Could fractional exhaled nitric oxide test be useful in predicting inhaled corticosteroid responsiveness in chronic cough? A systematic review

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Running title: Fractional exhaled nitric oxide in chronic cough

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Abstract

Background: Fractional exhaled nitric oxide (FeNO) is a safe and convenient test for assessing Th2 airway inflammation, which is potentially useful in the management of patients with chronic cough.

Objective: To summarise the current evidence on the diagnostic usefulness of FeNO for predicting inhaled corticosteroid (ICS) responsiveness in patients with chronic cough

Methods: A systematic literature review was conducted to identify articles published in peer-reviewed journals up to February 2015, without language restriction. We included studies that reported the usefulness of FeNO (index test) for predicting ICS responsiveness (reference standard) in patients with chronic cough (target condition). The data were extracted to construct a 2 × 2 accuracy table. Study quality was assessed with QUADAS-2.

Results: We identified five original studies (two prospective and three retrospective studies). We identified considerable heterogeneities in study design and outcome definitions, and thus were unable to perform a meta-analysis. The proportion of ICS responders ranged from 44% to 59%. Sensitivity and specificity ranged from 53% to 90%, and from 63% to 97%, respectively. The reported area under the curve (AUC) ranged from about 0.60 to 0.87; however, studies with a prospective design and a lower prevalence of asthma had lower AUC values. None measured placebo effects or objective cough frequency.

Conclusions: We did not find strong evidence to support the use of FeNO tests for predicting ICS responsiveness in chronic cough. Further studies need to have a randomised, placebo-controlled design, and should use validated measurement tools for cough. Standardisation would facilitate the development of clinical evidence.

Word count: 250

Highlight box

1. What is already known about this topic?

Th2 inflammation in the airways is a major factor contributing to cough hypersensitivity. Fractional exhaled nitric oxide (FeNO) is a safe and convenient test to measure the degree of Th2 inflammation in the airways.

2. What does this article add to our knowledge?

Current findings on the diagnostic usefulness of FeNO in predicting inhaled corticosteroid responsiveness (ICS) in chronic cough patients are conflicting.

3. How does this study impact current management guidelines?

Further well-designed prospective placebo-controlled studies with validated outcome measurement tools and standardized protocols are warranted to recommend the use of FeNO tests in predicting ICS responsiveness in clinical guideline of chronic cough.

64 **Keywords:** chronic cough; fractional exhaled nitric oxide; corticosteroid responsiveness;
65 systematic review

66

Abbreviations

ICS, inhaled corticosteroid

FeNO, fractional exhaled nitric oxide

eNO, exhaled nitric oxide

IL, interleukin

AUC, area under the curve

ROC, receiver operating characteristic

QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies 2

SROC, summary receiver operating characteristic

LCQ, Leicester Cough Questionnaire

VAS, visual analogue scale

BHR, bronchial hyper-responsiveness

FEV1, forced expiratory volume in 1 second

FVC, forced vital capacity

RTI, respiratory tract infection

SD, standard deviation

IQR, interquartile range

SE, standard error

95% CI, 95% confidence interval

Introduction

Chronic cough is a common clinical condition arising from hypersensitivity of cough reflex pathways.[1, 2] Among several peripheral triggers of cough reflex pathways, airway eosinophilic inflammation is one of the most well-known with respect to the mechanism of action and clinical implications. Th2 inflammatory mediators induced in conditions like asthma or eosinophilic bronchitis can directly activate or sensitise airway sensory nerves, leading to cough hypersensitivity.[3] Importantly, this type of airway inflammation responds well to inhaled corticosteroid (ICS) therapy.[2] Thus, it is of clinical relevance to identify 'ICS-responsive cough' at the early stage of diagnosis.[4]

Traditionally, induced sputum analysis has been utilised to guide decisions for ICS treatment initiation. Airway eosinophilic inflammation (usually defined by an induced sputum eosinophil count ≥ 2-3%), even in the absence of asthma, has been recognised to show good responsiveness to ICS.[5, 6] However, induced sputum analysis is technically demanding with respect to the standardisation of induction, processing, and interpretation procedures; thus, its use has mostly been restricted to specialised centres and the validation of more convenient alternative markers are warranted.[7]

