85.0% pred (77.8 to 92.3).	

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				Corporation, Sorrines, Belgium).		ratio.	FVC: from 95.3% pred (88.3 to 102.3) to 100.3% pred (93.7 to 107.0). FEV_1/FVC: from 0.6 (0.6 to 0.7) to 0.7 (0.6 to 0.7).	
Kharitonov, 1996 [140]	United Kinkdom, RCT with cross over, outpatient setting, unclear risk of bias.	FeNO, N=11	Mean age 32 years (SD: 0.9), 72% males, BMI 25 kg/m^2 (SD: 5.3), 42% ever smoker.	Measured using a chemiluminescence analyzer (Dasibi Environmental Corp., Glendale, CA) sensitive to NO from 2 to 4,000 parts per billion (ppb, by volume), adapted for on-line recording of NO concentration.	3 weeks Budesonide (800 Mg) twice daily vs placebo	FeNO was significantly reduced after 1 week of budesonide, with further reductions at 2 and 3 wk. There were no significant FeNO changes in patients taking placebo.	<u>Budesonide</u> Baseline 203 ppb (SD: 29) at 1 week 143 ppb (SD: 27) at 3 week 120 ppb (SD: 26) <u>Placebo</u> Baseline 169 ppb (SD: 290) at 1 week 184 ppb (SD: 22) at 3 week 184 ppb (SD: 16)	FeNO values were lower in ICS users
		Spirometry, N= 11		Measured with a dry spirometer (Vitalograph, Buckingham, UK). The best value of three maneuvers was expressed as a percentage of the predicted value.		There was no significant change in FEV_1 after budesonide or placebo.	Budesonide baseline FEV1 92% pred (SD:3.3) at 1 week FEV1 97% pred (SD:3.8) at 3 week FEV1 99% pred (SD:5.2)	

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							Placebo baseline FEV1 94% pred (SD:4.3) at 1 week FEV1 94% pred (SD:3.9) at 3 week FEV1 95% pred (SD:4.2)	
Kharitonov, 2002 [141]	United Kingdom, RCT, outpatient setting, low risk of bias.	FeNO, N=28	Mean age 28 years (25-30), 57% male, 0% current smokers.	A 4 week Measurement by online LR2000 analyzer (Logan Research Ltd, Rochester, Kent, UK), at several visits, corticosteroid and bronchodilators prior to test were 0%.	Inhaled 100 mg/day or 400 mg/day budesonide or placebo once daily for 3 weeks followed by 1 week off treatment.	A significant dose-dependent reduction was faster in 400 mg/day budesonide than 100 mg/day and placebo.	<u>At 3-5 days</u> 400 mg/day -2.06 (SD: 0.37) ppb/day vs 100 mg/day –0.51 (SD: 0.35) ppb/day vs placebo –0.89 (SD: 0.87) ppb/day. <u>At 3 weeks</u> 400 mg/day –0.90 (SD: 0.13) ppb/day vs 100 mg/day –0.54 (SD: 0.08) ppb/day.	There is a dose-dependent onset and cessation of FeNO of inhaled corticosteroids in patients with mild asthma. However, a significant reduction in exhaled nitrite/nitrate and S-nitrosothiols after budesonide treatment was not dose-dependent. There was no significant change in exhaled CO or 8-isoprostanes in breath condensate.
						Recovery of FeNO was faster in 400 mg/day budesonide than100 mg/day.	400 mg/day 1.89 (SD: 1.43) ppb/day) vs 100 mg/day 0.49 (SD: 0.34) ppb/day.	

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		Exhaled breath condensate, N=28		Nitrite (NO2) and nitrate (NO3) measured using a fluorimeter, Nitrosothiols were assessed using the Oxonon nitrosothiol detection kit (Alexis Biochemicals, Nottingham, UK), and 8-isoprostane by a specific enzyme immunoassay (EIA) kit (Cayman Chemical, Ann Arbor, USA).	Inhaled 100 mg/day or 400 mg/day budesonide or placebo once daily for 3 weeks followed by 1 week off treatment.	A non-dose dependent reduction was faster following 3-5 days of 400 mg/day budesonide than 100 mg/day, however, 100 mg/day showed a further reduction in 3 weeks than 400 mg/day.	<u>At 3-5 days</u> 400 mg/day –4.82 (SD: 0.99) mM/day vs 100 mg/day –3.55 (SD: 1.14) mM/day) vs placebo 0.95 (SD: 0.80) mM/day. <u>At 3 weeks</u> 100 mg/day –1.73 (SD: 0.44) mM/day vs 400 mg/day –0.82 (SD: 0.12) mM/day.	
						Recovery of NO2/NO3 was faster in 400 mg/day than 100 mg/day and placebo.	400 mg/day 4.03 (SD: 2.07) mM/day vs 100 mg/day 1.70 (SD: 1.79) mM/day vs Placebo –4.93 (SD: 1.39) mM/day.	
		Spirometry, N=28		Dry spirometer (Vitalograph-S, Vitalograph Ltd, Buckingham, UK). The highest of the three morning and evening PEF measurements was determined and recorded		FEV_1 and PEF did not change significantly in any of the patient groups.		

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				daily on the diary cards by the patients.				
		Symptoms score N=28		Daytime and night time symptom scores. Scale point from no symptoms to severe, the scores were recorded daily by each patient.		A significant dose-dependent difference was seen in the reduction of symptom scores between the groups and from placebo.	400 mg/day -0.1 (SD: 0.05) units/day) vs 100 mg/day 0.11 (SD: 0.05) units/day vs Placebo 0.28 (SD: 0.14) units/day.	
		carbon monoxide, N=28		Simultaneously with FeNO by LR2000 analyser (Logan Research Ltd, Rochester, Kent, UK).		There was no effect of either treatment or placebo CO, either during the onset or cessation of their action.		
Mallol, 2016[142]	Chile, RCT, outpatient setting, High risk of bias	FeNO, N=60	Ciclesonide (CIC) 80 Mg/day group, N = 27 Mean age 10.9 years Ciclesonide (CIC) 160 Mg/day group, N =29 Mean age 11.2 years.	Online single breath using (NIOX MINO, Aerocrine AB, Solna, Sweden) at 50 mL/s assisted by visual and auditory cues provided by the device.	Generic CIC (Disbronc, Neumobiotics, CIPLA) one puff of 80 or 160 g once daily for 12 Weeks.	A significant decrease in FeNO at two groups after four weeks of treatment without further significant changes in measurements at weeks 8 and 12 of treatment. There was no significant difference between groups in the proportion of children who showed a	CIC 80 mg group from 45.0 ppb (95% CI 37.8---53.7) to 32.7 ppb (95% CI 21.0---47.3). CIC 160 mg group from 47.3 ppb (95% CI 40.4---55.3) to 30.5 ppb (95% CI 24.1---38.7) (P < 0.001).	Once-daily generic ciclesonide (80 mg or 160 mg), for 12 weeks, is effective to improve airway inflammation and asthma control in atopic children with persistent asthma.

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						significant decrease in FENO after 12 weeks of treatment.		
		Spirometry, N =60		FeNO measurements and ACT were performed every 30 days. Spirometry and methacholine bronchial challenge were performed at baseline and after 12 weeks of treatment. Tests were carried out on two consecutive days in the same order (first FENO, then spirometry and methacholine).		There was a significant improvement of asthma control with both CIC doses but there was no significant change in BHR or FEV1 in either group.	CIC 80 mg group FEV from 105.4 to 103.5% predicted CIC 160 mg group FEV from 10.1.2 to 102.1% predicted.	
		Asthma control test (ACT), N=60						
		Bronchial hyperresponseiveness to methacholine challenge test, N=60					CIC 80 mg group from 19.2 to 23.1. CIC 160 mg group from 18.5 to 22.4.	
Nolte, 2013 [143]	United States, RTC, unclear risk of bias.	FeNO, N= 93	Group1 (N= 20); MF/F-MDI 100/ 10 mg Mean age 34.3 years (SD: 10.5), 35% male,	Measured online, using the Nitric Oxide Analyzer (NIOX; Aerocrine AB; Solna, Sweden), at 0.05 L/s.	Two weeks of twice a day of the following combination of mometasone/	All active treatments demonstrated significant reductions in FeNO compared	Mean difference from baseline Group 1: -35.3 Group 2: -45.4 Group 3: -61.4 Group 4: -46.1	In adults with allergic asthma, FeNO levels changed in a dose dependent manner with a

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
			BMI 25.3 Kg/m2 (SD: 5.6), 75% atopic (seasonal allergy rhinitis).		furoate (MF) or formoterol (F); Group1 MF/F-MDI 100/ 10 mg (N= 20) Group2 MF/F-MDI 200/10 mg, (N= 17) Group3 MF/F-MDI 400/10 mg, (N= 12) Group4 MF-MDI 200 mg, (N= 16) Group5 MF-DPI 200 mg, (N= 15) Group6 Placebo, (N= 15)	with placebo. Escalating MF/F doses significantly reduced FeNO in a dose-dependent manner.	Group 5: -51.3 Group 6: 0.1	combined ICS/LABA.
		Sputum eosinophilis, N= 93	Group2 (N= 17); MF/F-MDI 200/10 mg, Mean age 43 years (SD: 14.9), 41% male, BMI 25 Kg/m2 (SD: 4), 76% atopic (seasonal allergy rhinitis). Group3 (N= 12); MF/F-MDI 400/10 mg Mean age 39.8 years (SD: 15.2), 67% male, BMI 25.6 Kg/m2 (SD: 3.6), 67% atopic (seasonal allergy rhinitis). Group4 (N= 16); MF-MDI 200 mg Mean age 32.6 years (SD: 13.2),	conducted according to ERS recommendations: after inhalation of 1 mg terbutaline, sputum was induced by inhalation of hypertonic saline in increasing concentrations (3%, 4% and 5%) for 3 time periods each of 7 min (total duration, 21 min). Sputum plugs were selected and processed, cytospins were prepared using standard methods, and a differential cell count was performed.		With the exception of the MF/F 100/10 mg group, all active treatment groups demonstrated higher sputum eosinophil fold reductions from baseline compared with placebo. Escalating MF/F doses significantly reduced sputum eosinophil levels in a dose-dependent manner.	Mean difference from baseline Group 1: 21.1 Group 2: -35.3 Group 3: -75.4 Group 4: -33.7 Group 5: -55.3 Group 6: 71.7	
		Spirometry, N= 93		PEF was recorded using an electronic diary (e-diary) that included a mouthpiece to capture peak flow.		Mean percentage changes from baseline in AM PEF observed for all active treatment groups were significantly superior compared with placebo. MF/F 400/10 mg	AM PEF mean difference from baseline Group 1: 10.3 Group 2: 12.1 Group 3: 16.6 Group 4: 7.7 Group 5: 6.8 Group 6: -1.7	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
			62% male, BMI 24.9 Kg/m2 (SD: 5), 81% atopic (seasonal allergy rhinitis). <u>Group5</u> (N= 15); MF-DPI 200 mg Mean age 32 years (SD: 10.4), 60% male, BMI 25.1 Kg/m2 (SD: 4.3), 93% atopic (seasonal allergy rhinitis). <u>Group6</u> (N= 15); Placebo Mean age 42.2 years (SD: 15.1), male 38%, BMI 25.5 Kg/m2 (SD: 5.3), 77% atopic (seasonal allergy rhinitis).			was significantly superior to all other treatment groups. However, changes increased in a dose-response manner across escalating doses of MF/F.		
		Mannitol challenge test, N= 93				All active treatments afforded more protection against bronchial hyperresponsiveness compared with placebo. There was no observed MF/F dose response, and only the MF/F 100/10 mg treatment group achieved a statistically significant difference versus placebo	Mean difference from baseline Group 1: 0.7 (SD: 31.5) Group 2: 1.1 (SD: 62.2) Group 3: 1.1 (SD: 34) Group 4: 1.1 (SD:17.9) Group 5: 0.7 (SD: 18.3) Group 6: -0.2 (SD: -9)	
Park, 2016[144]	South Korea, longitudinal, outpatient	FeNO, N=33	Mean age 6.95 years (SD: 1.83), 72.7% male, 81.8% atopics.	Measured using Niox Mino device (Aerocrine, Solna, Sweden).	All subjects were treated with 160-mg ciclesonide per day for 3	Changes in FeNO level (ppb) after 3 months of ICS treatment	-0.28 ppb (SD: 0.33)	Bronchial hyperresponsiveness to AMP may better reflect the relationship

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	setting, medium risk of bias	Spirometry, N =33		All these tests were performed in all subjects on the same day. all patients were responsive to methacholine (provocative concentration causing a 20% fall in FEV1, PC20 <25 mg/mL) and AMP (PC20 < 400 mg/mL). The challenge was terminated if FEV1 dropped by >20% from post-saline value or if maximal concentration of methacholine or AMP was administered. PC20was calculated by linear interpolation of the log-dose-response curves.	months, which was administrated with or without a spacer (Vor-tex®, PARI GmbH, Starnberg, Germany) that was fitted to the mouthpiece depending on the patient age and inhaler performance.	Changes in FEV1% pred after 3 months of ICS treatment	12.21% (SD: 12.47)	between improved airway inflammation due to ICS treatment and asthma symptoms than FeNO.
		Methacholine challenge test, N=33				Changes in PC20 methacholine after 3 months of ICS treatment	2.91 (SD: 1.59)	
		adenosine 5-monophosphate (AMP), N = 33				Changes in PC20 AMP after 3 months of ICS treatment	2.16 (SD: 1.54)	
		Asthma control assessments, N =33		Six questions were scored on a 5-point scale and a high score indicated good asthma control. Patients were asked to recall their symptoms during the previous month at each visit, and symptom scores included wheezing, use of a short-acting bronchodilator, shortness of breath, nocturnal		Changes in Symptom score after 3 months of ICS treatment	3.36 (SD: 4.39)	

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				symptoms, activity limitation, and overall asthma control.				
Profita, 2013 [145]	France/Italy, RCT, outpatient setting, unclear risk of bias.	FeNO, N=40	nBDP group (nebulized beclomethasone di propionate): mean age 11.1 years (range 10.1-12.1), 70% males, BMI 13.7 kg/m^2 (range 12.7-14.7) Placebo group: Mean age 13.1 years (range 9.6-11.2), 70% males, BMI 14.3 kg/m^2 (range 9.6-11.2).	Nasal and oral FeNO were determined by chemiluminescence (N10x, Acrocrine, Solna, Sweden) following ATS/ERS recommendations.	4 weeks of nebulized beclomethasone di propionate (nBDP) (daily dose of 800 µg administered twice daily) or placebo with a face mask.	Change of nasal and oral FeNO level before treatment and difference after 4 weeks in each group.	Nasal FeNO mean difference nBDP group -9.3, 95% CI -212.1 to 193.6. Placebo group: -149.8, 95% CI -343 to 44.309. Oral FeNO mean difference nBDP group -29.5, 95% CI -41.6 to -17.5. Placebo group: -1.2, 95% CI -9.7 to 7.4.	In children with allergic asthma and rhinitis, nebulized beclomethasone dipropionate for 4 weeks significantly reduces FeNO.
		Spirometry, N = 40		Measured following ATS/ERS recommendations		Change of FEV_1 % level before treatment and difference after 4 weeks in each group	nBDP group 3.86% pred, 95 CI -2.02 to 9.73. Placebo group: -2.52% pred, 95% CI -4.80 to -0.23.	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Silkoff, 2001[146]	Canada, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N=15	Age range 17-40 years, 53.3% males.	Subjects inhaled medical-grade compressed air (Praxair) that contained 2 ppb NO and then exhaled via a high expiratory resistance while targeting a mouth pressure of 20 mm Hg. This produced an expiratory flow rate of 45 mL/s (including analyzer sampling rate). Exhalations were repeated until three plateau Feno values varied by 5%. The mean of the three replicate Feno values was used in all analyses.	Four 1-week periods (periods 1 to 4), the following were administered twice daily via metered dose inhaler: period 1, placebo; period 2, 100 g/d of iBDP; Period 3, 400 g/d of iBDP; Period 4, 800 g/d of iBDP.	There was a progressive fall in FeNO as the dose of iBDP was increased, and all doses of iBDP were associated with a significant change in Feno from baseline and placebo values, even after correcting for multiple comparisons.	Baseline: 103.5 (78.5 to 136.7) Period 1: 96.0 (67.9 to 135.6) Period 2: 59.0 (41.3 to 84.2) Period 3: 45.2 (35.7 to 57.2) Period 4: 37.4 (29.1 to 48.0).	In adults with non-steroid treated asthma, FeNO levels changed in a dose dependent manner with ICS.

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry, N=15		Performed according to American Thoracic Society guidelines using a dry rolling seal spirometer (model 130; P.K. Morgan; Gilling- ham, Kent, UK) and an XY recorder (model 7045A; Hewlett Packard; Palo Alto, CA).		No significant differences were seen for FEV_1 between any of the doses of iBDP. For FVC, there were no significant differences between any of the treatment levels, compared with baseline or placebo.	Baseline FEV_1: 3.01 L (SD: 0.73) Period 1: 3.00 L (SD: 0.84) Period 2: 3.29 L (SD: 0.71) Period 3: 3.36 L (SD: 0.73) Period 4: 3.41 L (SD: 0.80) Baseline FVC: 4.49 L (SD: 0.97 Period 1: 4.42 L (SD: 0.93) Period 2: 4.61 L (SD: 0.84) Period 3: 4.54 L (SD: 0.84) Period 4: 4.60 L (SD: 0.80)	
		Methacholine challengetest (PC20), N= 15		Methacholine challenge was performed with a tidal breathing pattern using a hand-held nebulizer according to American Thoracic Society guidelines.		No significant differences were seen for PC20 between 100 g/d and 400 g/d, between 100 g/d and 800 g/d, or between 400 g/d and 800 g/d of iBDP.	Baseline 0.01 mg/mL (0.00 to 0.19) Period 1: 0.02 (0.00 to 0.52) Period 2: 0.09 (0.00 to 3.22) Period 3: 0.31 (0.00 to 20.2) Period 4: 0.48 (0.01 to	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
							28.1).	
Smith, 2015 [147]	Canada, cross sectional, inpatient setting, medium risk of bias.	FeNO, N= 183	Mean age 12.8 years (SD: 2.76), 57.4% males, 29.5% Parental smoking, mean weight 53.1 Kg (SD: 23.3), 33.3% atopic (eczema).	Measured using asthma inflammation monitor (NIOX MINO, Aerocrine, Sweden).	Different doses of Fluticasone (36.1%), or ciclesonide (27.3%), or Beclomethasone dipropionate (hydrofluoroalkane or chlorofluorocarbon propellant), or Budesonide.	FeNO varied according to ICS type. Mean-adjusted FeNO was lowest in fluticasone users compared with no ICS. However, There was no statistically significant difference in adjusted FeNO between ciclesonide, beclomethasone or budesonide vs no ICS.	*Mean difference fluticasone vs no ICS; 18.6 ppb, 95% CI: (1.0 to 36.2), P=0.03. *Mean difference ciclesonide vs no ICS; 5.9 ppb, 95% CI: -(9.0 to 20.8), P>0.99. *Mean difference beclomethasone vs no ICS; 6.6 ppb, 95% CI: -(10.3 to 23.5) *Mean difference budesonide vs no ICS; 17.6 ppb, 95% CI: (-5.0 to 40.2)	In children with asthma, FeNO was reduced by ICS with variation according to ICS type, suggesting a difference in relative efficacy between ICS beyond their dose equivalents.

