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 | 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. | 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 | |
| Asthma predictive index (API), N= 52 | 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%). |
| 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. FeNO was correlated with respiratory allergy, and was borderline significantly correlated with wheezing, but not with the asthma predictive index (mAPI). |
| 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). |
| Castro-Rodriguez, 2013 165 | Chile/ Spain, cross section study, low risk of bias. | 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 age 11 months (SD: 8),  54.6% males.  FeNO= 4.1 ppb. | 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 (OR = 1.12, 95% CI: 0.99–1.27). | |
| Asthma predictive index (API), N= 27 | 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%). |
| 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 nonrandomized, low risk of bias. | FeNO, N=116 | Mean age 10.66 months (SD: 4.6),  47.5% males,  50% atopic (allergy sensitivity sitization) 50%. | Infants; measured online at a constant expiratory flow from raised lung volume. In 5 years old; measured online with a Niox eNO analyzer (Aerocrine, Solna, Sweden). | 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, 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). | 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). | |
| 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 age 3 years. | |
| 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 chemiluminescence analyser (GE Analytical Instruments; Boulder, CO, USA). | 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 exacerbation of wheezing between 2.5-3 years with 53% sensitivity, 61% specificity, 52% PPV, 60% NPV 60. |
| 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. |
| Klaassensitivity , 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 1.01 (0.99–1.04); respectively. | |
| 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. |
| 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 and outpatient setting, low risk of bias. | 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 balloons are analyzed in a NO-analyzer (Aerocrine AB; Sweden) within a time period of 6–8 hours after taking the samples. | Ongoing cohort study (The AiRway Complaints and Asthma Development, ARCADE). |  | |

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; FEV1: forced expiratory volume in the first second; FEV1% 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.