The fractional exhaled nitric oxide (FeNO) test is a recently developed inflammometer to detect Th2 inflammation in the airways. The main origin of exhaled nitric oxide (eNO) is the respiratory epithelium. Inducible NO synthase, the enzyme that produces NO, is mostly upregulated by interleukin (IL)-4 and IL-13.[8] Thus, FeNO levels may reflect the degree of Th2-type airway inflammation, and the test is considered as a safe and convenient alternative to induced sputum analysis or the methacholine challenge test.[9]

In asthma, FeNO levels showed a good correlation with induced sputum eosinophilia in a recent meta-analysis[7], and FeNO has also been considered as a good clinical predictor of ICS responsiveness, particularly in terms of reducing exacerbation.[10] In chronic cough, FeNO level was reported to be a good predictor of cough variant asthma or eosinophilic bronchitis among chronic cough patients.[11, 12] Moreover, the FeNO level was suggested to be more useful in predicting ICS responsiveness than any other markers, such as the induced sputum eosinophil count, among chronic persistent cough patients.[13] Thus, we hypothesised that the FeNO test would be useful in predicting 'ICS responsiveness' in unselected chronic cough patients. In the literature so far, this research question has not been systematically reviewed. Here, we conducted a systematic review to summarise the current evidence on the diagnostic usefulness of the FeNO test in predicting ICS responsiveness in chronic cough patients.

Methods

Literature search

We searched the PubMed, Embase, Web of Science and Scopus databases according to the recommendation of the PRISMA statement.[14] The search terms used were “cough” AND “nitric oxide” for articles published in peer-reviewed journals up to February 2015, without language restriction. Additional searches of Google Scholar and clinical trial registries (clinicaltrials.gov and isrctn.com) were performed. If full-text links were not available, we contacted the corresponding authors by electronic mail. We included studies if they had reported the usefulness of FeNO (set as an index test) for predicting ICS responsiveness (as a dichotomous outcome; set as the reference standard) in patients with chronic cough (set as the target condition). Any dichotomous criterion for determining ICS treatment responsiveness was accepted if it was specified within the manuscript. Studies were excluded if they were not original papers (review articles or case reports) or did not determine ICS responsiveness as a dichotomous outcome. Two independent authors screened the titles and abstracts of all of the search results and determined the eligibility of each study. Any discrepancy in the selection was resolved by consensus between the authors.

Data extraction and quality assessment

For all of the included articles, data were extracted pertaining to the first author, journal, publication year, country, study design, clinical setting, sample size, characteristics of the study participants (age, sex, corticosteroid treatment history, and asthma prevalence), and ICS treatment and responsiveness (%). Additionally, we extracted the results of index tests, the reference standard, test positivity thresholds, area under the curve (AUC) values, and data for constructing 2 × 2 tables

giving the index test results by reference standard results for each reported threshold. If 2 × 2 tables were not reported in the original papers, we reconstructed them from summary estimates or from the electronic mail contacts of the corresponding authors. In any case of an included study that did not report the optimal cut-off value of the index test (FeNO), we performed receiver operating characteristic (ROC) curve analysis using the original data provided by the corresponding authors and also determined the optimal cut-off value using the Youden index (sensitivity + specificity – 1). Two independent authors assessed the risk of bias, as well as applicability concerns, using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool.[15]

Statistical analysis

From each constructed 2 × 2 table, we calculated estimates of the sensitivity and specificity, as well as 95% confidence intervals. The extracted data were summarised as a forest plot. Additionally, because the sensitivity and specificity change according to the threshold level, summary ROC (SROC) curves were also generated.[16] Heterogeneity was defined as significant if $I^2 > 50\%$. We used Egger's test to assess the risk of publication bias. All of the statistical analyses were performed using RevMan software (ver. 5.3; Cochrane Collaboration, Oxford, UK) and the meta-analysis modules of Stata (ver. 14.1; Stata Corp., College Station, TX, USA) (metan, metabias and metandi).