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry, N= 183		Measured using a spirometer (Koko, PDS Instrumentation, USA).		Increased FeNO was associated with percent change in both FEV_1 and FEF 25-75 adjusted for allergic rhinitis, parental smoking and ICS type	*Coefficient FEV_1 and FeNO; 0.08, 95% CI: (0.04 to 0.12), P< 0.001. *Coefficient FEFF25-75 and FeNO; 0.13, 95% CI: (0.01 to 0.24), P=0.03.	
Spallarossa, 2001 [148]	Italy, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N=39	Mean age 11.9 years (SD: 0.6), 69% males, 100% atopic.	Online chemiluminescence analyzer (Logan LR 2000 System, Kent, UK), at 50 ml/sec, at several visits (0, 10, 40 days).	Low doses of inhaled steroids for 10–40 days.	A significant reduction in FeNO levels after low dose of inhaled steroid. However, follow up 16 patients showed that the improvement in FeNO were statistically significant after 10 days and remained stable after 40 days of treatment.	FeNO before vs after therapy 30.8 ppb (SD:3.04) vs 14.0 ppb (SD: 1.4). <u>At 10 days:</u> 14.7 ppb (SD: 2.3) <u>At 40 days:</u> 11.9 ppb (SD: 1.8).	In steroid-naive atopic children with mild intermittent asthma, ICS significantly lowered FeNO values at 10 days without further reduction at 40 days
		Spirometry, N=39		Measured by spirometry (Med Graphics, Pulmonary Function System 1070 series 2, Med Graphics Corp., St. Paul, MN). On each occasion, three forced		A significant improvement of FEV_1, FVC and FEEF 25-75% after low dose of inhaled steroid. However, follow	FEV_1 before vs after therapy 92.05 % (SD: 1.5) vs 103.1% (SD: 1.7).	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
				expiratory maneuvers were obtained and the best values were retained.		up 16 patients showed a significant improvement in FEV_1 and in FEF25–75% values after 10 days and remained stable after 40 days of treatment.	FVC before vs after therapy 99.8 % (SD: 2.3) vs 106.9 % (SD: 2.7). FEF25–75% before vs after therapy 80.9 % (SD: 3.5) vs 96.23 % (SD: 2.9). <u>At 10 days;</u> FEV_1 97.9% pred (SD: 2.6) and FEEF 25-75% 86.6% pred (SD: 4.3) <u>At 40 days;</u> FEV_1 95.7% pred (SD: 3.2) and PEEF 25-75% 81.2 % pred (SD: 4.7)).	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Thomas 2016[149]	Singapore, Cross sectional, Outpatient setting, Low risk of bias	FeNO, N=57	British Thoracic Society (BTS) step 2 group, N = 27 Mean age 10 years (8-13), 63% males, BMI 19.7 Kg/m2, 100% atopics (allergic rhinitis) BTS step 3, N = 30 Mean age 10.5 years (8-13), 63.3% males, BMI 19.8 Kg/m2, 100% atopics (allergic rhinitis)	FeNO was measured before spirometry using NioxMino (Aerocrine AB, Sweden) per the ATS/ERS guidelines.	BTS step 2 group received 8 weeks 400mg Beclomethasone Dipropionate [BDP] equivalent. BTS step 3 group received 8 weeks 400-800 mg BDP equivalent or combination 400mg BDP equivalent plus LABA or LTRA	The agreement between MCT (positive or negative), FeNO (>25 or >25 ppb) and clinical assessment of asthma control (controlled, partially controlled or uncontrolled) showed poor agreement between these measures.	Agreement between MCT and FeNO: 0.207 (p=0.1) Agreement between FeNO and asthma control: -0.103 (p=0.4) Agreement between MCT and asthma control: -0.201 (p=0.18)	In children with asthma on therapy, the concordance between clinical assessment of asthma control, BHR and FeNO was observed to be poor.
		Spirometry, N =57		Spirometry using the Vitalograph Spirotrac 6800 (Vitalograph Inc., Lenexa, KS) with Spirotrac Version 4.31 software per ATS/ERS guidelines.				
		Bronchial hyperresposiveness (BHR), N =57		Measured Manitol challenge test (MCT) PD15 which defined as dose of mannitol that causes a >15% fall in FEV1 from baseline.				
		Asthma control test (ACT), N =57						

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Verini, 2007 [150]	Italy, RCT with cross-over, outpatient setting, unclear risk of bias.	FeNO, N= 12	Mean age 9.5 years (SD: 3).	Measured by chemiluminescence analyzer CLD77 Echo Physics, at 5-6 L/minute.	4 weeks of inhaled fluticasone propionate 100 mg BID with either montelukast 5mg once a day or salmeterol 50 µm BID.	Additional treatment with montelukast reduced FeNO significantly (p< 0.01), however, no significant differences was observed when salmeterol was added.	Baseline 14 ppb (SD: 6.3) Montelukast 8.5 (SD: 5.0) vs salmeterol 10.7 (SD: 5.5).	In children on ICS, adding salmeterol did not change FeNO but adding montelukast does
		Spirometry, N= 12		evaluated by a pneumotachograph with an open-circuit nitrogen washout method (VMAX 22L; Sensor Medics, Yorba Linda, CA).		Additional treatment with montelukast showed no change from baseline for FEV_1 and FVC. The addition of salmeterol to FP induced a non-significant increase in both FEV_1 and FVC.	FEV_1 baseline 102.3% (SD: 21.1) Montelukast 101.6% (SD: 18.6) salmeterol 108.0% (SD: 13.5). FVC baseline 97.2% (SD: 17.4) Montelukast 97.5% (SD: 11.7) salmeterol 103.5% (SD: 11.3).	
Zeiger, 2006 [98]	United States, RCT with cross-over, outpatient setting,	FeNO, N= 99	Range age (6-13) years, 59% male.	Measured by (78% online) NIOX Aerocrine AB – chemiluminescence,	16 weeks of fluticasone propionate (FB) 100 mg BID, and montelukast (MT) 5-10 mg	Mean FeNO (ppb) decreased after fluticasone propionate (FB), and montelukast (MT) but the decrease was	Baseline 39.5 (34.2 to 44.7). FP 20.6 (15.0 to 26.2). MT	In an RCT of children with asthma, FeNO was significantly reduced from baseline by both fluticasone and

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
	unclear risk of bias.				once a day	greater after fluticasone. FeNO correlated with improvements in asthma control days (ASDs) in fluticasone but not with montelukast.	30.9 (25.5 to 36.2). FP-MT mean difference -10.3 (-16.9 to -3.7). FeNO vs ACDs FP -0.21 (-0.33 to -0.08). MT -0.04 (0.17 to 0.09).	montelukast; however, the reduction was significantly more with fluticasone
		Spirometry, N= 126				Fluticasone (FB) led to significant improvements in prebronchodilator FEV/FVC (% pred) while montelukast (MT) associated with a significant but small decrease. However, greater improvements in prebronchodilator FEV_1/FVC occurred after fluticasone (FB) than after montelukast (MT).	FEV_1/FVC % Baseline 80.1 (79.1 to 81.1) FP 82.2 (80.9 to 83.6) MT 79.0 (77.6 to 80.5) FP-MT mean difference 3.2 (2.3 to 4.1)	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Asthma control questionnaire, N= 127				Compared with baseline, both fluticasone (FB) and montelukast (MT) treatments were associated with significant improvements in mean ACQ scores, but better control was achieved with fluticasone.	Baseline 0.96 (0.89-1.03) FP 0.59 (0.50 to 0.69) MT 0.76 (0.66 to 0.87) FP- MT mean difference -0.17(-0.27 to -0.07)	

AST/ERS recommendation: American Thoracic Society/ European Respiratory Society/ recommendation; AUC: area under the curve; BMI: body mass index; CI: confidene interval; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: Long acting Beta-agonist; PC20: provocation concentration causing a 20% fall in FEV_1; PD20: provocation dose causing a 20% decline in FEV_1; PEF: he peak expiratory flow; RCT: randomized clinical trial; SD: standard deviation.

Table C.10. Characteristics of the included studies in KQ 1d FeNO response to administration of bronchodilators (beta agonists and anticholinergics)

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Fuglsang, 1998 [151]	Denmark, RCT with crossover, outpatient setting, low risk of bias.	FeNO, N= 22	Mean age 11.6 years (7-15).	Measured by online chemiluminescence-model LR200, Logan Research, at 5-6 L/min	3 weeks of inhaled 50 µg salmeterol BID, placebo or inhaled 200 µg budesonide BID.	There was no statistically significant difference in FeNO after salmeterol and placebo treatment, however, budesonide significantly decreased to normal level.	Endpoint FeNO salmeterol: 12.7. Placebo: 10.7. Budesonide: 5.2.	FeNO levels were unaffected by salmeterol treatment for 3 weeks but were significantly reduced during budesonide therapy.
		Spirometry, N= 22				The terbutaline dose–response curve appeared flatter after the salmeterol period than after the placebo period for both FEV_1 and FEF25-75.	FEV_1 (% pred) mean difference Placebo 18% Salmeterol 2% FEF25-75% mean difference Placebo 41% Salmeterol 4%.	
Inoue, 2016[152]	Japan, RCT, outpatient setting, Low risk of bias	FeNo, N=33	Tulobuterol Patch (TP) group, N=16 Mean age 56.7 years, 25% male, 6% ex-smoker, mean BMI 24.2 kg/m2 Salmeterol	FeNO was measured first using a chemiluminescence analyzer (NOA 280; Sievers Instruments, Boulder, CO, USA) according to the ATS at 50 mL/sec expiratory flow rare.	12 weeks add-on treatment with either Tulobuterol Patch (TP) or Salmeterol Inhaler (SA) on ICS.	FeNO showed no statistically significant in both decreased after TP and increased after SA.	TP 18.9 ppb (12.6-47.1) to 17.2 ppb (8.8-36.9) SA 22.8 ppb (8.1-69) to 25.2 ppb (6.9-63.2)	Add-on treatment of TP improved asthma control and health status, whereas SA improved pulmonary function measures among patients with adult-onset

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry, N=33	Inhaler (SI) group, N=17 Mean age 49.2 years, 24% male, 29% ex-smoker, mean BMI 23 kg/m2	Measured after FeNO according to the ATS standards using a ChestGraph HI-701 spirometer (Chest M.I., Tokyo, Japan) without taking a bronchodilator.		$FEF_{25-75\%}$ was significantly improved in SA vs no improvement in TP.	TP 2.8 L/s (0.92) to 2.61 L/s (0.83). SA 2.48 L/s (1.19) to 2.73 L/s (1.25).	mild-to- moderate asthma.
		Asthma control test (ACT), N = 33		Five questions questionnaire, with the best score of 25.		ACT significantly improved after TP, while non-significant increased after SA was observed.	TP 21 (5-25) to 24 (17-25). SA 21 (10-25) to 23 (10-25).	
Hoshino, 2016[153]	Japan, RCT, outpatient setting, High risk of bias	FeNo= 53	Group 1: add-on Tiotropium + ICS + LABA group, N= 25 Mean age 57 years, 44% male, mean BMI 25.6 kg/m2, 72% atopic patients Group 2: ICS +	Measured by electrochemical reaction by using a portable nitric oxide analyzer (NioxMino; Aerocrine, Solna, Sweden) at an exhalation flow rate of 50 mL/sec.	(Group1) 48 weeks of 5 mg daily Tiotropium add-on to maintenance therapy in asthma with ICS plus LABA (delivered	No significant change in FeNO was observed in add-on or no add-on groups from baseline to week 48.	Group1 -5.0 (SD:4.6) Group2 -1.6 (SD:6.1)	The addition of once-daily tiotropium to maintenance therapy improved airflow limitation and reduced airway T. A triple combination of tiotropium and ICS

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry =53	LABA group, N = 28 Mean age 53 years, 56% male, mean BMI 24.1 Kg/m2, 71% atopic patients	Using computed spirometry. Predicted values for forced vital capacity and FEV1 were calculated by using the formula proposed by the Japanese Respiratory Society.	through the Respimat SoftMist inhaler [Boehringer Ingelheim, Ingelheimam Rhein, Germany]) or no add-on (group 2).	A significant difference in change in FEV1% predicted was observed between the two groups.	Group1 change in FEV1% pred 3.4 (SD:3.1) Group2 0.8 (SD:3.4)	plus LABA may have additive protective effects of bronchodilation and remodeling.
		Asthma Quality of Life Questionnaire (AQLQ), N=53		A 32 items questionnaire covers symptoms, activities, emotions, and environment by using a seven- point scale. A change of >0.5 points represents a clinically meaningful improvement.		Significantly better scores for symptoms and emotions in the group 1unlike no improvement in group. The difference in symptom score between the groups was statistically significant.	Group1 Change in symptom 0.5 Change in emotion 0.2 Group2 Change in symptom 0.2 Change in emotion 0.1	
Yates, 1997 [154]	United Kingdom, RCT with cross-over, outpatient, low risk of bias.	FeNO, N= 20	Talking ICS (N= 10); mean age 30.1 years (21-39), 70% male, 90% atopic. Placebo (N= 10); mean age 29.6 years (22-63),	using an online chemiluminescence analyser (Dasibi Environmental Corporation Model, Glendale, CA, USA), at 1 L/min.	One week of nebulized salbutamol (5 mg), added to inhaled glucocorticosteroids (ICS) or placebo.	Salbutamol added to inhaled ICS result in significant increase in FeNO comparted when added to placebo where shows no difference.	Talking ICS 124 ppb (SEM: 38) to 165 ppb (SEM: 85). Placebo 205 ppb (SEM: 37) to 204 ppb (SEM: 44)	Single high dose salbutamol did not increase exhaled nitric oxide in asthmatics not taking inhaled glucocorticosteroids.

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry. N= 20	60% male, 80% atopic.	Using a dry wedge spirometer (Vitalograph, Buckingham, UK).		Salbutamol showed an improvement in FEV_1 (5 pred) when added to inhaled ICS or placebo.	Talking ICS 91 (SD: 6) to 98 (SD: 5). Placebo 94 (SD: 5) to 104 (SD: 5)	

FeNO: fraction exhaled nitric oxide; FEF25–75: forced expiratory flow at 25–75% of forced vital capacity; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; RCT: randomized clinical trial; SD: standard deviation; SEM: standard error of the mean.

Table C.11. Characteristics of the included studies in KQ 1d for FeNO use for ICS reduction or withdrawal

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
Cabral, 2009 [155]	Brazil, longitudinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N= 32	Mean age 10.3 years (SD: 2.2). 65.6% males. Moderate asthma: n=18, 12 males, age (mean +/-SD) 9.4 +/-1.9. Severe asthma n=14, 9 males, age 11.4+/-2.1.	FeNO was then measured using an off-line single-breath exhalation technique by chemiluminescence using a fast-responding analyzer (NOA 280; Sievers Instruments Inc, Boulder, Colorado). The analyzer was calibrated with a certified 47-ppb NO source (White Martins, Brazil) and 0 NO filter (Sievers Instruments Inc) before each measurement.	2 month run-in period, ICS were adjusted to equivalent doses of fluticasone administered with a metered-dose inhaler. During tapering, the dose of ICS was reduced by 25% every 2 weeks as long as the child remained stable. If the patient did not remain stable, the	FeNO level was not associated with future risk for asthma exacerbations in any of our regression models. The only factor that was associated with subsequent exacerbations in these models was an indicator of baseline severity (severe vs moderate). Even after further adjustment for exacerbations, children with severe asthma had a 2.7-fold	Baseline Moderate asthma (N=18): 29 ppb (SD: 13) severe asthma (N=14) 50 ppb (SD: 20)	In children with moderate-to severe asthma undergoing ICS reduction, FeNO measured biweekly and expressed as a continuous variable or dichotomized, was not associated with future risk for exacerbations

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry, N= 32		We performed spirometry using a spirometer that features a brass pneumotach and combines a portable unit with a computer system (KoKo spirometer; PDS Inc, Ferraris Cardio-pulmonary Systems Group, Louisville, Colorado). Children were asked to refrain from using their reliever medications for at least 4 hours before testing if possible.	ICS dose was either maintained or increased according to physician discretion; oral corticosteroids were given as needed for exacerbations.	(95% CI, 1.1 to 6.6) increased odds of having an exacerbation in the following 2 weeks when compared with children with moderate asthma.	FEV_1% pred Baseline Moderate asthma: 94.2 (SD: 16.2). Severe asthma: 50 (SD: 20).	
Hojo, 2013 [156]	Japan longitudinal nonrandomized outpatient setting, low risk of bias.	FeNO, N= 51	Global Initiative for Asthma (GINA) step1 group: (N=27) Mean age 50.2 years (SD: 8.8), 44% male, 8% ever smokers BMI 23.7 Kg/m2 (SD: 2.8), 56% atopic. Global Initiative for Asthma (GINA) step2 group: (N=24) Mean age 48.9	Online NIOX-MINO (Aerocrine Ltd., Solna, Sweden) every 8 weeks for 48 weeks.	GINA step1 group: Budesonide 400 µg and salmeterol 100 µg. GINA step2 group: Salmeterol/ fluticasone 250 at 2 puffs.	Moderate or more severe exacerbations of asthma were experienced by 6 patients (22%) in the step1 group, but only 3 in step2 group.	Baseline: step1 group 44.5 (SD: 28.7) step2 group 48.8 (SD: 31.1) At 8 weeks: step1 group 39.4 (SD: 25.5) step2 group No change At 24 weeks: step1 group: No change step2 group: 39.6 (SD: 23.6)	In adults with moderate asthma treated with either budesonide 400 µg and salmeterol 100 µg or salmeterol/ fluticasone 250 at 2 puffs, step down from medium to low dose was safely

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry, N= 51	years (SD: 11.3), 46% male, 5% ever smokers BMI 22.9 Kg/m2 (SD: 1.9), 76% atopic.	Spirometry was measured every 8 weeks.			FEV_1% pred at baseline: step1 group 72.6 (SD: 9.7) step2 group 76.5 (SD: 16.2) At 48 weeks: step1 group: 76.4 (SD: 13.5) step2 group: 79.4 (SD: 12.4)	performed using a combined FeNO and ACT approach at 8 week intervals
		Asthma control test (ACT), N= 51		ACT was measured every 8 weeks			Baseline Step1 group: 23.1 (SD: 1.4) Step2 group: 22.2 (SD:1.6)	
Jones, 2001 [157]	New Zealand, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N=77	Mean age 42.9 years (range 18-74), 38.9% male, 15.6% ex-smokers, 0% current smoker.	Measured by calibrated chemiluminescence analyzer with online measurement of single exhalations according to a standard protocol, with the exception of flow rate (250 ml/s)	Corticosteroid treatment was stopped following a 2- to 4-wk run-in during which the maintenance dose remained unchanged.	The loss of control group (LOC) (N=60) experienced a 2.16-fold increase in FeNO between first and last visit, which was significantly greater than the 1.44-fold increase for the no LOC	Loss of control mean difference: 2.16 (1.88 to 2.48). No loss of control mean difference: 1.44 (1.13 to 1.82)	In adults, both single measurements and changes of FeNO (10 ppb, 15 ppb, or an increase of > 60% over baseline) had positive

