Supplementary Tables

Supplementary Table S1

Search results for the database Medline (September 30, 2014)

Step	Search term	Results
1	((respirat$ or bronchial or airway$) adj1 (allerg$ or hyperre$ or hypersens$ or hyper-re$ or hyper-sens$ or obstruct$ or constrict$)).ab,cm,xm,xs,fs,kw,kf,sh,ot,oa,hw,tw,ti.	178639
2	(bhr or ahr or asthma$ or wheez$ or eosinophil$ or methachol$ or bronchial provocation or bronchial challenge).ab,cm,xm,xs,fs,kw,kf,sh,ot,oa,hw,tw,ti.	214814
3	1 or 2	272187
4	(feno or eno or ((exhal$ or ex?pir$ or breath$) adj3 (nitric or no))).ab,cm,xm,xs,fs,kw,kf,sh,ot,oa,hw,tw,ti.	5219
5	3 and 4	2542

Supplementary Table S2

Reasons for exclusion of studies undergoing closer scrutiny included in the meta-analysis by Li et al. 2015, the systematic review by Harnan et al. 2013, raising uncertainties among or disagreements between reviewers.

Study	Reason for exclusion
Backer V, Sverrild A, Porsbjerg C. FENO and AHR mannitol in patients referred to an out-of-hospital asthma clinic: a real-life study. J Asthma 2014;51(4):411-6	Population too selected: 48% had inhalative corticosteroids at inclusion
Berkman N, Avital A, Breuer R, et al. Exhaled nitric oxide in the diagnosis of asthma: Comparison with bronchial provocation tests. Thorax 2005;60(5):383-88#	Index test: FENO flow rate 250 ml/s
Bobolea ID, Barranco P, Lopez-Carrasco V, et al. Is methacholine challenge sufficient to rule out bronchial hyperresponsiveness in patients with suspected asthma? Journal of Allergy and Clinical Immunology 2012;1):AB3§	Highly selected population: only patients with negative bronchodilatation and negative metacholine challenge
Bommarito L, Migliore E, Bugiani M, et al. Exhaled nitric oxide in a population sample of adults. Respiration 2008;75(4):386-92#	Index test: FENO flow rate 350/ml/s; results presented for subgroup only
Chatkin JM, Ansarin K, Silkoff PE, et al. Exhaled nitric oxide as a noninvasive assessment of chronic cough. Am J Respir Crit Care Med 1999;159(6):1810-3	Index test: flow rate/expiration procedure not according to inclusion criteria
Cirillo I, Ricciardolo FLM, Medusei G, et al. Exhaled nitric oxide may predict bronchial hyperreactivity in patients with allergic rhinitis. International Archives of Allergy and Immunology 2013;160(3):322-28	Selected population: patients with allergic rhinitis
de la Barra SL, Smith AD, Cowan JO, et al. Predicted versus absolute values in the application of exhaled nitric oxide measurements. Respiratory Medicine 2011; 105(11):1629-1634§	Secondary analysis of data from Smith 2005
Ewald-Kleimeier S, Lotz A, Merget R, et al. Exhaled nitric oxide in specific inhalation challenge. Adv Exp Med Biol 2013;788:255-64	Population: more than 25% with steroids at inclusion
Grzelewski T, Witkowski K, Makandjou-Ola E, et al. Diagnostic value of lung function parameters and FeNO for asthma in schoolchildren in large, real-life population. Pediatr Pulmonol 2014;49(7):632-40	Insufficient and inconsistent data, no response of author to inquiries: large retrospective study presenting only (inconsistent) diagnostic data for subgroup only (allergic rhinitis, sensitization to perennial and seasonal rhinitis only)
Hahn PY, Morgenthaler TI, Lim KG. Use of exhaled nitric oxide in predicting response to inhaled corticosteroids for chronic cough. Mayo Clinic Proceedings 2007;82(11):1350-55§	Highly selected population: all patient were on inhaled corticosteroids for chronic cough
Hsu JY, Wang CY, Cheng YW, et al. Optimal value of fractional exhaled nitric oxide in inhaled corticosteroid treatment for patients with chronic cough of unknown cause. J Chin Med Assoc 2013;76(1):15-9§	Inadequate reference standard: only FENO compared to response in terms of improvement in symptoms to treatment with inhaled steroids reported/not asthma diagnosis
Jerzynska J, Majak P, Janas A, et al. Predictive value of fractional nitric oxide in asthma diagnosis-subgroup analyses. Nitric Oxide 2014;40:87-9#	Insufficient and inconsistent data, no response of author to inquiries: large retrospective study presenting only (inconsistent) diagnostic data for subgroup only (atopy and allergic rhinitis); did not respond to inquiries. Overlapping author team with Grzelewski et al. 2014
Malmberg LP, Pelkonen AS, Haahtela T, et al. Exhaled nitric oxide rather than lung function distinguishes preschool children with probable asthma. Thorax 2003;58(6):494-9#	Index test: tolerance interval of flow rate (40-60 mL/s) to wide according to ETS/ERS guidelines. Selected population: Study includes children with pre-diagnosed asthma, probable asthma, cough only and healthy controls
Malmberg LP, Pelkonen AS, Mattila PS, et al. Exhaled nitric oxide and exercise-induced bronchoconstriction in young wheezy children - interactions with atopy. Pediatr Allergy Immunol 2009;20(7):673-8	Selected population: study only includes children with positive prick tests and wheezing
Maniscalco M, Faraone S, Sofia M, et al. Extended analysis of exhaled and nasal nitric oxide for the evaluation of chronic cough. Respir Med 2015;109(8):970-4	Comparison of cough-variant asthma, non-asthmatic eosinophilic bronchitis, gastro-esophageal reflux disease and upper airway cough syndrome; no usable data for review question
Mathew S, Cliff I, Agarwal S, et al. Relationship between exhaled nitric oxide and methacholine challenge test in suspected asthma. Am J Resp Crit Care Med 2011; 183	Abstract neither reporting the FENO measurement device, flow rate nor cut-off value used. Only patients with normal spirometry and no evidence