Results

Characteristics of included studies

Among 916 initially retrieved abstracts, five original articles finally met the inclusion criteria (Figure 1).[17-21] Chaudhuri et al.[13] the first report on this topic, was excluded because responsiveness to treatment was not reported as a dichotomous outcome and the sensitivity and specificity data could not be retrieved after contacting the corresponding author. Zhang et al.,[22] which examined the usefulness of FeNO tests for ICS responsiveness was excluded at the final selection stage because ICS was selectively administered to a subgroup of patients with cough-variant asthma or eosinophilic bronchitis, but not to an unselected group of cough patients (Appendix Table 1). No discrepancy existed in the selection of articles among the co-authors.

The detailed characteristics of the five included studies are summarised in Table 1. For the study of Watanabe et al.[21], we extracted the datasets of all of the patients (n = 77) and the ICS-naïve patients (n = 34) separately. Across all of the studies, the number of participants ranged from 34 to 77. The mean age ranged from 47 to 56 years, and female gender was more frequent in all of the studies (from 51% to 74%); these findings are in line with the usual demographic findings of patients visiting cough clinics.[23] None of the studies included children. Four studies were based on referral clinics[17-19, 21]; however, one prospective study recruited participants via newspaper advertisements.[20] The definition of chronic cough was > 8 weeks in most of the studies[17-20] but was > 3 weeks in one Japanese study.[21] The median duration of cough before the study ranged from 12 months to 8.5 years.

Normal chest radiographs and not currently smoking were common criteria for selection (Table 2). All of included studies examined unselected patients presenting with chronic cough. All the

participants did not receive any specific diagnosis for cough before the studies. Major trigger conditions such as eosinophilic bronchitis, upper airway cough syndrome, or gastroesophageal reflux were not excluded. Previous history of doctor-diagnosed asthma was an exclusion criterion in one study; however, the results showed that 21% of study participants still had asthma and 50% of them showed mild responsiveness to histamine.[20] History of corticosteroid exposure was checked in all studies. Two studies had subgroups of ICS-naïve patients.[17, 21] In Hsu et al., ICS was not administered until at least 1–2 weeks before FeNO measurement, according to their stepwise protocol.[19] In Koskela et al., all subjects were naïve to inhaled or systemic corticosteroid therapy (personal communication with the corresponding author).[20]

The study characteristics related to the ICS treatment protocol and outcomes are summarised in Table 3. The dose and duration of ICS treatment were pre-specified in three studies[18-20], but were not specified in two retrospective studies.[17, 21] In these latter two studies, the ICS dose/duration was about 435 μg/day fluticasone for a median period of 5–6 months[17], or the usual dose ICS for ≥ 3 months[21], respectively. The criteria for ICS treatment responsiveness was heterogeneous; one prospective trial defined responsiveness by a reduction > 50% in the mean daily cough symptom score[18], and another prospective trial determined responsiveness by a ≥ 1.3-point improvement in the Leicester Cough Questionnaire (LCQ) score (corresponding to a minimally important change).[20] Three retrospective studies defined the outcome as 'significant improvement' or 'complete control of cough (determined by physician)'.[17, 19, 21]

Quality assessment

The detailed results of the QUADAS-2 assessment are provided in Figure 2. Two prospective studies had an unclear risk of bias in one domain (reference standard).[18, 20] Three retrospective

studies were determined to be at risk of bias in several domains[17, 19, 21]; in particular, we determined that they had a risk of bias during the process of participant recruitment (Table 1) or the decision to prescribe ICS (Table 3). In the domain of participant selection, the studies without random or consecutive recruitment (or without specific criteria for ICS prescription) were classified as having an unclear risk of bias.

In the domain of reference standard (ICS responsiveness), three retrospective studies used rather arbitrary criteria (significant improvement or complete control) and were classified as having an unclear or high risk of bias[17, 19, 21]; in a retrospective study, the decision of whether to administer ICS was partly based on the FeNO level; thus, the study was classified as having a high risk of bias.[19] Two prospective studies utilised a structured questionnaire (LCQ or daily cough symptom score) but did not include a placebo in determining ICS responsiveness, and thus were classified as having an unclear risk of bias.[18, 20] None of these included studies measured objective cough frequency.

Exclusion rates among retrospective studies were higher than 20% in two studies[17, 19], which were determined to have an unclear risk of bias in the domain of flow and timing. No risks of bias, and no concerns regarding applicability, were noted in conducting and interpreting the index test (FeNO measurement) because the test utilised standardised commercial instruments.