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		Spirometry, N=77		Spirometry was measured using a rolling seal spirometer.		group (p< 0.01). There were also significant differences between LOC and no LOC groups for the decrease in FEV, (p<0.01), the increase in sputum eosinophils (p= 0.04).	Loss of control FEV_1 mean difference -11.9 (-15.2 to -8.7). No loss of control FEV_1 mean difference -1.1 (-3.3 to 1.2).	predictive values that ranged from 80 to 90% for predicting and diagnosing loss of asthma control after ICS withdrawal.
		Sputum eosinophils, N=77					Loss of control mean difference 14.3 (8.0 to 20.6). No loss of control mean difference 3.3 (-1.5 to 8.0)	
Liu, 2010 [158]	United States, longitudeinal nonrandomized, outpatient setting, medium risk of bias.	FeNO, N= 21	Mean age 29.7 years (18-40), 14% male, 0% current smoker.	Measured by online NIOX (Aerocrine), flow rate per referenced guidelines, steroid priot to test was 100%,	6 months of stepwise fluticasone weaned from 220 ug twice daily to 220 ug once daily.	There is a linear increase pattern for FeNO associated with dose titration. However, FeNO was not a significant time-dependent predictor for the exacerbation.		Adults with moderate persistent asthma undergoing withdrawal of ICS had significant but heterogeneous rise in FeNO.
		Exhaled breath condensate (EBC), N= 21				For EBC pH, no significant trend was observed during titration, however, the fall in	Mean difference EBC PH in exacerbation vs non exacerbation: -	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
						EBC pH was greater in the 6 subjects who had an exacerbation than in the 7 who did not.	0.58 (SD: 0.7) vs 0.16 (SD: 0.13).	
		Spirometry, N= 21				There is a significant linear decrease pattern for FEV_1 during dose titration. However, FEV_1 was not significant time-dependent predictor for the exacerbation.		
Obase, 2013 [159]	Japan, RCT, unclear risk of bias.	FeNO, N= 29	Step-down group (N= 15) Mean age 46.5 years. Continued group (N= 14) Mean age 45.3 years	Flow of 50 mL/sec, using an online nitric oxide analyzer (NOA 280i; Sievers Instruments, Inc., Boulder, CO) in one visit several times.	Budesonide/ formoterol Step-down group: Baseline 538 mcg/day (424–653) At 8 weeks 331 mcg/day (285–376) Continued group: Baseline 500 mcg/day (385–615) At 8 weeks 500 mcg/day (385–615)		Step-down group: Baseline 51.0 (38.5 to 63.4) At 8 weeks: 65.7 (36.0 to 95.4) Continued group: Baseline 50.9 (33.9 to 67.9) At 8 weeks: 45.0 (25.9 to 64.1)	Adults newly diagnosed asthma received budesonide/ formoterol for 8 weeks or more then randomized to continue or step-down group. In both groups, pulmonary function indicators and symptoms did not
		Spirometry, N= 29		Dry spirometer (CHESTAC-33; CHEST MI, Tokyo, Japan), which			FEV_1Step-down group: Baseline	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
				meets the 1994 American Thoracic Society (ATS) recommendations for diagnostic spirometry			98.8 (84.2 to113.3) At 8 weeks: 105.2 (94.9 to 115.5) Continued group: Baseline 94.0 (80.6 to 107.3) At 8 weeks: 92.0 (76.8 to 107.3)	change. FeNO level decreased significantly in the dosage-continued group (from 50.9ppb to 45.0ppb), and increased significantly in the step-down group (from 51.0ppb to 65.7ppb).
		Asthma control test (ACT) , N= 29		In general, patients with a score below 0.75 have adequately controlled asthma; those with a score above 1.0 do not have well-controlled asthma. On the seven-point scale of the ACQ, a change of 0.5 in the score is the smallest that can be considered clinically important. In this study, we set a score of 0.5 or less as confirmation of adequate asthma control by ICS/LABA at baseline and after 8 weeks of treatment.			Step-down group: Baseline 24.3 (23.6 to 25.0) At 8 weeks: 22.9 (20.2 to 25.6) Continued group: Baseline 23.8 (22.8 to 24.8) At 8 weeks: 24.0 (22.4 to 25.6)	
		Asthma Control Questionnaire		Patients with a score below 0.75 have adequately controlled			Step-down group: Baseline	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
		(ACQ) , N= 29		asthma; those with a score above 1.0 do not have well-controlled asthma. On the seven-point scale of the ACQ, a change of 0.5 in the score is the smallest that can be considered clinically important. In this study, the score set of 0.5 or less as confirmation of adequate asthma control by ICS/LABA at second entry and 8 weeks after randomization.			0.04 (-0.02 to 0.10) At 8 weeks: 0.31 (-0.07 to 0.68) Continued group: Baseline 0.13 (0.03 to 0.22) At 8 weeks: 0.25 (-0.05 to 0.55)	
		Asthma Quality of Life Questionnaire (AQLQ) , N= 29		The questionnaire consists of 32 questions within four domains: symptoms, activity limitation, emotional function and environmental stimuli.			Step-down group: Baseline 6.66 (6.43 to 6.88) At 8 weeks: 6.34 (5.84 to 6.85) Continued group: Baseline 6.76 (6.56 to 6.96) At 8 weeks: 6.57 (6.16 to 6.99)	
Pijnenburg, 2005 [160]	Netherlands, longitudinal	FeNO, N=37	Group1 (without relapse) (N=28): mean age 12.2 years (range 7.3-	FeNO was measured online with an expiratory flow of 50 ml/s according to ATS and ERS	Baseline FeNO was measured at t = 22 and t = 0	Two and four weeks after withdrawal of steroids geometric	<u>Group1</u> Baseline: 10.5 (7.3 to 14.2).	In children, FeNO measurements 2 and 4

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
	nonrandomized, low risk of bias.		16.9), 75% atopic, Daily dose of ICS 400 (100-400), mean weight 10.2 Kg (range 7.3-14.2). Group2 (With relapse) (N=9): Mean age 12.3 years (range 10.0-15.8), 88% atopic, daily dose of ICS 200 (100-400), mean weight 14.8 Kg (range 8.5-25.8).	guidelines. NO was continuously sampled with a sampling flow of 175 ml/min and analyzed by a chemiluminescence analyzer (Sievers 280 NOA, Boulder, CO, USA). The analyzer was calibrated weekly using 0 and 115 ppb NO certified gases (BOC, Herenthout, Belgium).	weeks. FeNO was monitored 2, 4, 12, and 24 weeks after withdrawal of ICS.	mean FeNO in children who were about to relapse was higher than in those who did not relapse: at 2 weeks (ratio 2.3; 95% CI 1.2 to 4.1; p = 0.01) and at 4 weeks (ratio 2.6; 95% CI 1.3 to 5.1).	At 2 weeks 15.7 ppb At 4 weeks 15.9 ppb <u>Group2</u> Baseline: 14.8 (8.5 to 25.8). At 2 weeks 35.3 ppb At 4 weeks 40.8 ppb	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%) for asthma relapse.
		Spirometry, N=37		Flow-volume curves were obtained with a dry rolling seal spirometer (Jaeger, Wurzburg, Germany) according to ATS guidelines. After maximal inspiration, three reproducible loops with a maximum variability in FVC of 10% were obtained. FVC and FEV_1 are expressed as percentage predicted.	Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) before and after bronchodilation were measured at t = 22, 12 and 24 weeks. At t = 0 weeks, treatment with ICS was discontinued in patients with low symptom scores (below 14).		<u>Group1</u> Baseline FEV_1% 100 (73-134) FVC% 106 (80 to 139). Post-bronchodilation: FEV_1% 106 (80 to 139), Post-bronchodilation: FVC% 103 (66-127). <u>Group2</u> Baseline: FEV_1% 99 (88 to 109), FVC% 105 (87 to 118). Post-bronchodilation: FEV_1% 107 (91 to 119),	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
							Post-bronchodilation: FVC% 105 (78 to 118).	
Prieto, 2003 [161]	Spain, longitudinal non randomized, outpatient setting, high risk of bias.	FeNO, N=37	Mean age 32.2 years, (range 28.7–35.6), 30 % males, 27% ex-smoker, 81% atopic.	Measured on-line by the restricted breath analysis according to the recommendations of the American Thoracic Society using a chemiluminescence analyzer (NiOx; Aerocrine; Solna, Sweden)	2-week run-in of beclomethasone dipropionate, 500 to 1,000 ug or equivalent daily. Then, 12 weeks with ICS at half the previous dose.	FeNO changes from the run-in period to the visit performed 2 weeks after the reduction of ICS.	FeNO ≥ 10 ppb OR 1.89, 95% CI (0.36 to 9.97).	In adults with asthma on high dose ICS that was reduced by 50%, FeNO values at baseline >15 ppb perdict reduction failure.
		Spirometry, N =37		Measured using a calibrated pneumotachograph (Jaeger MasterScope; Erich Jaeger GmbH; Wurzburg, Germany) according to standardized guidelines.				
Tsurikisawa, 2012 [162]	Japan, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 90	Exacerbation-free group (N=50); Mean age 49.1 years (SD:14.6), 34% male, 28% ever smoker, 74% atopic. Exacerbation	Mesured by online (80%) NO chemiluminescence analyzer (NOA model 280A, Sievers Instruments) at 70 ml/sec, steroid prior to test was 100%.	12 months of the daily inhaled corticosteroid dose that reduced by half.	FeNO was lower in exacerbation-free compared with exacerbation group after treatment. However, FeNO was a more significant predictor of success in ICS reduction than	Exacerbation-free group 25.6 ppb (SD: 12) Exacerbation group 43.4 ppb (SD: 27.3). 0.961, 95% CI (0.93 to 0.99).	In adult patients with moderate or severe asthma but no clinical symptoms of asthma for at least 6 months in whom ICS doses

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Medication (Frequency, Dose, Duration, etc.)	Asthma Outcomes	Test Findings (Mean, SD)	Conclusions
			group (N=40); Mean age 50.9 years (SD:15.9), 37.5% male, 30% ever smoker, 60% atopic.			FEV_1 (p = 0.028).		reduced by half, FeNO was a statistically independent predictor of success.
		Spirometry, N= 90		Measured by spirometer (Auto Spiro AS-303, Minato Medical Science, Osaka, Japan) after each inhalation.		FEV_1 was higher in exacerbation-free group before and after treatment compared with exacerbation group, however, FEV_1 was a less predictor of success in ICS reduction than FeNO (p = 0.03).	Exacerbation-free group 85.9 % pred (SD: 20.9) to 91.1 % pred (SD: 15.1) Exacerbation group 79.6 % pred (SD: 21.3) to 84.1 % pred (SD: 16.7). 1.1, 95% CI (1.0-1.2)	

AST: American Thoracic Society;BMI: body mass index; CI: confidence interval; EBC: Exhaled breath condensate; ERS: European Respiratory Society; FeNO: fraction exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; OR: odds ratio; PH: potential hydrogen; RCT: randomized clinical trial; SD: standard deviation.

Table C.12. Characteristics of the included studies in KQ 1e

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)	Conclusion
Balinotti, 2013 [163]	Argentina, cross section study, outpatient setting, low risk of bias.	FeNO, N=52 Asthma predictive index (API), N= 52	Positive API (N= 31) Mean age 19.8 months (SD: 11), 71% males, mean weight 12.2 Kg (SD: 2). FeNO= 13.5 ppb, 70.9% atopic (eczema+ allergic rhinitis). Negative API (N= 21) Mean age 15.6 months (SD: 8), 62% male, mean weight 10 Kg (SD: 3). FeNO= 5.6 ppb, 0% atopic (eczema+ allergic rhinitis).	Measured by Chemiluminescence Ecomedics CLD 88 Analyzer (Duernten Switzerland, online with tidal breathing manover, one visit several times, at flow rate 50 ml/sec. API was positive if meet 1 major (Parent with asthma or eczema diagnosis) or 2 minor criteria (allergic rhinitis diagnosis, wheeze unrelated to cold, peripheral eosinophilia >4%).	FeNO > 8 ppb predict positive asthma predictive index (API) with a sensitivity of 74%, specificity of 76%, PPV of 82% and NPV of 66.6%.	In children < 3 years, FeNO was higher in those with positive (compared with negative) Asthma Predictive Index
Bloemen, 2010 [164]	Belgium, longitudinal nonrandomized, outpatient setting, high risk of bias.	FeNO, N= 39	53.9% male, Median BMI 16.1 Kg/m2, range 14.6–17.5.	FeNO was measured online using a rapid response chemiluminescence analyser (CLD88sp; EcoMedics, Duernten, Switzerland)	Meadian FeNO 3.1 ppb, range 1.3 to 13.2 FeNO in mAPI positive: 3.6 (1.6 to 4.3). FeNO mAPI negative: 2.9 (2.1 to 5.1). No significant differences were found in FeNO based on mAPI groups, although values were slightly increased in the mAPI-positive group (3.6 ppb) compared with those in the mAPI-negative group (2.9 ppb). However, FeNO values were borderline not significantly increased in the wheezing group (p=0.06), and significantly increased in skin prick tests-positive children, especially for respiratory allergens (p=0.04).	It is possible to apply non-invasive markers (in urine, exhaled nitric oxide (FeNO) and exhaled breath condensate (EBC)) in 3-year-old children, and evaluated the biomarkers in relation to health outcomes and potential modifiers.

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)	Conclusion
		modified Asthma Predictive Index (mAPI), N=134	Mean age 3.1 years, 53% male, Median BMI 15.7 Kg/m2, range 14.5–16.7.	Symptoms of wheeze were assessed by International Study of Asthma and Allergies in Childhood core questions (Pearce et al. 1993). Based on the longitudinal questionnaire, children were classified into a mAPI-positive and a mAPI-negative group (Guilbert et al. 2004). The mAPI is based on four or more episodes of wheezing in the first 3 years of life, of which one is diagnosed by a physician, and at least one of the major criteria (parental history of asthma, atopic dermatitis and allergic sensitivity sitization to at least one aeroallergen) or at least two of the minor criteria (allergic sensitivity sitization to milk, egg or peanuts, wheezing unrelated to colds and blood eosinophils above 4%). The test is categorized as positive/negative.	mAPI were positive in: 10% of total population (N=134) and 13% of children who underwent FeNO test (N= 39).	FeNO was correlated with respiratory allergy, and was borderline significantly correlated with wheezing, but not with the asthma predictive index (mAPI).
Castro-Rodriguez, 2013 [165]	Chile/ Spain, cross section study, low risk of	FeNO, N= 27	Positive API (N=18) Mean age 13.5 months (SD: 6.3), 75% males. FeNO= 12.3 ppb. Negative API (N=9) Mean	Measured by ChemiluminescenceCLD 88 sp; Eco Physics AG, Duernten, Switzerland, Online with multiple breaths asleep post prandial, at 40-60 ml/sec.	In infants (mean age 12 months), FeNO was correlated with Asthma Predictive Index (OR = 1.12, 95% CI: 0.99 to 1.27).	In infants (mean age 12 months), FeNO was correlated with Asthma Predictive Index

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)	Conclusion
	bias.	Asthma predictive index (API), N= 27	age 11 months (SD: 8), 54.6% males. FeNO= 4.1 ppb.	Defined using the stringent index, which requires recurrent episodes of wheezing (3 episodes/ year) during the first 3 years of age and one of two major criteria (physician-diagnosed eczema or parental asthma) or two of three minor criteria (physician-diagnosis allergic rhinitis, wheezing without colds, or peripheral eosinophilia 4%).		(OR = 1.12, 95% CI: 0.99–1.27).
Caudri, 2010 [166]	Netherlands, longitudinal nonrandomized, outpatient setting, low risk of bias.	FeNO, N= 306	Mean age 4 years, 53% male.	FeNO was measured offline according to European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines using exhaled air samples and an ambient air sample were collected in Mylar balloons, and analysed using a chemoluminescence analyser (Sievers NOA 280B, Boulder, Colorado, USA).	A higher FeNO at 4 years were associated with more wheezing and asthma at 8 years; OR 1.6 (95% CI, 1.1 to 2.2).	In pre-school children, with symptoms suggestive of asthma, FeNO measures could predict later asthma symptoms up to the age of 8 years.
		Interrupter resistance (RINT), N= 482		Rint was measured in kPa/l with MicroRint (MicroMedical, Rochester, Kent, UK) during expiration, with occlusion of the airway at peak expiratory flow. Median values for at least five acceptable measurements were calculated.	RINT was significantly associated with wheezing at age 6, but not at 7 and 8 years, OR at 8 years is 1.1 (95% CI 0.7 to 1.6).	
Chang, 2015 [167]	United States, longitudinal	FeNO, N=116	Mean age 10.66 months (SD: 4.6), 47.5% males, 50% atopic (allergy	Infants; measured online at a constant expiratory flow from raised lung volume. In 5 years old; measured online with a	Subjects with asthma at 5 years of age had significantly higher FeNO at study entry as infants prior to any wheezing (FeNO difference: 3.5 ppb,	Infants with eczema (mean age 11 months) and high FeNO

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)	Conclusion
	nonrandomized, low risk of bias.		sensitivity sitization) 50%.	Niox eNO analyzer (Aerocrine, Solna, Sweden).	95% CI 0.12 to 6.84; p=0.04), as well as a significantly higher FeNO as 5-year-olds compared with subjects without asthma (FeNO difference: 10.8 ppb, 95% CI 1.53 to 19.99; p=0.02). Higher FeNO at study entry was significantly associated with a greater risk of asthma at 5 years of age; each 1 ppb increase in FeNO at entry was associated with an increased risk of asthma at 5 years of age (OR 1.13, 95% CI 1.01 to 1.26; p=0.04).	had greater risk of developing asthma at 5 years of age (for each 1 ppb, OR 1.13, 95% CI 1.01–1.26).
		Spirometry, N=116		FEF were obtained using the raised volume technique. FVC and FEF25–75% were expressed as z-scores using normative data from our laboratory.		
		Airway reactivity, N=116		In infants, airway reactivity to increasing concentrations of inhaled methacholine was assessed using FEF and quantified by PC30. In 5-year-olds, airway reactivity was assessed using IOS with increasing inhaled MCh using a five-breath technique according the ATS guidelines.		
		Allergen sensitivity sitization, N=116		Allergen sensitivity sitize considered when the specific IgE level was >0.35 IU/mL.		
Elliot, 2013 [168]	United States, longitudinal nonrandomized, outpatient setting, high risk of bias.	Single breath (SB)-FeNO, N=45	67% males, 27% tobacco exposed 36% atopic.	At least three flow-regulated SB-FeNO measurements by Sievers NOA 280 chemiluminescence analyser (GE Analytical Instruments, at several visits, flow rate 50 mL/sec, 2x per month, Alcohol 0%, Mouthwash 0%.	SB-FeNO > 30 ppb predicts wheezing after the age of 3 years with 77% sensitivity, 94% specificity, 95% PPV, and 73% NPV. SB-FeNO>30 ppb predict exacerbation of wheezing between 2.5-3 years with 84% sensitivity, 78% specificity, 76% PPV, and 86% NPV.	In wheezy infants/toddlers, single breath-FeNO was superior to tidal-FeNO, bronchodilator responsiveness, and the API in predicting future exacerbations and persistence of wheezing at
		Tidal-breathing mixed expired FeNO, N=45		30 seconds of quiet regular breathing with a full facemask following five breaths to washout circuit dead space measured by Sievers NOA 280	Tidal-FeNO > 62 ppb predicts wheezing after the age of 3 years with 48% sensitivity, 56% specificity, 61% PPV and 43% NPV. Tidal-FeNO>62 ppb predict	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)	Conclusion
				chemiluminescence analyser (GE Analytical Instruments; Boulder, CO, USA).	exacerbation of wheezing between 2.5-3 years with 53% sensitivity, 61% specificity, 52% PPV, 60% NPV 60.	age 3 years.
		Bronchodilator responsiveness (BDR), N=45		Was defined as ≥ 12% improvement in FEV0.5, or ≥ 25% improvement in FEF25–75.	BDR predict wheezing after the age of 3 years with 32% sensitivity, 91% specificity, 85% PPV and 43% NPV. BDR predict exacerbation of wheezing between 2.5-3 years with 38% sensitivity, 88% specificity, 71% PPV and 65% NPV.	
		The Castro-Rodriquez Asthma Predictive Index (API), N=45		Defined as meeting 1 major, or 2 minor criteria. Major Criteria included a history of parental physician-diagnosed asthma or a history of physician-diagnosed eczema in the subject. Minor Criteria included a history of physician-diagnosed allergic rhinitis or a history of wheezing apart from colds.	API predicts wheezing after the age of 3 years with 46% sensitivity, 63% specificity, 67% PPV and 42% NPV. ABI predicts exacerbation of wheezing between 2.5-3 years with 47% sensitivity, 61% specificity, 50% PPV 50%, and 58% NPV.	
Klaassen sitivity , 2012 [169]	Netherlands, longitudinal nonrandomized, low risk of bias.	FeNO, N=170	Mean age 3.3 years (SD: 0.6), 54.1% males, 30% tobacco exposure, 26% atopic.	Measured by offlien monitoring system (NIOX, Aerocrine, Solna, Sweden), 18% corticosteroid and 40% bronchodilators use prior to FeNO test.	Odds ratio for FeNO and FeNO change after 8 weeks of inhaled corticosteroids to predicted asthma after the age of 6 years are 1.02 (95% CI: 0.98 to 1.05) and 1.01 (95%CI: 0.99 to 1.04); respectively.	In children age 2-4 with recurrent wheeze, neither FeNO nor FeNO change after 8 weeks of inhaled corticosteroids predicted asthma at the age 6 years. Odds ratios were 1.02 (0.98–1.05) and
		Clinical assessment, N=170		Two paediatric pulmonologists made the diagnosis based on symptoms, lung function (reversibility to a β2- agonist and bronchial hyperresponsiveness), and medication use.		