(1 Meeting Abstracts)§	of reversibility
Matsunaga K, Hirano T, Akamatsu K, et al. Differences in cutoff values of exhaled nitric oxide for asthma diagnosis according to rhinitis and smoking status. Am J Resp Crit Care Med 2011; 183 (1 Meeting Abstracts)#	Selected population: case-control study in steroid-naïve asthma patients and controls. While asthma diagnosis was made after FENO measurement the selection process is unclear
Ng HL, Law JLM, Tee AKH. Exhaled nitric oxide measurements and airway hyperresponsiveness. Ann Acadf Med Singapore 2011;(suppl 1):S201	Unclear selection of patients – congress abstract only, no author contact data
Nickels A, Parker K, Scanlon P, et al. Exhaled nitric oxide performance compared to methacholine challenge in pediatric patients. J Allergy Clin Immunol 2015;(suppl 1):AB150	FENO measurement flow rate/brand not reported (congress abstract only), unclear selection of patients (retrospective chart reviews)
Prieto L, Ferrer A, Ponce S, et al. Exhaled nitric oxide measurement is not useful for predicting the response to inhaled corticosteroids in subjects with chronic cough. Chest 2009;136(3):816-22§	Inadequate reference standard: only FENO compared to response to treatment with inhaled steroids reported/not asthma
Ramser M, Hammer J, Amacher A, et al. The value of exhaled nitric oxide in predicting bronchial hyperresponsiveness in children. J Asthma 2008;45(3):191-5§	Study investigates atopy, not asthma. 37% of participants had pre-diagnosed asthma
Sachs-Olsen C, Lodrup Carlsen KC, Mowinckel P, et al. Diagnostic value of exhaled nitric oxide in childhood asthma and allergy. Pediatr Allergy Immunol 2010;21(1 Pt 2):e213-21#	Selected patients: FENO measurement embedded in the follow-up of a birth cohort after asthma diagnosis
Sastre J, Costa C, del Potro MG, et al. Changes in exhaled nitric oxide after inhalation challenge with occupational agents. J Investig Allergol Clin Immunol 2013;23(6):421-27	48% of participants (suspected occupational asthma) already on inhalative corticosteroids
Schneider A, Tilemann L, Schermer T, et al. Diagnosing asthma in general practice with portable exhaled nitric oxide measurement--results of a prospective diagnostic study: FENO < or = 16 ppb better than FENO < or =12 ppb to rule out mild and moderate to severe asthma [added].[Erratum appears in Respir Res. 2009;10: 64 doi:10.1186/1465-9921-10-64]. Respir Res 2009;10:15§	Subgroup analysis of included study Tilemann 2011
Schneider A, Faderl B, Schwarzbach J, et al. Prognostic value of bronchial provocation and FENO measurement for asthma diagnosis -results of a delayed type of diagnostic study. Respir Med 2014;108(1):34-40	Long-term follow-up of included study Schneider 2013 with 302 of the original participants providing data
Yune S, Lee JY, Choi DC, et al. Fractional exhaled nitric oxide: comparison between portable devices and correlation with sputum eosinophils. Allergy Asthma Immunol Res 2015;7(4):404-8	Focus on sputum eosinophilia, no data on asthma diagnosis in relation to FENO presented
Zhu H, Yu X, Hao C, et al. [The diagnostic value of the fractional exhaled nitric oxide for cough variant asthma in children]. Zhonghua Jie He He Hu Xi Za Zhi 2015;38(5):352-5	Impossible to construct a plausible two-by-two table based on the data presented in the paper; no response of authors to inquiry for clarification

study included in meta-analysis by Li et al. 2015; § study included by Harnan et al. 2013