Usefulness of FeNO for predicting ICS responsiveness

The proportion of ICS responders ranged from 44% to 59% (Table 2). A 2 × 2 table was constructed to summarise the diagnostic usefulness of FeNO tests. The sensitivity and specificity ranged from 53% to 90% and from 63% to 97%, respectively. The optimal cut-off values also varied, from 16.3 to 38 ppb. Two prospective studies had lower values in terms of Youden indices relative to three

retrospective studies (0.16[18], 0.36[20] vs. 0.59[21], 0.71[19], and 0.74[17]). The AUC ranged from 0.74 to 0.87; one prospective study did not report the AUC value but apparently had a low AUC value, close to 0.60 (based on the ROC curve figure in the original paper).[18] The SROC curve is presented in Figure 4, with additional subgroup representation by study design (prospective study vs. retrospective study). The retrospective studies had a higher diagnostic usefulness with respect to the FeNO level and a higher proportion of asthma sufferers (ranging from 19.7% to 48.4%; Table 1). There was no significant risk of publication bias (p=0.448). I^2 value was 76.4%. We decided not to perform meta-analyses because there was considerable heterogeneity among the study designs and outcome measurements.

Discussion

In the present systematic review, we did not find sufficient evidence to advocate the use of FeNO measurement for predicting ICS responsiveness among unselected chronic cough patients. First, due to considerable heterogeneities in the study protocols and outcome definitions, we could not perform pooled analyses. Second, mixed results were identified with methodological concerns; the studies with a relatively lower risk of bias and prospective design reported a lower diagnostic usefulness of the FeNO test, whereas those reporting a high diagnostic usefulness of FeNO tests had retrospective designs and included a higher proportion of asthma patients. However, none of the included studies measured placebo effects. Collectively, these results warrant further prospective placebo-controlled trials using standardised protocols and validated measurement tools.

The study of Chaudhuri et al. was the first investigation of the effects of ICS on the FeNO levels among an unselected sample of 88 patients with chronic persistent cough (consisting of 30 postnasal drip cough syndrome, 18 gastroesophageal reflux, 13 cough variant asthma, 9 bronchiectasis and 10 idiopathic cough patients).[13] In their double-blind, randomised, placebo-controlled study, treatment with inhaled fluticasone 500 mcg twice daily for 14 days resulted in a mean improvement of 22.3% in cough visual analogue scale (VAS) score. Notably, the improvement in the cough VAS score was more strongly correlated with baseline FeNO level (r^2 = 0.151, p<0.001) than with sputum eosinophil (r^2 = 0.08, p=0.019) or sputum eosinophil cationic protein level (r^2 = 0.064, p=0.05). These results led to positive speculation on the usefulness of FeNO tests in predicting ICS responsiveness.

In contrast to the previous positive expectation, however, we found that the discriminating power of the FeNO test for ICS responsiveness remains questionable. The prospective study of Prieto et al.[18], which had a relatively lower risk of bias, demonstrated that FeNO tests did not appear to have sufficient power to discriminate between ICS-responsive and -unresponsive cough (sensitivity, 53%; specificity, 63% [at a cut-off of 20 ppb]). The question arises as to whether the treatment dose or duration was insufficient (fluticasone propionate 100 mcg twice daily for 4 weeks); however, the response to ICS therapy in eosinophilic bronchitis is known to be very rapid; i.e. within 1 or 2 weeks of treatment initiation.[5, 6] Moreover, the positive response rate (defined as a reduction of > 50% in the mean daily cough symptom score) was 44%, which was comparable to other studies.[17-19, 21] Another prospective study with a relatively lower risk of bias, by Koskela et al.[20], also reported fair but less than expected diagnostic usefulness of the FeNO test (AUC, 0.74; sensitivity, 47%; specificity, 89% [at a cut-off of 16.3 ppb]). The positive response rate to budesonide 400 mcg, twice daily for 12 weeks, was as high as 77% (defined as an improvement in the LCQ score > 1.3 [minimally important change]).