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)	Conclusion
						1.01 (0.99–1.04); respectively.
Prado, 2011 [170]	Spain, cross section study, medium risk of bias.	FeNO, N=38	Mean age 10.9 months (SD: 5), 59.4% males, Eos >4% in 34.4%, 34.37% atopic (eczema).	Measured by Chemiluminescent CLD88 sp (Eco Physics AG), once in 6 months, at one visit several times, online with multiple respirations during post prandial sleep, at 40-60 ml/sec	Patients with +ve API had significantly higher values of FeNO; 16.31 ppb (SD: 9.36) vs 4.43 ppb (SD: 3.13). High FeNO was also associated with high total IgE; 75.9 (SD: 22.2) vs 6.24 (SD: 8.17) ($p < 0,001$). There was no significant association between eczema and elevated FeNO, or peripheral eosinophilia >400 Eos/mcL and FeNO.	In children age 2-24 months, post-prandial multiple breaths online FeNO was significantly higher in patients with higher Asthma Predictive Index.
		Asthma predictive index (API), N=38		API was positive if they had more than three episodes of wheezing or obstructive bronchitis a year during the first three years of life, while meeting 1 major criterion (parent with asthma, atopic dermatitis diagnosis and/or allergic sensitivity sitization to one or more pneumoallergens) or 2 minor criteria (milk, egg or nut food allergy, wheezing unassociated with colds in the first three years of life and/or eosinophilia in peripheral blood ≥ 4%).		
van Wonderen, 2009 [171]	Netherlands, longitudinal nonrandomized, Inpatient	FeNO, N= 131	Age range; 1-5 years, 56% male.	FeNO is measured in the hospital or general practice at age 5 using an offline technique. Exhaled air is collected in a NO-impermeable Mylar balloon (ABC balloons, Zeist, The Netherlands). All	Ongoing cohort study (The AiRway Complaints and Asthma Development, ARCADE).	

Author, Year (ref)	Study Country, Study Design, Study Settings, Risk of Bias	FeNO and Comparisons	Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc)	Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test)	Test Findings (Mean, SD)	Conclusion
	and outpatient setting, low risk of bias.			balloons are analyzed in a NO-analyzer (Aerocrine AB; Sweden) within a time period of 6–8 hours after taking the samples.		

AMP: adenosine-5' monophosphate; ATS: American Thoracic Society; API: Asthma predictive index; BDR: Bronchodilator responsiveness; BMI: body mass index; EBC: exhaled breath condensate; Eos: eosinophils; 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; FEV_1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; NPV: negative predictive value; OR: odds ratio; PPV: positive predictive value; RINT: Interrupter respiratory resistance measurement; SD: standard deviation.

Appendix D. Figures

Figure D.1 Pooled sensitivity, specificity and HSROC curve for diagnosis of asthma when FeNO cutoff <=20 ppb

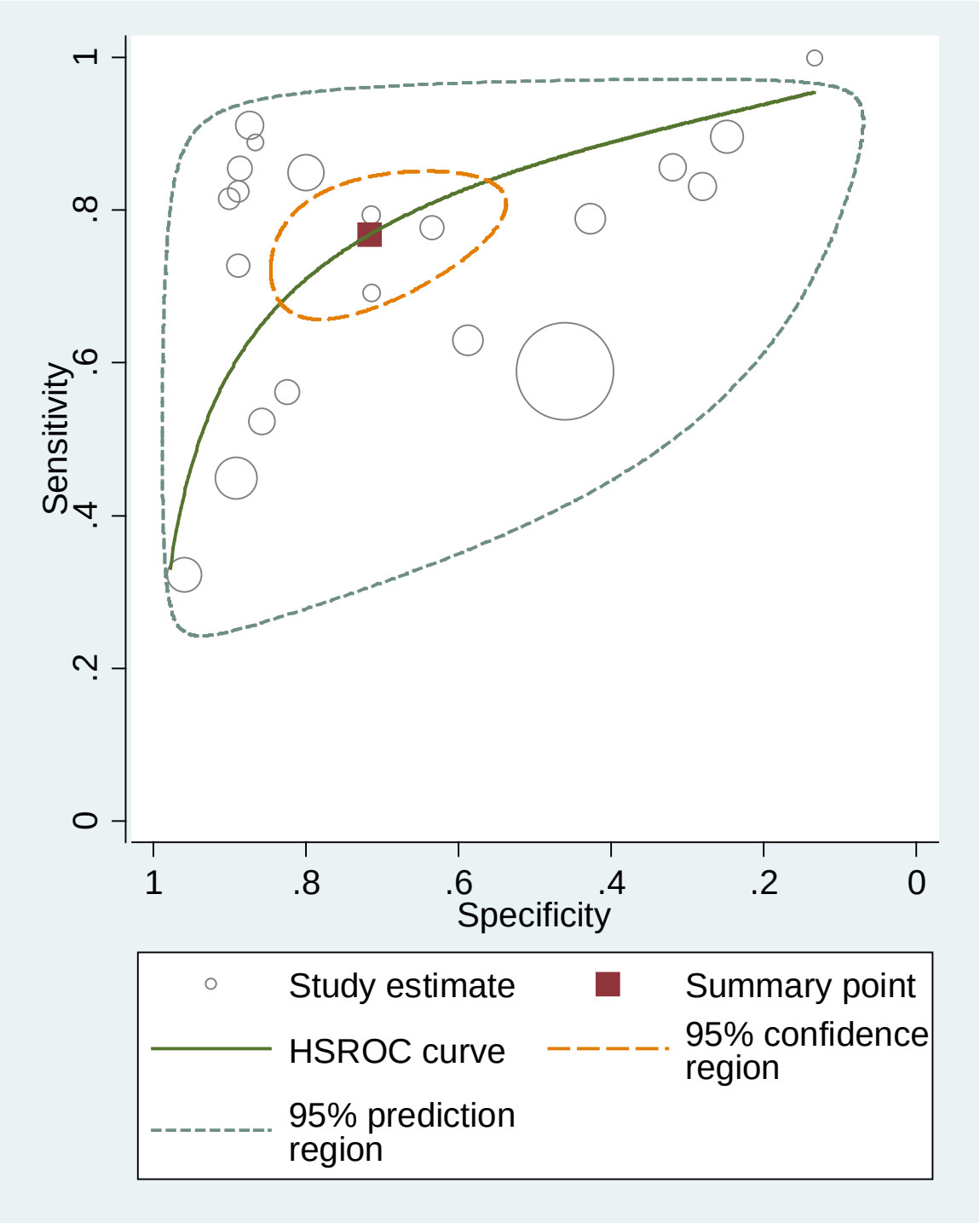


Figure D.2 Pooled sensitivity, specificity and HSROC curve for diagnosis of asthma when FeNO cutoff between 20 and 30 ppb

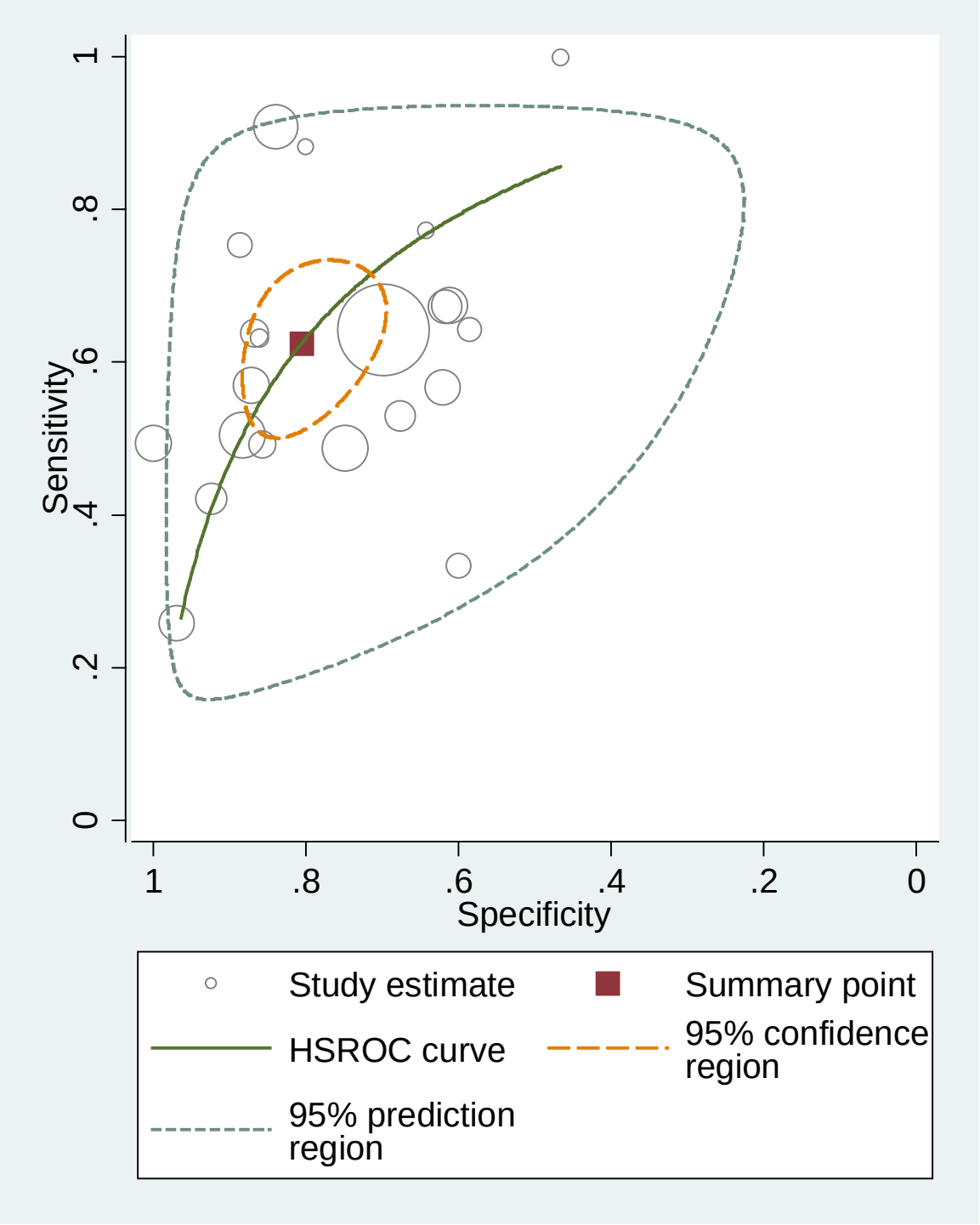


Figure D.3 Pooled sensitivity, specificity and HSROC curve for diagnosis of asthma when FeNO cutoff between 30 and 40 ppb

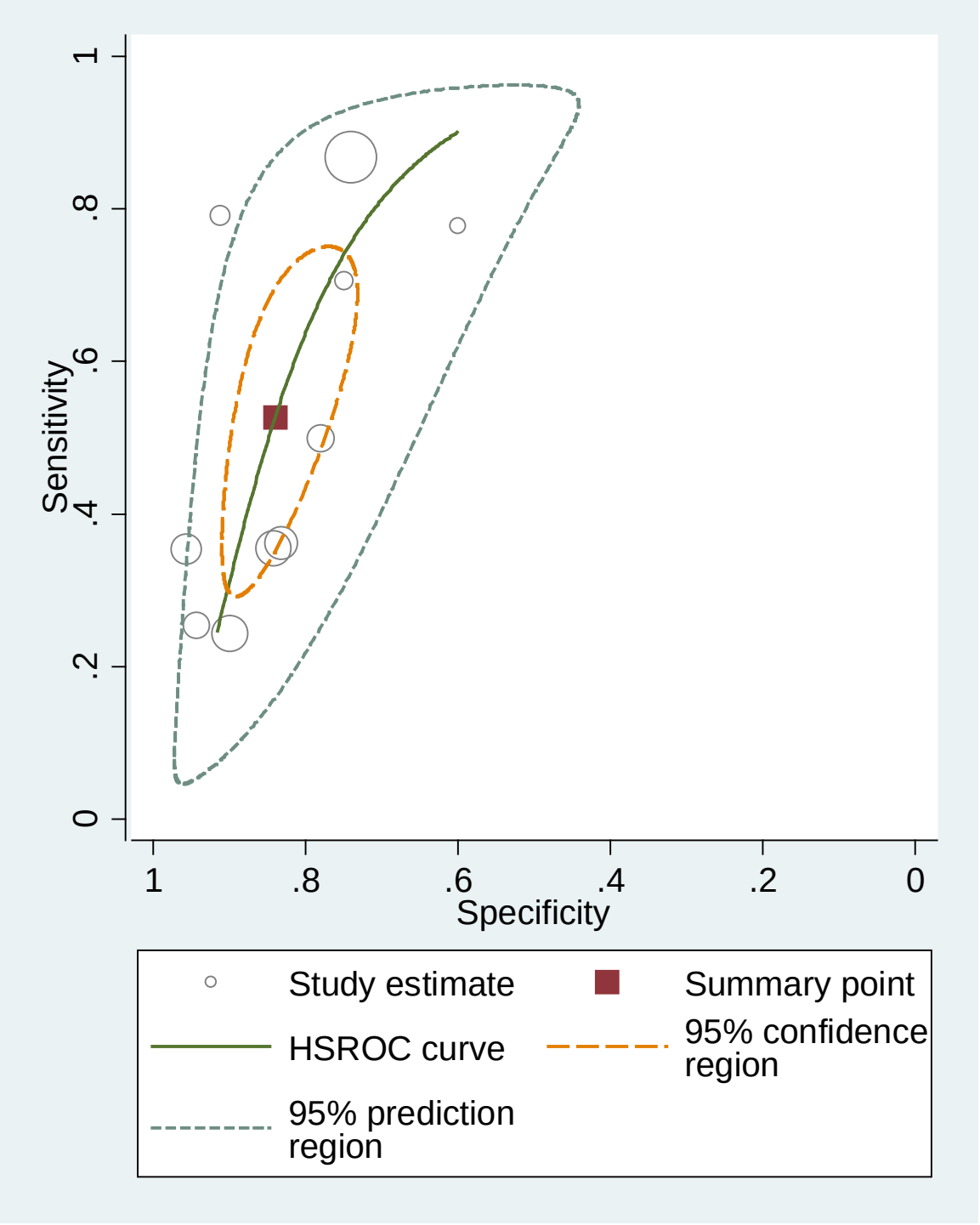


Figure D.4 Pooled sensitivity, specificity and HSROC curve for diagnosis of asthma when FeNO cutoff larger than 40 ppb