Supplementary Table S3

Additional information on participants in included studies

First author	Year	Symptoms in population	Setting/remarks	Current smokers included	Respiratory infection last 7 days included
Arora	2006	Dyspnea, cough, wheezing, chest tightness	Participants were basic military trainees	Unclear	Unclear
Cordeiro	2011	"Typical respiratory symptoms" (U)	General allergy outpatient clinic	Unclear	Unclear
ElHalawani	2003	Suspected diagnosis of exercise-induced bronchoconstriction	Pulmonary clinic	No	Not stated
Florentin	2014	Wheezing, breathlessness, chest tightness, cough, sputum	Occupational medicine (participants bakers or hairdressers)	Yes	Unclear
Fortuna	2007	Dry cough, wheezing, shortness of breath (U)	Respiratory medicine outpatient clinic	Yes	No
Fukuhara	2011	Recurrent cough, wheezing, dyspnea, chest tightness	Department of pulmonary medicine	Yes	Unclear
Giovannini	2014	Cough, wheezing, dyspnea (U)	Probably department of pulmonary medicine	Yes	Unclear
Heffler	2006	Cough, dyspnea, chest tightness, wheezing, nasal symptoms (rhinitic patients with asthmatic symptoms)	Allergy outpatient clinic	No	No
Katsoulis	2013	At least one symptom in an asthma screening questionnaire	Outpatient clinics of two hospitals	Yes	No
Kostikas	2008	At least one symptom in an asthma screening questionnaire	Recruitment of university students	Yes	No
Kowal	2009	Chronic cough (among non-smokers)	Referral from family doctors to asthma clinic	No	No
Linkosalo	2012	Asthma-like symptoms in atopic children	Pediatric allergologist	Unclear	Unclear
Malinovschi	2012	Individuals with two or more respiratory symptoms in a random population sample	Part of a population-based study on asthma treatment	Yes	Yes
Pedrosa	2010	Shortness of breath, wheezing, cough (U)	Referred patients (probably to allergy department)	Yes	Unclear
Pizzimenti	2009	Cough lasting at least 8 weeks	Respiratory medicine outpatient clinic	Yes	Not stated
Sato	2008	Prolonged cough, wheezing (U)	Department of pulmonary medicine	Yes	Yes
Schleich	2012	No details reported	Referral methacholine challenge after failed brochodilatation test	Yes	Unclear
Schneider	2013	Shortness of breath, wheezing, cough, dyspnea (U)	Patients referred to pulmonologist	Yes	No
Sivan	2009	Cough, wheezing, shortness of breath (U)	Referral to pediatric pulmonary outpatient clinic	Unclear	No
Smith	2004	Respiratory symptoms (U)	Referral from family practitioner for possible asthma	No	No
Smith	2005	Respiratory symptoms (U)	Referral from family practitioner for possible asthma	Yes	No

Tilemann	2011	dyspnoea, coughing, expectoration > 2 months (U)	Referral by general practitioners to lung function laboratory	Yes	No
Voutilainen	2013	Cough, dyspnoea, wheezing	Part of a study comparing sedentary patients and athletes	Unclear	No
Wang	2015	Wheezing, dyspnea, chest tighness, cough (U)	Referral to hospital outpatient clinic	Yes	No
Woo	2012	Coughing, wheezing, shortness of breath (U)	Referral to specialist outpatient clinic	Unclear	No
Zhang	2011	Chronic cough	Respiratory clinic	No	No

U = studies recruiting unselected patients with typical asthma symptoms from naturalistic population not restricted to specific patients groups (e.g. individuals with specific professional exposure), not recruited by screening procedures etc.