The results from two prospective studies might collectively suggest that FeNO tests do not sufficiently differentiate ICS-responsive from ICS-unresponsive cough in unselected patients with chronic cough. However, neither study tested for placebo effects,[18, 20] and the possibility of spontaneous cough remission could not be fully excluded. Spontaneous recovery might be a reason for high ICS responder rates (44–77%) observed in two prospective studies with low baseline FeNO levels.[18, 20] Placebo-controlled studies demonstrated that FeNO is a very good predictor of ICS treatment responses in patients with asthma or undiagnosed respiratory symptoms.[24, 25] Therefore, placebo-controlled trials are required to confirm the diagnostic utility of FeNO for predicting ICS responsiveness in patients with chronic cough.

Due to the relatively higher risk of bias, the results from the three included retrospective studies may need to be carefully interpreted (AUC 0.85-0.87).[17, 19, 21] Above all, the criterion to initiate ICS treatment and determine the treatment responsiveness was not prospectively specified by the studies, but was instead determined subjectively; furthermore, it was not clearly stated whether the study participant selection criteria were pre-specified.

Another consideration is that these three retrospective studies included higher proportions of patients with asthma or bronchial hyperresponsiveness (BHR) (48.4%, 21.1% and 35.3%, respectively[17, 19, 21]) than did the two prospective studies (9% and 21%, respectively).[18, 20] When eosinophilic bronchitis was included, the prevalence of asthma syndrome (asthma or non-asthmatic eosinophilic bronchitis), which is considered to be ICS-responsive cough[2], increased to 53.1–56.6% in these retrospective studies.[17, 19] Within the subgroup of cough-variant asthma or eosinophilic bronchitis, the changes in FeNO levels were reported to correlate well with the improvement in cough symptom scores after ICS treatment (n = 48; $r = 0.48$, $p = 0.004$).[22] In a placebo-controlled study involving 52 patients with undiagnosed respiratory symptoms, ICS treatment effects were clearly shown in a subgroup with high FeNO levels (> 47 ppb) but not in subgroups with lower FeNO levels (<15 or 15–47 ppb).[24] Collectively, these findings could indicate improved predictive usefulness of FeNO tests in clinical settings characterised by a high proportion of asthma syndrome sufferers, or high baseline FeNO levels among chronic cough patients, such as primary or early referral clinics, or in Asian regions.[26, 27] The comparison of the five studies included in our systematic review also suggested such potential (Figure 4). This speculation warrants a prospective investigation under these particular conditions, which could achieve a high diagnostic yield.

The utility of FeNO for differentiating ICS responsiveness in non-asthmatic and non-eosinophilic cough patients remains to be clarified; such trials have not been published to our knowledge. Non-asthmatic and non-eosinophilic patients are less likely to have Th2 inflammation and FeNO elevation.[28] Prieto et al.[18] and Koskela et al.[20], in which study participants had near-normal FeNO levels, suggested poor predictive value of FeNO in clinical settings with low FeNO. However, as discussed earlier, placebo-controlled trials are necessary to confirm the diagnostic utility.

Reports of diagnostic test accuracy are often based on routinely collected clinical data rather than prospectively registered trials,[29] and studies with a retrospective design are not excluded in systematic reviews of diagnostic utility of nitric oxide in different diseases.[7, 30] However, considering the significance of placebo effects in the therapeutic evaluation of cough patients,[31] further investigations on this topic should have a randomised, placebo-controlled design. In addition, a cross-over design should be avoided due to possible carry-over effects of ICS treatment.[32] Participants need to be consecutively or randomly recruited, as a case-control comparison study could overestimate diagnostic usefulness.[29] Several parameters also need to be assessed at baseline, such as atopy, smoking, BHR, sputum eosinophil counts, and previous history of corticosteroid treatment, as they could influence FeNO levels[8] and thus enable subgroup analyses.

There is still no consensus on the dosage and duration of ICS for this research topic. The Cochrane review suggested that high-dose ICS for 2 weeks is an appropriate option[32], but longer treatment duration could be helpful in patients with longstanding cough. It would be ideal if a consensus on the research protocol is made to guide further clinical trials on treatment responsiveness of cough in patients with chronic cough, or other respiratory conditions. Finally, as the outcomes for cough

326 responsiveness, the use of validated questionnaires such as the LCQ[33] and Cough Quality of Life
327 Questionnaire[34] are recommended.[35] Combination with objective cough frequency measurement
328 is also recommended, as it has the potential to reflect different aspects of cough.[35, 36]
329 Standardisation would help to collect clinical evidence and draw specific recommendations on the
330 use of FeNO as guidance for ICS therapy in further clinical guidelines.