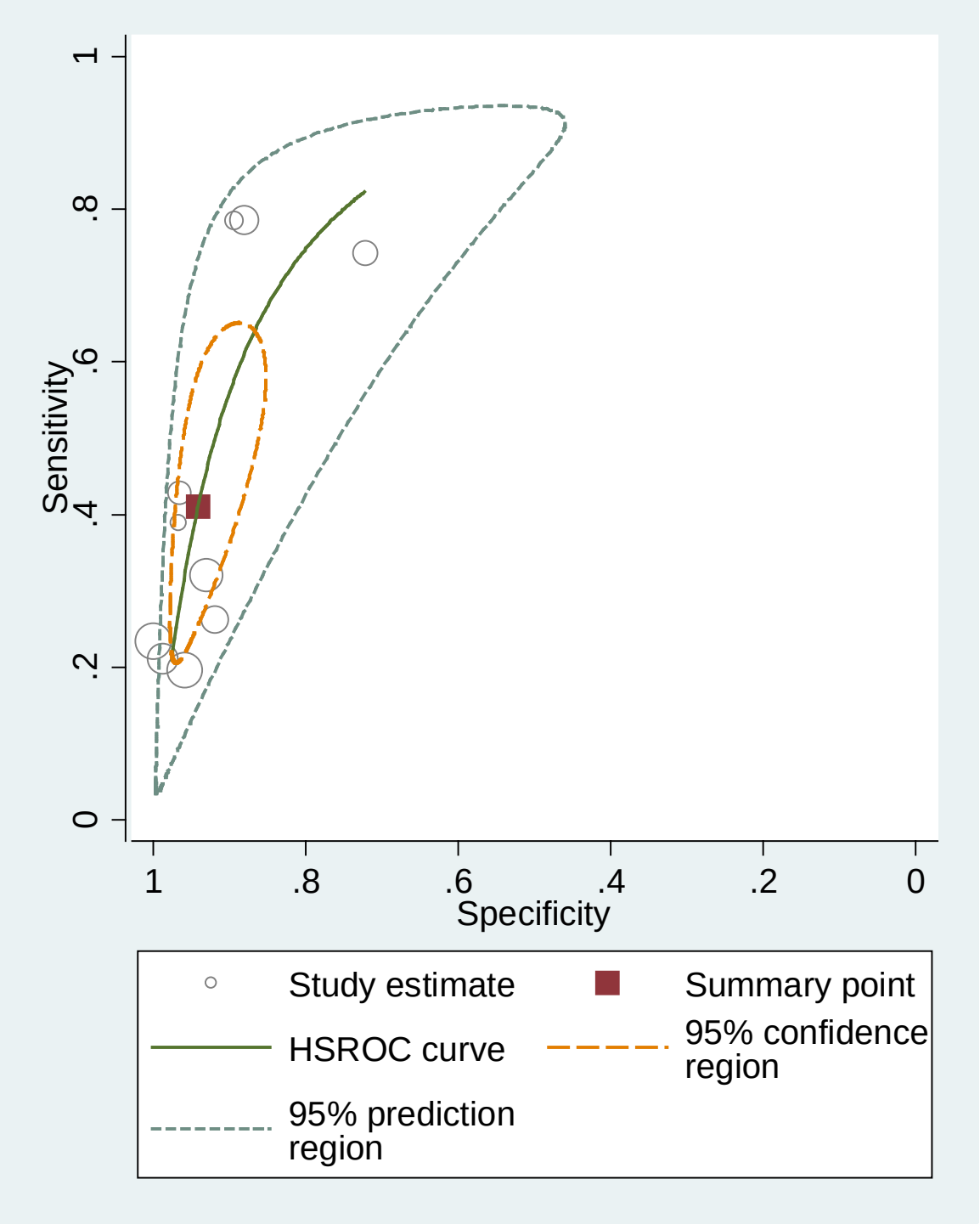
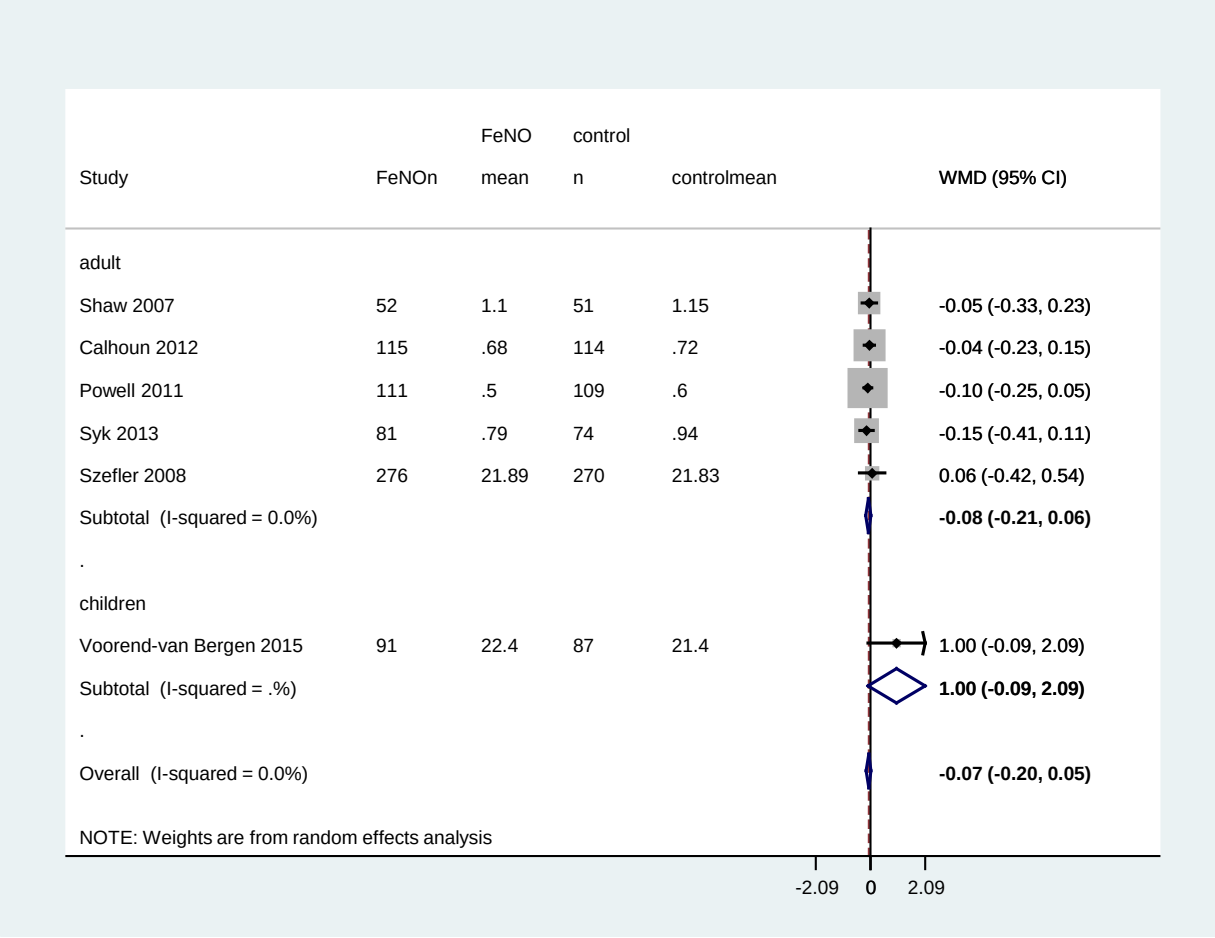
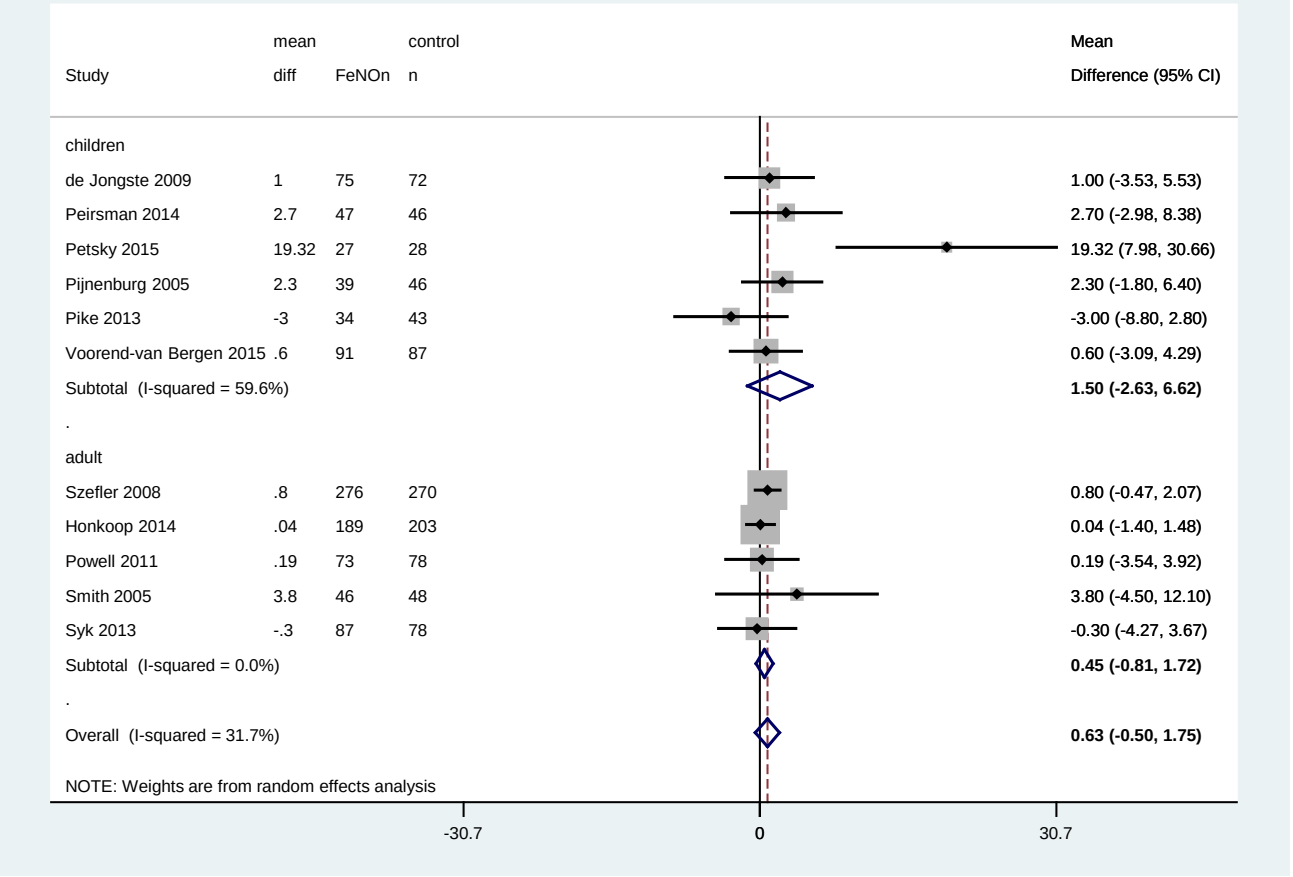


Figure D.5 Asthma Control Test score – FeNO versus other tests in guiding asthma treatments in children and adults



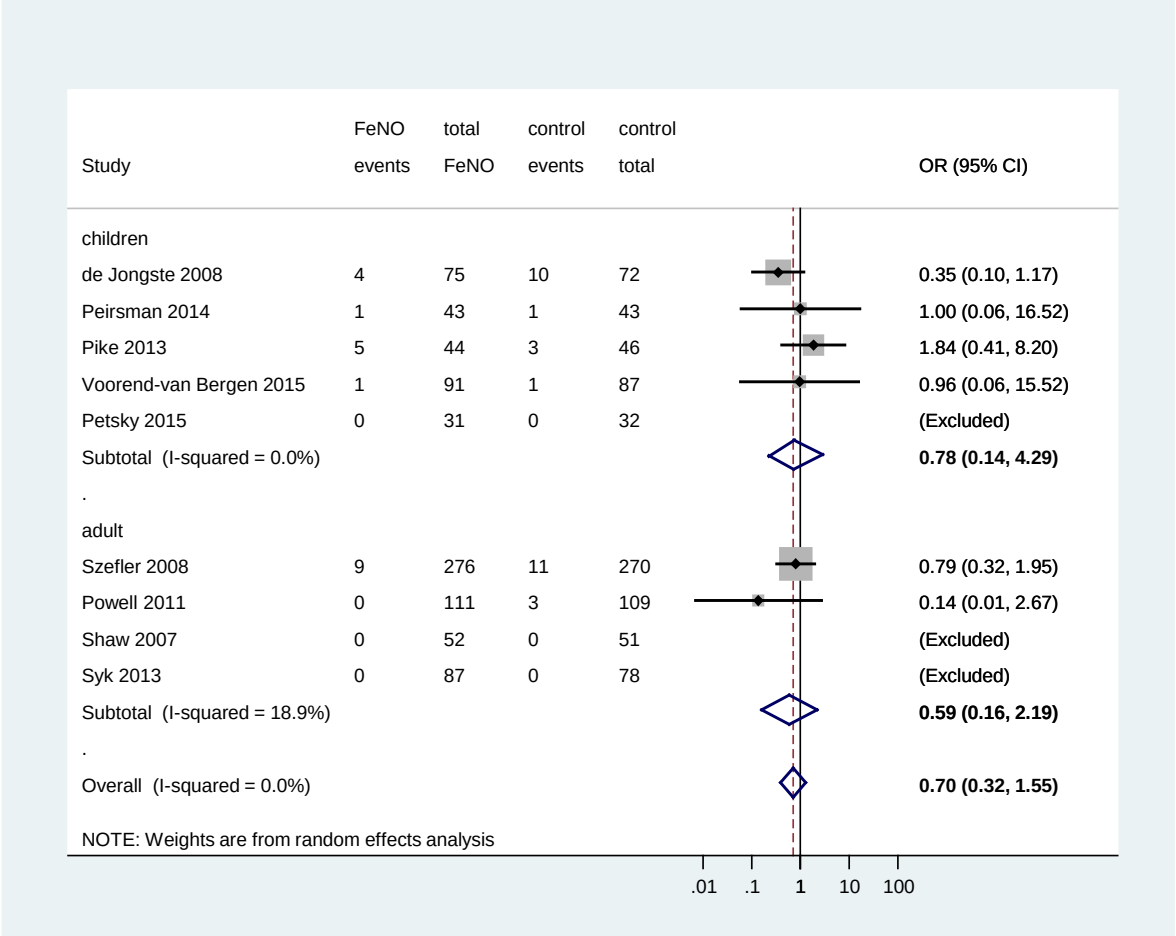
Some estimates were extracted from 2 Cochrane systematic reviews because data were not reported in published trial reports.

Figure D.6 FEV_1% - FeNO versus other tests in guiding asthma treatments in children and adults



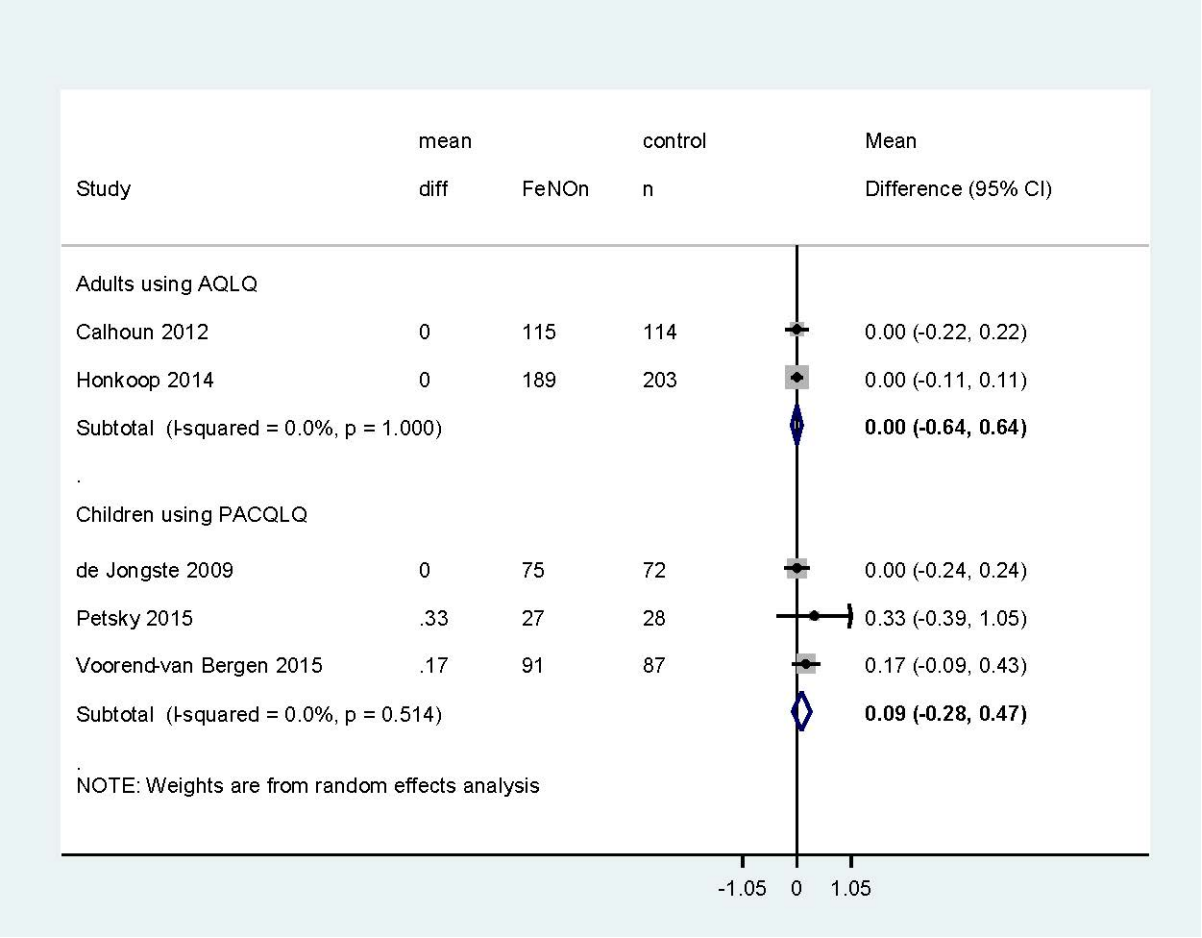
Some estimates were extracted from 2 Cochrane systematic reviews because data were not reported in published trial reports.

Figure D.7 Hospitalizations - FeNO versus other tests in guiding asthma treatments in children and adults



Some estimates were extracted from 2 Cochrane systematic reviews because data were not reported in published trial reports.

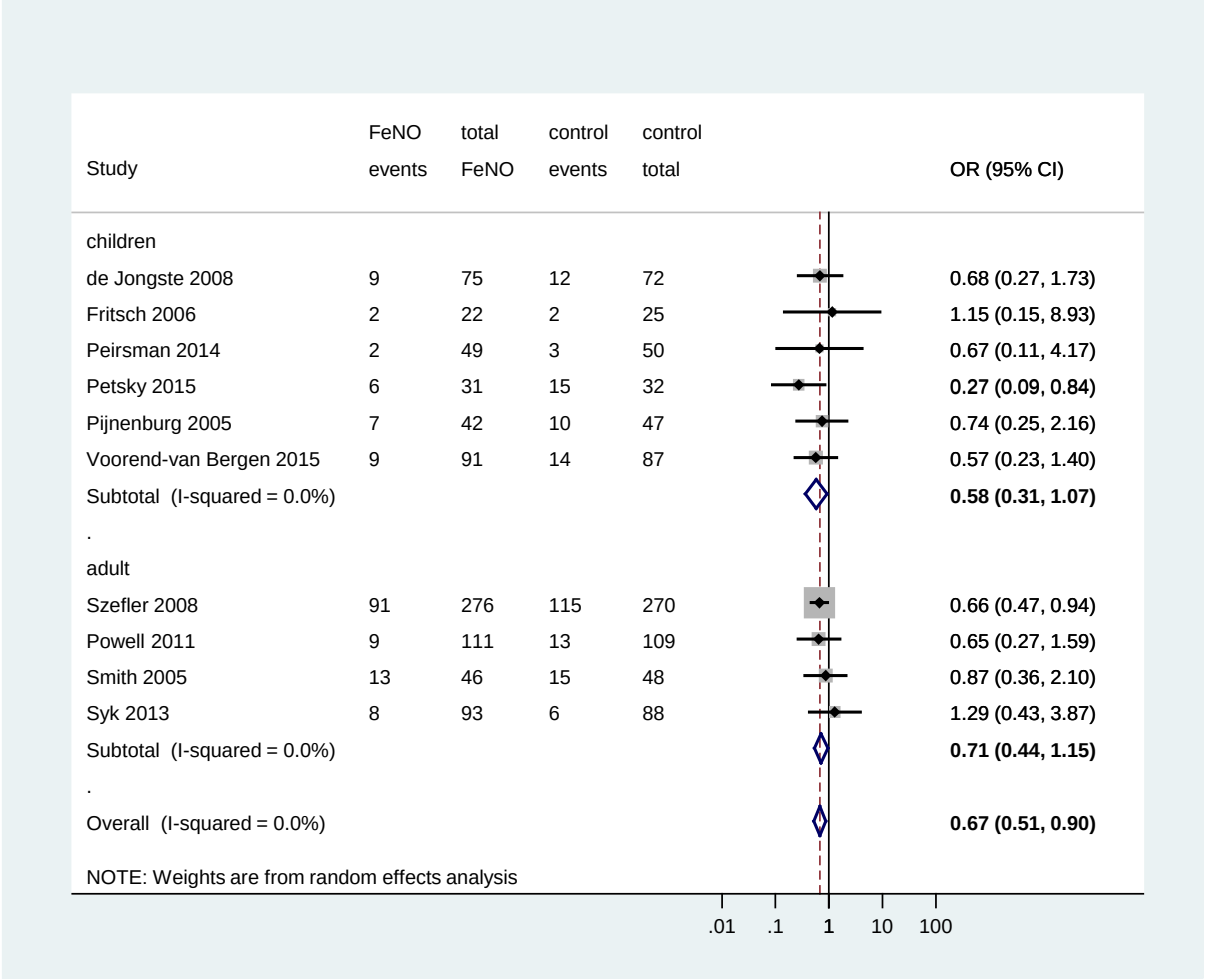
Figure D.8 Quality of life - FeNO versus other tests in guiding asthma treatments in children and adults



AQLQ: Asthma Quality of Life Questionnaire; PACQLQS: Pediatric Asthma Caregiver Quality of Life Questionnaire with Standardized activities.