Supplementary Table S4

Risk of bias assessments for included studies (+ = low risk, ? = unclear risk, - = high risk)

First author	Year	I	II	III	IV	V	VI	VII
Arora	2006	?	+	-	+	+	+	+
Cordeiro	2011	+	+	-	+	+	+	?
El Halawani	2003	+	?	-	+	?	?	+
Florentin	2014	-	?	-	+	?	?	-
Fortuna	2007	+	+	?	+	+	+	+
Fukuhara	2011	+	+	?	+	?	+	?
Giovannini	2014	?	?	-	+	?	+	?
Heffler	2006	+	+	-	+	?	+	?
Katsoulis	2013	-	+	-	+	?	+	+
Kostikas	2008	+	+	-	+	+	+	?
Kowal	2009	+	+	-	+	?	+	?
Linkosalo	2012	+	+	-	+	?	?	+
Malinowschi	2012	?	?	-	+	?	+	?
Pedrosa	2010	-	+	-	+	?	+	+
Pizzimenti	2009	+	+	-	+	?	+	?
Sato	2008	+	+	-	+	?	+	+
Schleich	2012	+	+	-	+	+	+	+
Schneider	2013	+	+	-	+	+	+	+
Sivan	2009	+	+	-	+	+	+	-
Smith	2004	+	+	-	+	+	+	+
Smith	2005	+	+	-	+	?	+	?
Tilemann	2011	+	+	-	+	+	+	+
Voutilainen	2013	+	+	?	+	?	+	+
Wang	2015	+	+	-	+	?	?	?
Woo	2012	+	+	-	+	?	+	+
Zhang	2011	?	+	-	+	?	?	?

I = Could the selection of patients have introduced bias?; II = Is there concern that the included patients do not match the review question? III = Could the conduct or interpretation of the index test have introduced bias?; IV = Is there concern that the index test, its conduct, or interpretation differ from the review question? V = Could the reference standard, its conduct, or its interpretation have introduced bias? VI = Is there concern that the target condition as defined by the reference standard does not match the review question? VII = Could the patient flow have introduced bias?

Supplementary Table S5

Results of univariable metaregression. Estimates represent either probabilities (for the intercept, if the covariate is continuous, and for all categories, if it is categorical) or odds ratios (OR, in case of regression coefficients for continuous covariates). All p-values represent the comparison to the reference category.

			Estimate (95%CI)	**p-value**
Prevalence	sensitivity	intercept	0.709	
		each 10% increase (OR)	0.942 (0.774; 1.146)	0.552
	specificity	intercept	0.745	
		each 10% increase (OR)	1.111 (0.909; 1.359)	0.305
Cut-off	sensitivity	intercept	0.720	
		each 10ppb increase (OR)	0.904 (0.708; 1.155)	0.420
	specificity	intercept	0.579	
		each 10ppb increase (OR)	1.462 (1.199; 1.783)	< 0.001
Age	sensitivity	children	0.719 (0.492; 0.871)	
		adults	0.646 (0.197; 0.931)	0.519
	specificity	children	0.855 (0.663; 0.947)	
		adults	0.814 (0.313; 0.977)	0.607
> 90% Bronchial provocation	sensitivity	no	0.705 (0.571; 0.811)	
		yes	0.631 (0.322; 0.860)	0.347
	specificity	no	0.757 (0.635; 0.847)	
		yes	0.841 (0.595; 0.950)	0.138
Diagnosis only with bronchial provocation	sensitivity	no	0.691 (0.609; 0.762)	
		yes	0.549 (0.300; 0.775)	0.080
	specificity	no	0.801 (0.731; 0.856)	
		yes	0.857 (0.655; 0.950)	0.305
Risk of bias	sensitivity	all kinds of bias present	0.712	
		each dimension of low bias (OR)	0.937 (0.748; 1.173)	0.568
	specificity	all kinds of bias present	0.738	
		each dimension of low bias (OR)	1.121 (0.890; 1.412)	0.331
FENO Device	sensitivity	other chemoluminescence	0.838 (0.758; 0.896)	
		NioxMino®	0.588 (0.314; 0.816)	< 0.001
		NioxFlex®	0.577 (0.274; 0.832)	0.001
		other electrochemical	0.159 (0.021; 0.627)	< 0.001
	specificity	other chemoluminescence	0.773 (0.649; 0.863)	
		NioxMino®	0.806 (0.512; 0.943)	0.612
		NioxFlex®	0.877 (0.590; 0.973)	0.142
		other electrochemical	0.977 (0.480; 1.000)	0.124

Deviations for protocol

Remark: it should be noted that parts of the protocol refer to a smaller additional review on studies investigating the prediction of response to steroids which is not part of the manuscript.

- section 3.4. Index test: In the early phase it was decided to only include studies following the ATS guideline to reduce heterogeneity
- sections 4.1. and 4.4.: It was not possible to build reasonably large, well-defined subgroups of patients with distinct symptoms, mainly because of small numbers, strong overlaps and insufficient reporting. Also, the preplanned subgroup analysis primary care vs. clinical setting was not feasible.
- Section 4.3.: Instead of the ROC curve proposed by Moses we present the curve according to Rücker and Schumacher (as this curve is methodologically preferable).