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, 20061 | 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, 20012 | Israel,  longitudinal nonrandomized, outpatient setting, medium risk of bias. | Reference test;  positive bronchial challenge  adenosine-5’ monophosphate (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 after FeNO measured. |
| Backer, 20143 | 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, 20054 | 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 FEV1 >10%. | FeNO 7 ppb vs. Exercise-induced bronchoconstriction had sensitivity 91.3% and specificity 70.1% |
| Reference test;  Positive bronchial challenge  Methacoline challenge, N= 85 | 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% |
| 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, 20005 | 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 FEV1/FVC was 70% or greater or an improvement of the FEV1 from predicted of 15% or greater after 200 µg of inhaled salbutamol if the FEV1/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, 20076 | Italy,  cross sectional study, low risk of bias. | Reference test;  clinical diagnosis European Community Respiratory Health Survey II (ECRHS II) questionnaire, N= 55 | 13 asthmatic, mean age 43.6 years (SD: 0.72), 46.2% males, 23.1% current 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. | A short, self-completed questionnaire identical to that used for stage 1 in the ECRHS I. Subjects with ‘current asthma’ were defined as those 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. | Compared with ECRHS II, FeNO > 18.7 ppb had the best combination of sensitivity (69.2%) and specificity (71%), with a 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, 20117 | 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 FEV1 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, 20028 | 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 FEV1 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%  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% |
| 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. |
| Dupont, 20039 | 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-acting B2-mimetics in the 8 h prior to the measurements. |
| Florentin, 201410 | 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, 200711 | 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= 57 | 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 |
| FeNO, N= 57 | Aerocrine (NioxMinor, Solna, Sweden) following the recommendations of the ERS and ATS. |
| Fukuhara, 201112 | Japan,  prospective study, outpatient setting, low risk of bias. | Reference test;  Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge)  Conventional criteria:, 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 FEV1 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.  . | Compared to conventional criteria or AHR or BDR or Eos%, FeNO 40 ppb had sensitivity 78.6% and specificity 89.5% in asthma diagnosis. |
| FeNO, N= 61 | 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. |
| Grzelewski,  201413 | Poland, retrospective, cross sectional, outpatient setting, medium risk of bias. | Reference test;  Combined (Clinical Diagnosis + Bronchodilator response)  clinical symptoms plus bronchodilator response, N= 3612 | 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 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, 200614 | 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 FEV1 after inhalation of a β-agonist or a methacholine PC20 of ≤ 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, 200015 | Norway, cross sectional study, outpatient setting, high risk of bias. | Reference test,  Combined (Clinical Diagnosis +Positive bronchial challenge)  Survey and methacholine challenge test, N= 331 | Suspected asthma (N=138)  Mean age 16.3 years,  44% males,  21% Smokers,  BMI 22.5 Kg/m2.  Control subjects (N= 193)  Mean age 16 years,  46% male,  13% smokers,  BMI 21.9 Kg/m2. | Methacholine reactivity defined as >20% drop FEV1 (PD20). If baseline spiro showed obstruction, broncho-dilator response defined as >15% 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. | 52% of the suspected asthmatics and 20% of the control subjects had elevated levels of FeNO (>8 ppb).  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/minat One visit. |
| Ishizuka, 201116 | 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, 201417 | 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 FEV1 > 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%). |
| 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, 201318 | Greece, longitudinal nonrandomized study, outpatient setting, medium risk of bias. | Reference test;  Positive bronchial challenge  methacholine challenge test, 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. | 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. |
| FeNO, N =122 | Measured by (NIOX MINO, airway inflammation monitor; Aerocrine, Solna, Sweden) that provides measurements at 50 ml/sec exhalation flow rate. |
| Kostikas 200819 | Greece, cross sectional study, medium risk of bias. | Reference test;  Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge)  clinical diagnosis, bronchodilator response and bronchial challenge, N= 149 | 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),  33.3% smokers.  29 non-specific symptoms;  mean age 22.1 years (SD: 3.1),  37.9% smokers. | 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 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, 201020 | 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.  19 non-asthmatics  mean age 44.8 years (SD: 10.8)  63.4% males,  26.8% current smokers,  53.8% 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 | 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, 201221 | Denmark,  cross sectional study, low risk of bias. | Reference test;  Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge)  Methacoline challenge test or asthma symptoms, N=282 | 96 asthmatic patients  mean age of 32.7 years,  40.6% males,  53.1% ever smoked.  186 symptomatic non-asthmatic patients  mean age of 32.7 years,  39.8% males,  64.1% 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.  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. | 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%, 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. |
| FeNO, N=282 | 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. |
| Martin, 201622 | 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 | 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 FEV1, 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 | 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%). |
| FeNO, N= 74 | Measured by (NIOX MINO; Aerocrine, Tolna, Sweden). |