Some estimates were extracted from 2 Cochrane systematic reviews because data were not reported in published trial reports.

Figure D.9. Exacerbations requiring steroids - FeNO versus other tests in guiding asthma treatments in children and adults



Some estimates were extracted from 2 Cochrane systematic reviews because data were not reported in published trial reports.

Figure D.10. Funnel plot for FeNO cutoffs <20 ppb

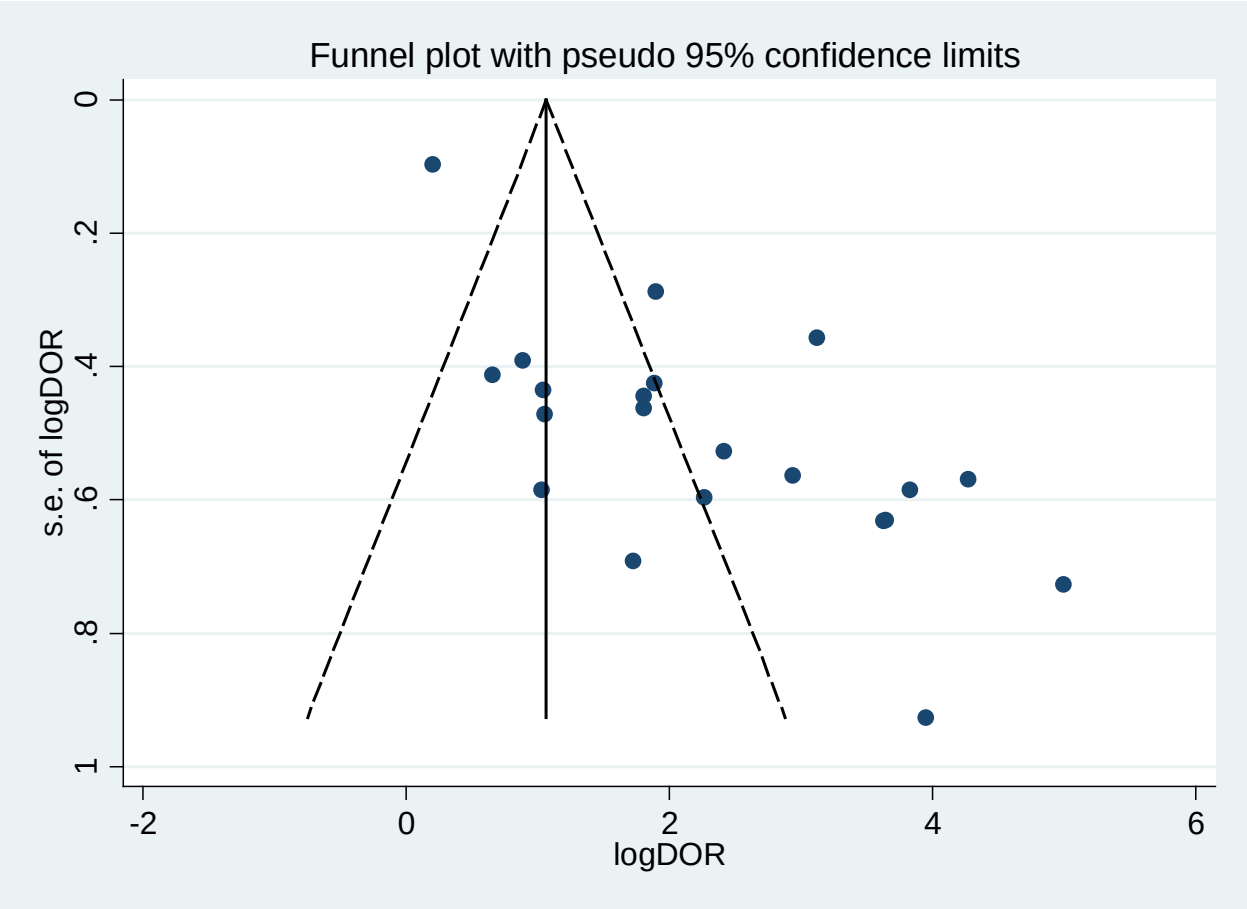
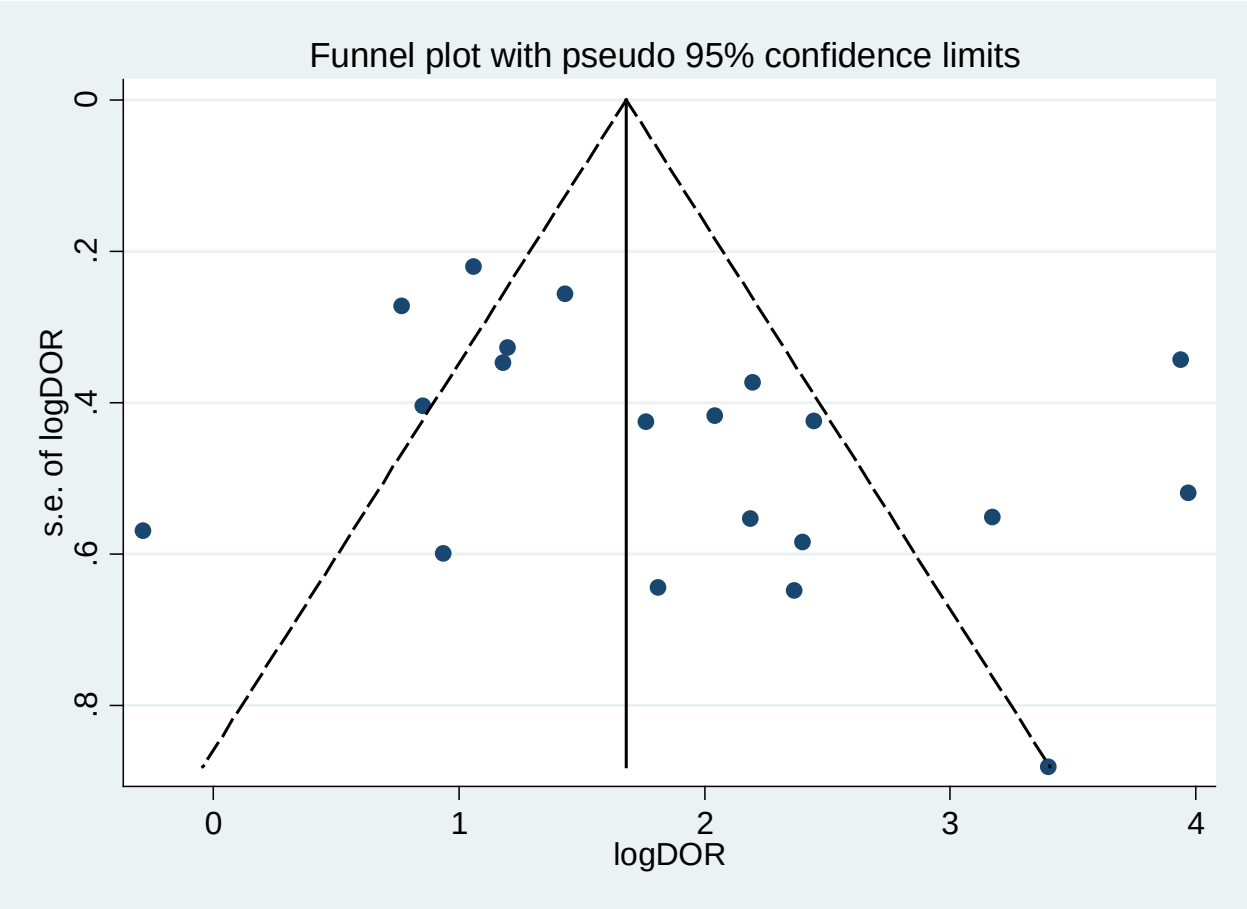


Figure D.11 Funnel plot for FeNO cutoffs 20-30 ppb



Appendix E. Subgroup Analyses

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

Table E.1. Subgroup analysis (reference group: healthy versus symptomatic individuals without asthma)

FeNO CutOff	Subgroup	Number of Included Studies	Conclusion
<20 ppb	Healthy	13 studies	Sensitivity 0.82; 95% CI (0.72 to 0.90) Specificity 0.78; 95% CI (0.62 to 0.88) DOR 16.45; 95% CI (7.85 to 34.49) LR+ 3.71; 95% CI (2.14 to 6.43) LR- 0.23; 95% CI (0.14 to 0.36)
	Symptomatic no asthma	9 studies	Sensitivity 0.73; 95% CI (0.60 to 0.83) Specificity 0.62; 95% CI (0.45 to 0.77) DOR 4.42; 95% CI (2.33 to 8.35) LR+ 1.92; 95% CI (1.32 to 2.78) LR- 0.43; 95% CI (0.30 to 0.63)
20-30 ppb	Healthy	10 studies	Sensitivity 0.67; 95% CI (0.52 to 0.79) Specificity 0.77; 95% CI (0.64 to 0.86) DOR 6.82; 95% CI (2.87 to 16.17) LR+ 2.92; 95% CI (1.74 to 4.88) LR- 0.43; 95% CI (0.28 to 0.66)
	Symptomatic no asthma	13 studies	Sensitivity 0.57; 95% CI (0.47 to 0.67) Specificity 0.84; 95% CI (0.76 to 0.90) DOR 7.30; 95% CI (4.57 to 11.66) LR+ 3.68; 95% CI (2.51 to 5.39) LR- 0.50; 95% CI (0.41 to 0.62)
30-40 ppb	Symptomatic no asthma	6 studies	Sensitivity 0.57; 95% CI (0.32 to 0.79) Specificity 0.87; 95% CI (0.76 to 0.93) DOR 8.89; 95% CI (4.65 to 17.01) LR+ 4.38; 95% CI (2.96 to 6.50) LR- 0.49; 95% CI (0.29 to 0.84)

CI: confidence interval; DOR: diagnostic odds ratio; FeNO: fraction exhaled nitric oxide; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NA: not available; ppb: parts per billion

Table E.2. Subgroup analysis based on risk of bias

FeNO CutOff	Subgroup	Number of Included Studies	Conclusion
<20 ppb	Low risk of bias	11 studies	Sensitivity 0.80; 95% CI (0.67 to 0.88) Specificity 0.69; 95% CI (0.48 to 0.84) DOR 8.81; 95% CI (4.27 to 18.20) LR+ 2.57; 95% CI (1.50 to 4.45) LR- 0.29; 95% CI (0.19 to 0.45)
	Moderate risk of bias	6 studies	Sensitivity 0.74; 95% CI (0.62 to 0.84) Specificity 0.78; 95% CI (0.64 to 0.88) DOR 10.33; 95% CI (3.68 to 29.02) LR+ 3.4; 95% CI (1.85 to 6.27) LR- 0.33; 95% CI (0.20 to 0.54)
	High risk of bias	5 studies	Sensitivity 0.84; 95% CI (0.60 to 0.95) Specificity 0.68; 95% CI (0.41 to 0.86) DOR 11.29; 95% CI (2.75 to 46.30) LR+ 2.63; 95% CI (1.28 to 5.41) LR- 0.23; 95% CI (0.09 to 0.64)
20-30 ppb	Low risk of bias	13 studies	Sensitivity 0.68; 95% CI (0.56 to 0.78) Specificity 0.78; 95% CI (0.67 to 0.85) DOR 7.29; 95% CI (4.12 to 12.91) LR+ 3.03; 95% CI (2.09 to 4.40) LR- 0.42; 95% CI (0.30 to 0.57)
	Moderate risk of bias	6 studies	Sensitivity 0.53; 95% CI (0.43 to 0.62) Specificity 0.84; 95% CI (0.61 to 0.94) DOR 5.77; 95% CI (1.65 to 20.21) LR+ 3.26; 95% CI (1.18 to 8.99) LR- 0.56; 95% CI (0.43 to 0.75)
30-40 ppb	Low risk of bias	5 studies	Sensitivity 0.57; 95% CI (0.37 to 0.74) Specificity 0.79; 95% CI (0.72 to 0.85) DOR 5.02; 95% CI (2.66 to 9.44) LR+ 2.75; 95% CI (2.05 to 3.67) LR- 0.55; 95% CI (0.37 to 0.81)
	Moderate risk of bias	4 studies	Sensitivity 0.37; 95% CI (0.21 to 0.57) Specificity 0.91; 95% CI (0.82 to 0.95) DOR 5.83; 95% CI (3.28 to 10.37) LR+ 4.04; 95% CI (2.52 to 6.46) LR- 0.69; 95% CI (0.54 to 0.89)
>=40 ppb	Low risk of bias	7 studies	Sensitivity 0.41; 95% CI (0.24 to 0.59) Specificity 0.92; 95% CI (0.85 to 0.96) DOR 8.3; 95% CI (5.38 to 12.79) LR+ 5.33; 95% CI (3.59 to 7.91) LR- 0.64; 95% CI (0.50 to 0.83)

CI: confidence interval; DOR: diagnostic odds ratio; FeNO: fraction exhaled nitric oxide; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NA: not available; ppb: parts per billion.

Table E.3. Subgroup analysis based on smoking status

Subgroup	Number of Included Studies	Conclusion
Non smokers	17 studies	Sensitivity 0.70; 95% CI (0.61 to 0.78) Specificity 0.80; 95% CI (0.74 to 0.85) DOR 9.49; 95% CI (5.62 to 16.01) LR+ 3.51; 95% CI (2.62 to 4.70) LR- 0.37; 95% CI (0.27 to 0.50)
Current Smokers	1 study	Sensitivity 0.63 Specificity 0.86 DOR 10.64 LR+ 4.50 LR- 0.43
Ex-smokers	1 study	Sensitivity: 0.53 Specificity: 0.83 DOR: 5.46 LR+: 3.10 LR-: 0.57
Smokers	1 study	Sensitivity 0.29 Specificity 0.86 DOR 2.53 LR+ 2.07 LR- 0.83

CI: confidence interval; DOR: diagnostic odds ratio; LR+: positive likelihood ratio; LR-: negative likelihood ratio.

Table E.4. Subgroup analysis based on age

FeNO CutOff	Subgroup	Number of Included Studies	Conclusion
<20 ppb	18 years or older	12 studies	Sensitivity 0.80; 95% CI (0.72 to 0.86) Specificity 0.64; 95% CI (0.46 to 0.79) DOR 7.28; 95% CI (4.04 to 13.11) LR+ 2.25; 95% CI (1.47 to 3.44) LR- 0.31; 95% CI (0.23 to 0.41)
	Younger than 18 years	6 studies	Sensitivity 0.78; 95% CI (0.59 to 0.90) Specificity 0.79; 95% CI (0.55 to 0.92) DOR 13.44; 95% CI (3.56 to 50.71) LR+ 3.76; 95% CI (1.53 to 9.26) LR- 0.28; 95% CI (0.14 to 0.56)
20-30 ppb	18 years or older	6 studies	Sensitivity 0.69; 95% CI (0.57 to 0.79) Specificity 0.78; 95% CI (0.66 to 0.86) DOR 7.70; 95% CI (4.12 to 14.40) LR+ 3.10; 95% CI (2.02 to 4.74) LR- 0.40; 95% CI (0.29 to 0.56)
	Younger than 18 years	6 studies	Sensitivity 0.61; 95% CI (0.44 to 0.76) Specificity 0.89; 95% CI (0.80 to 0.94) DOR 12.13; 95% CI (5.98 to 24.63) LR+ 5.34; 95% CI (3.12 to 9.14) LR- 0.44; 95% CI (0.30 to 0.65)
30-40 ppb	18 years or older	9 studies	Sensitivity 0.53; 95% CI (0.35 to 0.70) Specificity 0.85; 95% CI (0.77 to 0.90) DOR 6.27; 95% CI (3.70 to 10.64) LR+ 3.46; 95% CI (2.57 to 4.66) LR- 0.55; 95% CI (0.39 to 0.78)
>=40 ppb	18 years or older	7 studies	Sensitivity 0.41; 95% CI (0.24 to 0.62) Specificity 0.93; 95% CI (0.86 to 0.97) DOR 9.84; 95% CI (5.46 to 17.75) LR+ 6.18; 95% CI (3.64 to 10.47) LR- 0.63; 95% CI (0.47 to 0.85)
	Younger than 18 years	NA	NA

CI: confidence interval; DOR: diagnostic odds ratio; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NA: not available; ppb: parts per billion.

Appendix F. Sensitivity Analysis

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

Table F.1. Including only studies with ICS naiive or atopy

FeNO CutOff	Number of Included Studies	Conclusion
Not taking ICS	13 studies	Sensitivity 0.57; 95% CI (0.46 to 0.67) Specificity 0.85; 95% CI (0.78 to 0.91) DOR 7.76; 95% CI (4.94 to 12.18) LR+ 3.91; 95% CI (2.73 to 5.61) LR- 0.50; 95% CI (0.41 to 0.62)
<20 ppb	6 studies	Sensitivity 0.79; 95% CI (0.67 to 0.87) Specificity 0.77; 95% CI (0.56 to 0.90) DOR 12.25; 95% CI (5.73 to 26.21) LR+ 3.40; 95% CI (1.75 to 6.61) LR- 0.28; 95% CI (0.19 to 0.40)
20-30 ppb	8 studies	Sensitivity 0.59; 95% CI (0.45 to 0.71) Specificity 0.84; 95% CI (0.69 to 0.92) DOR 7.25; 95% CI (2.70 to 19.44) LR+ 3.60; 95% CI (1.73 to 7.47) LR- 0.50; 95% CI (0.35 to 0.70)
30-40 ppb	6 studies	Sensitivity 0.37; 95% CI (0.26 to 0.49) Specificity 0.88; 95% CI (0.81 to 0.93) DOR 4.16; 95% CI (2.71 to 6.39) LR+ 3.01; 95% CI (2.11 to 4.28) LR- 0.72; 95% CI (0.62 to 0.84)
Atopic	4 studies	Sensitivity 0.63; 95% CI (0.43 to 0.80) Specificity 0.79; 95% CI (0.65 to 0.89) DOR 6.67; 95% CI (1.59 to 27.95) LR+ 3.07; 95% CI (1.35 to 6.97) LR- 0.46; 95% CI (0.24 to 0.87)

CI: confidence interval; DOR: diagnostic odds ratio; FeNO: fraction exhaled nitric oxide; ICS: inhaled corticosteroid; LR+: positive likelihood ratio; LR-: negative likelihood ratio; ppb: parts per billion.

Appendix G. Risk of Bias

Table G.1. Risk of Bias (QUADAS-2) for studies answering KQ 1a

Author, Year (ref)	Consecutive or Random Sample of Patients	Case-Control Design Avoided	Inappropriate Exclusions Avoided	Concerns Regarding Applicability	The Index Test Results Interpreted	The Threshold Pre-specified	Concern About the Index Test	The Reference Standard Correctly Classify the Target Condition	The Reference Standard Results Appropriately Interpreted	Concern That the Target Condition Does not Match the Question	An Appropriate Interval Between Index Test(s) and Reference Standard	All Patients Received a Reference Standard	Patients Received the Same Reference Standard	All Patients Included in the Analysis	Overall RoB
Arora, 2006 [1]	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Avital, 2001 [2]	High	Low	Unclear	High	Low	High	Low	Low	Low	Low	Unclear	Low	Low	Low	Medium
Backer, 2014 [3]	Low	Low	Medium	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Medium
Berkman, 2005 [4]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Berlyne, 2000 [5]	High	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High
Bommarito, 2007 [6]	High	Low	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low
Cordeiro, 2011 [7]	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Medium	Medium
Deykin, 2002 [8]	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	Unclear	Unclear	Low	Medium
Dupont, 2003 [9]	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low	Low	Medium
Florentin 2014 [10]	High	High	Low	Medium	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	High
Fortuna, 2007 [11]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Fukuhara, 2011 [12]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

Author, Year (ref)	Consecutive or Random Sample of Patients	Case-Control Design Avoided	Inappropriate Exclusions Avoided	Concerns Regarding Applicability	The Index Test Results Interpreted	The Threshold Pre-specified	Concern About the Index Test	The Reference Standard Correctly Classify the Target Condition	The Reference Standard Results Appropriately Interpreted	Concern That the Target Condition Does not Match the Question	An Appropriate Interval Between Index Test(s) and Reference Standard	All Patients Received a Reference Standard	Patients Received the Same Reference Standard	All Patients Included in the Analysis	Overall RoB
Grzelewski, 2014 [12]	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Medium
Heffler, 2006 [14]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Henriksen, 2000 [15]	High	Low	Low	Low	Low	Low	Low	High	Low	High	Low	Low	Low	High	High
Ishizuka, 2011 [16]	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	High
Jerzynska, 2014 [17]	High	Low	Low	Low	Low	Low	Low	High	High	High	High	High	Low	High	High
Katsoulis, 2013 [18]	Low	Low	Low	Unclear	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	High	Medium
Kostikas, 2008 [19]	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Medium
Lemiere, 2010 [20]	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low	Low
Malinovschi, 2012 [21]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Martin, 2016 [22]	Unclear	Low	Low	Low	Low	High	High	Low	Low	Low	Low	Low	Low	High	High
Matsunaga, 2011 [23]	Unclear	Low	Low	Low	Low	Low	Low	High	High	High	Low	Low	Low	Low	High
Menzies, 2007 [24]	High	Low	Unclear	Low	Unclear	Unclear	Low	High	Low	High	Unclear	High	High	Low	High

Author, Year (ref)	Consecutive or Random Sample of Patients	Case-Control Design Avoided	Inappropriate Exclusions Avoided	Concerns Regarding Applicability	The Index Test Results Interpreted	The Threshold Pre-specified	Concern About the Index Test	The Reference Standard Correctly Classify the Target Condition	The Reference Standard Results Appropriately Interpreted	Concern That the Target Condition Does not Match the Question	An Appropriate Interval Between Index Test(s) and Reference Standard	All Patients Received a Reference Standard	Patients Received the Same Reference Standard	All Patients Included in the Analysis	Overall RoB
Miedinger, 2007 [25]	High	Low	High	High	Low	Unclear	Low	Low	Unclear	Low	Unclear	Low	Low	Low	Medium
Miedinger, 2009 [26]	Unclear	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Low
Munnik, 2009 [27]	High	Low	High	Low	Low	Unclear	Low	Low	Low	Low	Unclear	Low	Low	Low	Medium
Nayak, 2013 [28]	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Medium
Pedrosa, 2010 [29]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	Low
Perez Tarazona, 2011 [30]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Pizzimenti, 2009 [31]	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Unclear	Unclear	Medium
Ramser, 2008 [32]	Low	Low	Unclear	Low	Low	Unclear	Low	High	Low	High	Unclear	Low	Low	Low	Low
Sachs-Olsen, 2010 [33]	Unclear	Low	Unclear	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low
Sato, 2008 [34]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Schleich, 2012 [35]	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Medium
Schneider, 2009 [38]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Schneid	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

Author, Year (ref)	Consecutive or Random Sample of Patients	Case-Control Design Avoided	Inappropriate Exclusions Avoided	Concerns Regarding Applicability	The Index Test Results Interpreted	The Threshold Pre-specified	Concern About the Index Test	The Reference Standard Correctly Classify the Target Condition	The Reference Standard Results Appropriately Interpreted	Concern That the Target Condition Does not Match the Question	An Appropriate Interval Between Index Test(s) and Reference Standard	All Patients Received a Reference Standard	Patients Received the Same Reference Standard	All Patients Included in the Analysis	Overall RoB
er, 2012 Schneider, 2014[36, 37]															
Sivan, 2009 [39]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Smith, 2004 [40]	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Medium	Low
Thomas, 2005 [41]	High	Low	Low	Low	Medium	Low	Low	High	High	High	Low	Low	Low	High	High
Traves, 2007 [42]	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Woo, 2012 [43]	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Yao, 2011 [44]	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low	Medium

Table G.2. Risk of Bias for RCTs (Cochrane ROB tool) for studies answering KQ 1b

Author, Year (ref)	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall RoB
	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	
Beck-Ripp, 2002 [100]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Beerthuizen, 2016 [46]	Low	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Fritsch, 2006 [54]	Low	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear
Powell, 2011 [111]	Low	Low	Low	Low	Low	Low	Low	Low
Szefler, 2008 [88]	Low	Low	Low	Low	Low	Low	Low	Low
Voorend-van Bergen, 2015 [93]	Low	High	Low	High	Low	Low	Low	High
Zeiger, 2006 [98]	Low	Unclear	Low	Low	Low	Low	Unclear	Unclear

Table G.3. Risk of Bias for observational studies (Newcastle-Ottawa Quality Assessment Scale) for studies answering KQ 1b

Author, Year (ref)	Representativeness of the Study Population	Ascertainment of Exposure	Comparability of Cohorts On the Basis Of the Design or Analysis	Assessment of Outcome	Follow-up Long Enough for Outcomes to Occur	Adequacy of Follow up Of Cohorts	Overall RoB
Agache, 2012 [45]	Low	Low	Low	Low	Low	High	Low
Bernstein, 2009 [48]	Unclear	Unclear	Low	Low	Low	Low	Medium
Berg, 2008 [47]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Bora, 2011 [49]	High	High	High	Low	Low	Low	High
Cano-Garcinuño, 2010 [50]	Low	Low	Unclear	Low	Unclear	Low	Low
Ciprandi, 2013 [51]	Low	Low	Low	Low	Unclear	Low	Low
de Bot, 2013 [52]	Low	Low	Unclear	Low	High	Low	Medium
Delclaux, 2008 [53]	Low	Low	Low	Low	Unclear	High	Medium
Gelb, 2006 [55]	Low	Low	Low	Low	Low	Low	Low
Gill, 2005 [56]	High	Low	High	Low	Low	Low	High
Griese, 2000 [57]	Low	Low	Low	Low	Low	Low	Low
Gruffydd-Jones, 2007 [58]	Low	Low	Low	Low	Low	Low	Low
Habib, 2014 [59]	High	High	High	High	High	High	High
Hanson, 2013 [60]	Low	High	High	Low	High	High	High
Harkins, 2004 [61]	Low	Low	High	Low	Medium	Low	Medium
Hayata, 2013 [62]	Unclear	Low	High	Low	High	Low	Medium
Hsu, 2013 [63]	Unclear	Unclear	Low	Low	Unclear	Unclear	High
Kavitha, 2017[64]	Low	Low	Unclear	Low	Medium	High	Medium
Ko, 2011 [65]	Unclear	Low	Low	Low	Low	Low	Low
Kostikas, 2011 [66]	Medium	Low	Medium	Low	Unclear	Low	Medium
Kwok, 2008 [67]	Unclear	Low	Unclear	Low	High	Low	High
Leblanc, 2013 [68]	Unclear	Low	High	Low	Low	Low	Medium
Lex, 2007 [69]	Low	Low	Unclear	Low	Unclear	Unclear	Medium
Mahut, 2010 [70]	Low	Low	Unclear	Low	Unclear	Low	Low
Malerba, 2012 [118]	Low	Low	Unclear	Low	Low	Low	Low
Martins, 2008 [71]	High	High	High	High	Low	High	High
McCormack, 2013 [72]	Low	Low	Low	Low	Low	Low	Low
Menzies, 2008 [73]	Unclear	Low	Low	Low	Low	Low	Low
Meyts, 2003 [74]	High	Low	High	High	Low	Low	High
Michils, 2008 [75]	Low	Low	Unclear	Low	Low	Low	Low
Michils, 2009 [76]	Low	Unclear	Low	Unclear	Low	Unclear	Medium
Nayak, 2013 [28]	Unclear	Low	Low	Low	High	Unclear	Medium
Nittner-Marszalska, 2013 [77]	Unclear	Low	Low	Low	Low	Low	Low
Ozier, 2011 [78]	Low	Low	Low	Medium	Low	Low	Medium

Author, Year (ref)	Representativeness of the Study Population	Ascertainment of Exposure	Comparability of Cohorts On the Basis Of the Design or Analysis	Assessment of Outcome	Follow-up Long Enough for Outcomes to Occur	Adequacy of Follow up Of Cohorts	Overall RoB
Papakosta, 2011 [79]	Low	Low	Unclear	Low	Low	Unclear	Medium
Plaza, 2013 [80]	Low	Low	Unclear	Low	Low	Low	Low
Quaedvlieg, 2009 [81]	Low	Low	Low	Low	Unclear	Low	Low
Raj, 2014 [82]	Low	Unclear	Unclear	Low	Unclear	Unclear	Medium
Ricciardolo, 2016 [83]	Low	High	Unclear	Low	Unclear	High	High
Robroeks, 2007 [84]	High	High	High	Low	High	High	High
Rosias, 2004 [85]	Low	Low	Unclear	Low	Unclear	Low	Medium
Sato, 2009 [86]	Unclear	Unclear	Low	Unclear	Low	Unclear	Medium
Shirai, 2008 [87]	Medium	Medium	Low	Low	High	Low	High
van der Valk, 2012 [89]	High	Unclear	Unclear	Low	Low	Low	Medium
van Vliet, 2015 [90]	Unclear	Low	Unclear	Low	Low	Low	Low
Vijverberg, 2012 [101]	Low	Low	Low	Low	High	Low	Medium
Visitsunthorn, 2013 [91]	High	High	Low	High	High	High	High
Visitsunthorn, 2017[92]	Low	Low	Medium	Low	Low	Low	Low
Warke, 2004 [94]	High	Low	Unclear	Low	Low	Unclear	High
Yamashita, 2015 [95]	Low	Low	Medium	Low	Low	High	High
Yang, 2015 [96]	High	Low	Unclear	Low	Low	Low	Medium
Yavuz, 2012 [97]	Low	Low	Low	Low	Low	High	Low
Zeiger, 2011 [99]	Low	Unclear	Low	Low	Unclear	Low	Medium

Table G.4. Risk of Bias for RCTs (Cochrane ROB tool) for studies answering KQ 1c

Author, Year (ref)	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall RoB
	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	
Calhoun, 2012 [102]	Unclear	Unclear	Low	Low	Low	Low	Unclear	Unclear
De Jongste, 2009 [103]	Low	Unclear	High	Unclear	Low	Low	Low	High
Hashimoto, 2011 [104]	Low	Unclear	High	High	Low	Low	Low	High
Honkoop, 2015 [105]	Low	Low	High	High	Low	Low	Low	High
Malerba, 2015 [106]	High	High	Low	High	Low	Low	Low	Unclear
Peirsman, 2014 [107]	High	High	Low	High	Low	Low	Low	High
Petsky, 2015 [108]	Low	Low	Low	Low	Low	Low	Low	Low
Pijnenburg, 2005[109]	High	High	High	High	Low	Low	Low	High
Pike, 2013 [110]	Low	Low	Low	Low	Low	Low	Low	Low
Powell, 2011 [111]	Low	Low	Low	Low	Low	Low	Low	Low
Shaw, 2007 [112]	Low	Low	Low	High	Low	Low	Low	Low
Smith, 2005[113]	Low	Unclear	Low	High	Low	Low	Low	Unclear
Syk, 2013 [114]	Low	Low	High	High	Low	Low	Low	High
Verini, 2010 [115]	Low	Unclear	High	Unclear	Low	Low	Low	High

Table G.5. Risk of Bias for observational studies (Newcastle-Ottawa Quality Assessment Scale) for studies answering KQ 1c

Author, Year (ref)	Representativeness of the Study Population	Ascertainment of Exposure	Comparability of Cohorts On the Basis Of the Design or Analysis	Assessment of Outcome	Follow-up Long Enough for Outcomes to Occur	Adequacy of Follow up Of Cohorts	Overall RoB
	High/Medium/Low/Unclear	High/Medium/Low/Unclear	High/Medium/Low/Unclear	High/Medium/Low/Unclear	High/Medium/Low/Unclear	High/Medium/Low/Unclear	High/Medium/Low
Ciolkowski, 2016 [120]	High	High	High	Low	Low	Low	High
Cowan, 2015 [121]	Low	Low	Low	Low	Unclear	Low	Low
Griese, 2000 [57]	Low	Low	Low	Low	Low	Low	Low
Laforce, 2014 [116]	High	High	Low	Low	Unclear	Unclear	High
Mahut, 2011 [122]	Unclear	Low	Low	Low	High	Low	Medium
Malerba, 2008 [117]	Unclear	Low	Unclear	Low	Low	Low	Medium
Malerba, 2012 [118]	Low	Low	Unclear	Low	Low	Low	Low
Martin, 2016 [22]	Low	Low	High	Low	Low	Low	Low
Smith, 2005 [123]	Low	Low	Low	Low	Low	Low	Low
Wan, 2014 [119]	High	Low	High	Low	Low	Low	High

Table G.6. Risk of Bias for RCTs (Cochrane ROB tool) for studies answering KQ 1d

Author, Year (ref)	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall RoB
	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	High/Low/ Unclear	
Beck-Ripp, 2002 [100]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Bisgaard, 1999 [124]	Low	Unclear	Low	Low	Unclear	Low	Low	Unclear
Ehrs, 2010 [135]	Low	Unclear	Low	Low	Low	Low	Low	Low
Erin, 2008 [136]	Low	Low	Low	Low	High	Low	High	High
Fuglsang, 1998 [151]	Low	Unclear	Low	Low	Low	Low	Low	Low
Hoshino, 2016[153]	High	High	High	Unclear	Low	Low	Low	High
Hozawa, 2014 [138]	Low	Unclear	Low	High	Low	Low	High	High
Inoue, 2016[152]	Low	Low	Unclear	unclear	Low	Low	Low	Low
Kharitonov, 1996 [140]	Unclear	Unclear	Low	Low	Low	Low	Unclear	Unclear
Kharitonov, 2002 [141]	Low	Unclear	Low	Low	Low	Low	Low	Low
Mallol, 2016[142]	High	High	Low	Unclear	Low	Low	Low	High
Montuschi, 2007 [126]	Low	Unclear	Low	Low	Low	Low	Low	Low
Nolte, 2013[143]	Low	Unclear	Low	Low	Low	Low	Unclear	Unclear
Obase, 2013 [159]	Low	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Profita, 2013 [145]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear
Sandrini, 2003 [128]	Low	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Silkoff, 2004 [129]	Low	Low	Low	Low	Low	Low	Unclear	Low
Verini, 2007 [150]	Low	Unclear	High	Low	Low	Low	Low	Unclear
Yates, 1997 [154]	Low	Unclear	Low	Low	Low	Low	Low	Low
Zeiger, 2006 [98]	Low	Unclear	Low	Low	Low	Low	Unclear	Unclear

Table G.7. Risk of Bias for for observational studies (Newcastle-Ottawa Quality Assessment Scale) for studies answering KQ 1d

Author, Year (ref)	Representativeness of the Study Population	Ascertainment of Exposure	Comparability of Cohorts On the Basis Of the Design or Analysis	Assessment of Outcome	Follow-up Long Enough for Outcomes to Occur	Adequacy of Follow up Of Cohorts	Overall RoB
Baraldi, 1997 [131]	Low	Low	Unclear	Low	High	Low	High
Bratton, 1999 [125]	Low	Low	Low	Low	High	High	High
Bulac, 2015 [132]	Low	Low	Low	Low	Low	Low	Low
Byrnes, 1997 [133]	Medium	Low	Unclear	Low	Medium	Unclear	Medium
Cabral, 2009 [155]	Low	Low	Unclear	Low	Low	High	Medium
Dupont, 1998 [134]	Medium	Low	Unclear	Low	High	High	High
Gelb, 2008 [137]	Unclear	Low	High	Low	Unclear	Low	High
Hojo, 2013 [156]	Unclear	Low	Low	Low	Low	Low	Low
Jones, 2001 [157]	Low	Low	Low	Low	Low	Low	Low
Kermode, 2011 [139]	Low	Low	High	Low	Low	Low	Medium
Liu, 2010 [158]	Low	Low	Unclear	Low	Low	High	Medium
Ohkura, 2009 [127]	Low	Low	Unclear	Low	Low	Low	Low
Park, 2016[144]	Low	Low	High	Low	Low	Low	Medium
Pijnenburg, 2005 [160]	Low	Low	Low	Low	Low	Low	Low
Prieto, 2003 [161]	High	Low	Low	Low	Low	Low	High
Silkoff, 2001 [146]	Unclear	Low	Low	Low	High	Unclear	High
Smith, 2015 [147]	Unclear	Unclear	High	Low	Low	Low	Medium
Spallarossa, 2001 [148]	Low	Low	Low	Low	Unclear	High	Medium
Tajiri, 2014 [130]	Low	Low	Unclear	Low	High	Low	Medium
Thomas 2016	Low	Low	Low	Low	Low	Low	Low
Tsurikisawa, 2012 [162]	Low	Low	Low	Low	Low	Low	Low

Table G.8. Risk of Bias for observational studies (Newcastle-Ottawa Quality Assessment Scale) for studies answering KQ 1e