| Matsunaga, 201123 | 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.  224 healthy controls  mean age of 39.4 years, 44% males,  23% 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 specified) | FeNO at 22 ppb cut-off, compared with medical history had sensitivity 90.8%, specificity 83.9% and AUC 0.896. |
| 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, 200724 | 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, 200725 | 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 ( PD20) and/or provocative dose of mannitol causing a 15% fall in FEV1 ( PD15) | 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%. |
| Reference test;  Positive bronchial challenge  Mannitol challenge (PD15) , N= 101 | If the FEV1 fell by 10% based on the FEV1, the dose producing this fall was repeated. The challenge was stopped if the FEV1 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, 200926 | 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%. |
| 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, 200927 | 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, 201328 | 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 years,  49% males | 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 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, 201029 | 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, 201130 | 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. |
| Pizzimenti, 200931 | Italy, prospective study, outpatient clinic, medium risk of bias. | FeNO, N= 156 | 14 asthmatics and 142 controls.  41% males,  47.4% atopic,  9% smokers | Bronchial hyperresponsiveness (PD20 FEV-1<800 mu) in asthmatic patients. | 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. |
| Reference test;  Combined (Clinical Diagnosis + Positive bronchial challenge)  Methacoline challenge test and spirometry, N= 156 | Measured by portable analyzer NIOX-MINOA (Aerocrine AB, Solna, Sweden). |
| Ramser, 200832 | Switzerland,  cross sectional study, outpatient setting, low risk of bias. | Reference test;  Positive bronchial challenge  Exercise induced bronchoconstriction (EIB) , 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 FEV1 by ≥15% of baseline. | 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% |
| Reference test;  Positive bronchial challenge  Methacholine challenge (MCH), N= 169 | 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, N= 169 | 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 a flow rate of 50 mL/sec. |
| Sachs-Olsen, 201033 | 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, 200834 | Japan, longitudinal nonrandomized, outpatient setting, low risk of bias. | Reference test;  Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge)  Clinical diagnosis, airway hyper-responsiveness or Bronchodilator reversibility, N= 71 | 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 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. | Spirometry measured using Chestac-11 Cyber S-type; Chest MI, Inc., Tokyo, Japan).  Positive bronchodilator reversibility is defined as an increase in FEV1 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 at the end of inhaling the highest dose was 50 units. | 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. |
| 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,  201235 | 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 FEV1 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, 201436, 37 | Germany, prospective diagnostic study, outpatient setting, medium risk of bias. | Reference test;  Combined (Clinical Diagnosis + Bronchodilator response + Positive bronchial challenge)  Whole body plethysmography (WBP) and bronchial provocation, N= 388 | 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.  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. | Spirometry were performed, patients with FEV1 < 80% predicted received salbutamol with an additional WBP investigation 20 min later. Asthma if FEV1/VC was <0.70, clinical symptoms and history fitted and the change in FEV1 was > 12% compared with baseline and > 200 mL and lung function returned to the predicted normal range. | 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: 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, 200938 | 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 FEV1 < 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 FEV1 from the baseline value (PC20) after inhaling methacholine step wise until the maximum concentration (16 mg/mL) | Compared with a 20% fall of FEV1 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 FEV1 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%.  Other cutoffs results are reported in detailed in the analysis as well. |
| 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. |
| Sivan, 200939 | 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 FEV1> 15% in response to bronchodilators at any time during the follow-up period (reversibility), or documented variability in FEV1> 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 200440 | New Zealand, prospective study, outpatient setting, low risk of bias. | Reference test;  Combined (Clinical Diagnosis + Bronchodilator response)  relevant symptom history, bronchodilator reversibility and bronchial hyperresponsiveness, N=47 | 17 asthmatics  mean age 41.6 years, range 9–72,  53% males.  30 healthy controls  mean age 31.8 years, range 9–64,  37% 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 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. | Compared with symptom history, bronchodilator reversibility and bronchial hyperresponsiveness, FeNO > 20 ppb had sensitivity 88% and specificity 79% in 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, 200541 | 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 FEV1 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) |
| Travers, 200742 | 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 FEV1> 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, 201243 | 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 (>12% improvement in FEV1 in response to inhaled b2-agonist) and/or airway hyper responsiveness (methacholine PC20 <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%. |
| 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, 201144 | 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; 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; 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 FEV1; PC20: provocation concentration causing a 20% fall in FEV1; PD15: provocation dose causing a 15% declaine in FEV1; PD20: provocation dose causing a 20% decline in FEV1; PPV: positive predictive value; ROC curve: receiver operating characteristic curve; RCT; randomized clinical trial; SD: standard deviation.