Author, Year (ref)	Representativeness of the Study Population	Ascertainment of Exposure	Comparability of Cohorts On the Basis Of the Design or Analysis	Assessment of Outcome	Follow-up Long Enough for Outcomes to Occur	Adequacy of Follow up Of Cohorts	Overall RoB
Balinotti, 2013 [163]	Low	Low	Low	Low	Low	Low	Low
Bloemen, 2010 [164]	High	High	Low	Low	High	Low	High
Castro-Rodriguez, 2013 [165]	Low	Low	Low	Low	Low	Low	Low
Caudri, 2010 [166]	Low	Low	Low	Low	Low	Low	Low
Chang, 2015 [167]	Low	Low	Low	Low	Low	Low	Low
Elliot, 2013 [168]	Unclear	Unclear	Unclear	Low	Low	High	High
Klaassen, 2012 [169]	Low	Low	Unclear	Low	Low	Low	Low
Prado, 2011 [170]	Low	Unclear	High	Low	Unclear	Unclear	Medium
van Wonderen, 2009 [171]	Low	Low	Unclear	Low	Low	Low	Low

Appendix H. Assessment of the Strength of Evidence

Table H. 1. Assessment of the Strength of Evidence KQ1a

FeNO CutOff	Reference Test	Study Design and Sample Size	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Strength of Evidence
<20 ppb	Clinical Diagnosis	8 observational studies[4, 6, 15, 23, 24, 28, 30, 33] (1,199 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
	Positive bronchial challenge	5 observational studies [1, 2, 4, 8, 32] (320 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
	Combination of clinical diagnosis, bronchial challenge, and/or Bronchodilator response	9 observational studies [5, 9, 10, 13, 14, 19, 21, 38, 39] (2,683Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
	Overall (all available studies regardless of reference test)	21 observational studies [1, 2, 4-6, 8-10, 13-15, 19, 21, 23, 24, 28, 30, 32, 33, 38, 39] (4,129 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
20-30 ppb	Clinical Diagnosis	5 observational studies [7, 23, 33, 38, 44] (2,637 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
	Combination of clinical diagnosis, bronchial challenge/ Bronchodilator response	15 observational studies [9-11, 14, 17, 19, 21, 25, 26, 36-40, 42, 43] (2,327Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
	Overall (all available studies regardless of reference test)	22 observational studies [1, 3, 7, 9-11, 14, 17, 19, 21, 23, 25, 26, 30, 33, 36-40, 42-44] (5,189 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
30-40 ppb	Overall (all available studies regardless of reference test)	10 observational studies [8, 9, 14, 16, 19, 26, 32, 34, 35, 38] (1,753 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate
>=40 ppb	Combination of clinical diagnosis,	8 observational studies [10, 12, 14, 25, 31, 38,	Medium	Consistent	Direct	Precise	Undetected	Moderate

FeNO CutOff	Reference Test	Study Design and Sample Size	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Strength of Evidence
	bronchial challenge/ Bronchodilator response	[42, 43] (1,142 Patients)						
	Overall (all available studies regardless of reference test)	10 observational studies [10, 12, 14, 25, 29, 31, 32, 42, 43, 172] (1,368 Patients)	Medium	Consistent	Direct	Precise	Undetected	Moderate

Table H. 2. Assessment of the Strength of Evidence KQ1b. Narrative Evaluation.

Question	Study Design and Sample Size	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Strength of Evidence
Can FeNO levels predict the current control of asthma or the risk of future exacerbations?	19 observational studies in adults [48, 49, 55, 59, 61-63, 65, 66, 73, 75-77, 79-81, 86, 87, 99] (4,146 Patients) 21 observational in children [45, 46, 50-52, 54, 57, 60, 69, 71, 72, 74, 85, 89-91, 93, 94, 96-98, 101] (3,926 Patients)	Low	Consistent	Direct	Precise	Undetected	Low (Observational studies)
Can FeNO be used to monitor asthma status during acute exacerbations?	4 observational studies [53, 56, 67, 82] (1,013 patients)	Low	Consistent	Direct	Precise	Undetected	Low (Observational studies)
Can FeNO be used to monitor adherence to asthma medications?	3 observational studies [88, 100, 101] (1,035 patients)	Low	Consistent	Direct	Precise	Undetected	Low (Observational studies)

Table H. 3. Assessment of the Strength of Evidence KQ1c.

Question	Study Design and Sample Size	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Strength of Evidence
Adults							
Exacerbations[1]	6 RCTs[88, 105, 111-114] (1,536 patients)	Low[a]	Consistent	Direct	Precise	Undetected	High
Exacerbations requiring systemic steroids	4 RCTs[88, 111, 113, 114] (1,041 patients)	Low	Consistent	Direct	Imprecise[b]	Undetected	Moderate (Imprecision)
Hospitalizations	4 RCTs[88, 111, 112, 114] (1,034 patients)	Low	Consistent	Direct	Severely Imprecise	Undetected	Low (Severe imprecision)
Quality of life	2 RCTs[102, 105] (621 patients)	Low	Consistent	Direct	Severely Imprecise	Undetected	Low (Severe imprecision)
FEV_1 % predicted	5 RCTs[88, 105, 111, 113, 114] (1,348 patients)	Low	Consistent	Indirect	Severely Imprecise	Undetected	Insufficient (Severe imprecision and indirectness)
Asthma control test	5 RCTs[88, 102, 111, 112, 114] (1,523 patients)	Low	Consistent	Direct	Severely Imprecise	Undetected	Low (Severe imprecision)
Children							
Exacerbations[1]	7 RCTs[54, 93, 103, 107-110] (733 patients)	Low[a]	Consistent	Direct	Precise	Undetected	High
Exacerbations requiring systemic steroids	6 RCTs[54, 93, 103, 107-109] (733 patients)	Low	Consistent	Direct	Imprecise[b]	Undetected	Moderate (Imprecision)
Hospitalizations	(623 patients) 5 RCTs[93, 103, 107, 108, 110] (564 patients)	Low	Consistent	Direct	Severely Imprecise	Undetected	Low (Severe imprecision)
Quality of life	3 RCTs[93, 103, 108] (380 patients)	Low	Consistent	Direct	Severely Imprecise	Undetected	Low (Severe imprecision)
FEV_1 % predicted	5 RCTs[93, 103, 107-110] (635 patients)	Low	Inconsistent	Indirect	Severely Imprecise	Undetected	Insufficient (Severe imprecision, indirectness and inconsistency)

Asthma control test	1 RCT[93] (178 patients)	Low	Consistent	Direct	Severely Imprecise	Undetected	Low (Severe imprecision)

[a] Six trials were unblinded (3 in adults and 3 in children). Therefore, it is also reasonable to reduce the strength of evidence due to study limitations making it moderate. We did not rate down because results were consistent in blinded vs unblinded trials.

[b]The pooled effect of adults and children is precise, suggesting that the outcome in either subgroup (adults or children) is underpowered and the apparent imprecision is just due to small sample size. The effect size in children becomes statistically significant using the DerSimonian-Laird method.

Table H. 4. Assessment of the Strength of Evidence KQ1e. Narrative Evaluation.

Question	Study Design and Sample Size	Risk of Bias	Consistency	Directness	Precision	Publication Bias	Strength of Evidence
FeNO testing done at age 0-4 years for the prediction of a future diagnosis of asthma.	3 observational studies[166, 167, 169] (346 patients)	Low	Inconsistent[a]	Direct	Precise	Undetected	Insufficient (inconsistency)
The association between FeNO testing done at age 0-4 years with the Asthma Predictive Index	5 observational studies[163-165, 168, 170] (959 patients)	Low	Consistent	Direct	Precise	Undetected	Low (Observational studies)
The association between FeNO testing done at age 0-4 years with wheezing	7 observational studies[173-179] (1,126 patients)	Low	Consistent	Direct	Precise	Undetected	Low (Observational studies)

[a] Studies were showing opposing and inconsistent conclusions

Appendix I. Additional Tables

Table I.1. Studies correlating FeNO performed in early childhood to current wheezing (excluded from this systematic review)

Author	Year of Publication	Conclusions
Sayao [173]	2016	In children (age 3-5 years), FeNO at 6ppb and 10ppb diagnoses wheezers from non-wheezers and from non-current wheezers; respectively
Malmberg [174]	2003	In children (age 3.8–7.5 years) with probable asthma, FeNO was higher than control children
Oh [175]	2013	In children age 4-6, FeNO was higher in persistent wheezers than transient wheezers and non-wheezers. Among persistent wheezers, FeNO was higher in those with atopy and airway hyperresponsiveness.
Wildhaber [179]	1999	In healthy infants 3-24 months, single breath FeNO was higher in wheezy infants and those with a family history of atopy
Latzin [177]	2006	FeNO measured after birth was associated with increased risk of subsequent respiratory symptoms and in infants of smoking mothers
Ratjen [176]	2000	Reduced airway NO concentrations in infants with virus-associated acute wheezy bronchitis
Franklin [178]	2004	In infants (5-100 weeks), no significant difference in FeNO found between healthy and wheezy ones, but those with doctor-diagnosed eczema had significantly raised levels

Table I.2. FeNO based algorithms used in randomized trials

Author, Year (ref)	Intervention
Calhoun, 2012 [102]	Asthmatics had their inhaled corticosteroids adjusted (inhaled beclomethasone or equivalent dose) adjustedevery 6 weeks for each group; Physician Assessment based adjustment (PABA) group; based on National Heart, Lung and Blood Institute guidelines. Biomarker - based adjustment (BBA) group; using FeNO measurement as following; If FeNO < 22 ppb, step down one level of therapy, 22-35 ppb, maintaine current level, > 36 ppb, step up one level. Symptom based adjustment (SBA) group; clinical symptoms promoting albuterol rescue use. After randomization, all outcomes were measured at 2, 4, 6, 12, 18, 24, 30, and 36 weeks visit. Primary outcomes: time to first treatment failure, hospitalizations, urgent care visits and other adverse events. Secondary outcomes: spirometry, albuterol reversibility, methacholine responsiveness, sputum eosinophils, daytime and nighttime symptom and rescue beta-agonist diaries, Asthma Control Questionnaire, Asthma Symptom Utility Index, and AQLQ.
De Jongste, 2009 [103]	Participants were seen after randomization at 3, 12, 21, and 30 weeks. Assessments included FeNO. Spirometry before and after salbutamol, and recording of adverse events. PACQLQS was administered at the first and last visits. All parents were phoned every 3 weeks between visits, and medication (inhaled budesonide or equivalent ICS doses) was adapted as following; FeNO group: according to geometric mean FeNO over the preceding 3 weeks and cumulative symptom scores. If FeNO > 20-25 ppb, increase ICS. If FeNO < 20-25 ppb, then decrease ICS if symptoms score < 60 cumulative in 3 weeks or no change in ICS doses if symptoms score > 60 cumulative in 3 weeks. Symptom group: adjusted only for symptoms.
Hashimoto, 2011 [104]	Monthly clinic visit for 6 months. FeNO were measured on a daily basis before medicine intake. ACT and spirometry were completed weekly. AQLQ was completed at baseline and every 3 months afterward. Internet strategy group: oral prednisone or equivalent oral steroid dose was adjusted based on the 3 components: electronic diary, monitoring support by nurses, and algorithm (which includes ACQ and daily FeNO measurement). If FeNO increase by > 10 ppb, step up ICS. If FeNO decrease by > 10 ppb, step down ICS. Conventional strategy group: steroids were down-titrated based on GINA guidelines at monthly visits.
Honkoop, 2015 [105]	Participants were seen every 3 months over the course of 1 year. At each visit, a patient's asthma control status was classified based on the ACQ score as controlled (ACQ score < 0.75), partially controlled (ACQ score > 0.75) or uncontrolled (ACQ score> 1.5). Additionally in the FeNO controlled (FCa) strategy as 3 subcategories of FeNO: low/absence of airway inflammation for values < 25 ppb, intermediate at 26 to 50 ppb, and high/presence of airway inflammation > 50 ppb. Treatment (inhaled beclomethasone or equivalent ICS doses) decisions were based on a dedicated algorithm for each strategy. If FeNO low, step down ICS, if FeNO intermediate, no change in ICS doses, if FeNO high, step up ICS.
Malerba, 2015 [106]	Patients attended five visits after recruitment; 3, 6, 12, 18 and 24 months. At each visit, patients underwent clinical evaluation, lung function tests, sputum induction, and FeNO measurements were carried out according to the ATS guidelines. In group A, treatment (inaheld beclomethasone or ICS equivalent doses) was based on FeNO as following: if FeNO < 10ppb, step down therapy, if FeNO 11-20 ppb, no change in ICS dose, and if FeNO > 20 pbb, step up therapy. Also, sputum eosinophil values, symptoms and bronchodilator use were considered. In group B, treatment was prescribed according to the clinical symptoms score.
Peirsman, 2014 [107]	All patients attended five visits; one every 3 months over a year. Clinical group, at each visit, asthma control and treatment (LTRA, LABA, and inhaled budesonide or equivalent ICS doses) adjustments were determined by the reporting of symptoms, the need for rescue treatment during the two preceding weeks and spirometry, based on the GINA guidelines. FeNO group, FeNO measurements were primarily used to adjust the treatment. If FeNO < 20 ppb and controlled, add LTRA, decrease ICS stop LABA. If FeNO < 20

Author, Year (ref)	Intervention
	ppb and uncontrolled, add LTRA, consider decrease ICS and stop LABA. if FeNO > 20 ppb regardless of symptoms, then increase ICS, add LTRA and stop LABA.
Petsky, 2015 [108]	Monthly visits for the first 4 months and every 2 months thereafter over a year. At each visit, patients assessed with FeNO first, then spirometry before and after 400 mg inhaled salbutamol. Group 1: treatment strategy was based on FeNO levels, adjusted for atopy. If FeNO was elevated (FeNO > 10 ppb in children with no positive skin prick test (SPT), >12 ppb in children with one positive SPT, and >20 ppb in children with 2 or more positive SPT), then therapy was stepped up. If FeNO was low for two consecutive visits, medications were stepped down. Group 2: symptoms-based management.
Pijnenburg, 2005 [110]	Participants were seen for a year, at five visits with 3-month intervals. At each visit, FeNO was measured and the ICS dose was then adapted to FeNO and/or symptom scores recorded during the previous 2 weeks. At visits 1 and 5, pulmonary function tests and bronchoprovocation tests with methacholine were performed. FeNO Group: treatment (inhaled budesonide or equivalent ICS doses) was made on both FeNO and symptoms. If FeNO > 30 ppb regardless of symptoms, increase ICS dose, if FeNO < 30 ppb and symptoms > 14, then continue with ICS dose, if FeNO < 30 ppb and symptoms < 14, then decrease ICS dose. Symptom Group: treatment was made only on symptoms.
Pike, 2013 [110]	Participants were assessed 2 monthly for 12 months. At each visit, a single measure of FeNO and FEV_1 were taken according to ATS/ERS guidelines. Finally, an assessing clinician assessed treatment adherence by direct questioning, recorded exacerbations and administered a questionnaire reviewing symptoms and reliever use over the preceding 2 months. Group 1: therapy (LTRA, LABA and inhaled beclomethasone or equivalent doses of budesonide or fluticasone) adjusted by FeNO measurements. If asthma poor controlled; FeNO > 25 ppb, increase ICS or add LTRA, FeNO <25 ppb, increase LABA. If asthma well controlled; FeNO > 25 ppb, increase ICS or add add LTRA, FeNO 15-25 ppb, continue current treatment, FeNO < 15 ppb, reduce ICS and LABA. Group 2: standard management
Powell, 2011 [111]	Women were reviewed monthly at the antenatal clinic until delivery. At each visit, clinical symptoms, ACQ score, present treatment, FeNO, and FEV_1 were measured. ACQ score, FeNO concentration, and treatment (inhaled budesonide or equivalent ICS doses) were sent by facsimile to the algorithm keeper for treatment changes recommendation. FeNO group: they used a sequential process, first, the FeNO concentration to adjust inhaled corticosteroids dose and second, the ACQ score to adjust the dose of long acting β2 agonist. Clinical group: they were based on asthma control using Juniper ACQ with cutoff points defined as: well controlled asthma (ACQ score < 0.75), partially controlled (ACQ score 0.75-1.50) and uncontrolled (ACQ score > 1.5).
Shaw, 2007 [112]	Participants were seen monthly for the first 4 months and every 2 months thereafter. At each visit, FeNO, FEV_1 and Juniper asthma control questionnaire were taken. At the 6- and 12-month visit, induced sputum and methacholine challenge testing were also performed. FeNO group: when FeNO > 26 ppb, ICS ICS (daily beclomethasone diproprionate (BDP) or equivalent ICS doses) was increased. If < 16 ppb, or < 26 ppb on 2 separate occasions, treatment was decreased Control group: when JACS > 1.57, treatment was doubled. If JACS < 1.57 for 2 consecutive months, the treatment was halved
Smith, 2005[113]	A 12 months phase where patients were evaluated on six occasions at intervals of two months. At each visit, FeNO were measured. If the FeNO > 15 ppb or if the asthma was uncontrolled, treatment (inhaled fluticasone) was increased by one step. If the FeNO level < 15 ppb or if the asthma was controlled for two consecutive visits, the dose was titrated back down one step. However, treatment was not decreased below the optimal dose or to placebo.
Syk, 2013 [114]	Participants were seen after baseline at 2, 4, 8, and 12 month. At each visit, FeNO, ACT, and registration of exacerbations were taken. mAQLQ and GQLI were taken at baseline, month 4, and month 12.

Author, Year (ref)	Intervention
	FeNO group: treatment (inhaled budesonide or equivalent ICS dose) was adjusted according to a FeNO algorithm and 6 fixed treatment steps. Control group: treatment was adjusted according to usual care including patient-reported symptoms, SABA use, physical examination, and lung functions results.
Verini, 2010 [115]	ASS, AEf, ATS, and immunoallergological and functional data were evaluated at the start of the study, 6 months, and 1 year later. FeNO group: therapy consisted of ICS, LABA and LTRA was assessed by FeNO measurements (as the mean of three readings represent the value for each measurement, FeNO > 12 ppb were considered as an indication to increase the number of drugs, whereas < 12 ppb lead to a reduction or to a maintenance in the amount of drugs) and GINA guidelines. GINA group: therapy was assessed based on symptoms, short acting β2-agonist use, and lung function, according to GINA guidelines.

ACQ score: Asthma Control Questionnaire score; ACT score: asthma control test; AEf: Asthma Exacerbation frequency; AQLQ: Asthma Quality of Life Questionnaire; ASS: Asthma Severity score; ATS guidelines: American Thoracic Society guidelines; ATS/ERS guidelines: The American Thoracic Society/ European Respiratory Society guidelines; ATS: Asthma Therapy score; FeNO: Fractional exhaled nitric oxide; FEV_1: forced expiratory volume in the first second; FEV_1% pred: forced expiratory volume in the first second percentage predicted; GINA guidelines: Global Initiative for Asthma guidelines; GQLI: Gothenburg Quality of Life Instrument; ICS: Inhaled corticosteroid; LABA: Long-acting beta-2-agonists; LTRA: Leukotriene receptor antagonist; mAQLQ: Mini Asthma Quality of Life Questionnaire; PACQLQS: Pediatric Asthma Caregiver Quality of Life Questionnaire with Standardized activities; SABA: Short-acting beta-2 agonist.

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