331 Choice of empirical treatment in cough patients without initial indicators for specific cough may
332 differ by population or clinical settings. First-generation anti-histamine/decongestant or ICS
333 therapy has been recommended in current guidelines by the American College of Chest
334 Physicians[37], or the European Respiratory Society[38] respectively. Thus, the ideal position of FeNO
335 measurement, as a guidance for ICS therapy, in the clinical pathway of chronic cough is still not
336 determined. Considering that the benefits of ICS therapy and FeNO test may depend on the patient
337 characteristics or clinical settings, further clinical trials evaluating FeNO need to be tailored for
338 expected target population.

339 In conclusion, we did not find strong evidence to support the use of FeNO tests to predict ICS
340 responsiveness in unselected patients with chronic cough. Only a few studies were identified, but
341 they had mixed results with methodological heterogeneities and concerns. Future studies should
342 have a randomised, placebo-controlled design and use validated measurement tools for cough.

343

Table 1. Baseline characteristics of five original papers that reported the usefulness of fractional exhaled nitric oxide tests for predicting inhaled corticosteroid treatment response among patients with chronic cough

Study[ref]	Design	n	Age (yr)	Female (%)	Location	Definition of chronic cough	Recruitment	FeNO measurement	Median cough duration	Cough variant asthma (%)*
Hahn 2007[17]	Retrospective	64	47	59.4%	USA	Cough ≥8 weeks	Selected from clinical database of 114 patients referred to specialist clinics for evaluation of chronic cough	Sievers Model 280i (Sievers, Boulder, CO, USA)	41 months	48.4%[a]
Prieto 2009[18]	Prospective, open-label	43	48	58.1%	Spain	Cough ≥8 weeks	Consecutively recruited from patients referred to specialist clinics	NIOX (Aerocrine; Solna, Sweden)	ND	9%[a]
Hsu 2013[19]	Retrospective	81	49	59.3%	Taiwan	Cough ≥8 weeks	Selected from medical record of	Sievers Model 280i (Sievers,	12 months	21.1%[a]

							114 patients who visited specialist clinics	Boulder, CO, USA)		
Koskela 2013[20]	Prospective, open-label	43	55.6	74%	Finland	Cough ≥8 weeks	Consecutively recruited via newspaper advertisement	Sievers Model 280 (Sievers, Boulder, CO, USA)	8.5 years	21%[b]
Watanabe 2014[21]	Retrospective	77	50.5	59.5%	Japan	Cough ≥3 weeks	Selected from clinical records of 86 adult patients referred to a university hospital for persistent cough	NIOX MINO (Aerocrine; Solna, Sweden)	16.8 months	50.6%[c]
Watanabe 2014 (steroid naïve	Retrospective	34	44.6	51.4%	Japan	Cough ≥3 weeks	Selected from clinical records of 86 adult patients referred to a	NIOX MINO (Aerocrine; Solna, Sweden)	13.7 months	35.3%[c]

sample)[21]							university hospital for persistent cough			

Abbreviations: FeNO, fractional exhaled nitric oxide; ND, not described

*Asthma was defined by (a) methacholine challenge tests, (b) questionnaire, or (c) clinical diagnosis by specialist.

Table 2. Summary of the selection criteria for participants in included studies

Study[ref]	Age	Chest X-ray	Lung function	Smoking history	Medication history	History of other lung diseases	History of respiratory tract infection	Other
Hahn 2007[17]	≥18 years	Normal	ND	No current smoker	No current ACE inhibitor use	ND	ND	
Prieto 2009[18]	18-70 years	Normal	FEV1≥80% predicted	Non-smoker	No current ACE inhibitor or β-blockers use No previous history of corticosteroid use	No other lung diseases on the basis of history, clinical examination, and computed tomography scan if necessary	No RTI within 4 weeks	
Hsu 2013[19]	ND	Normal	ND	No current smoker No previous smoking history >10 pack-year	ND	ND	ND	
Koskela 2013[20]	ND	Normal	ND	No current smoker	ND	No previous history of doctor diagnosed asthma	No febrile RTI within 6 weeks	
Watanabe 2014[21]	≥15 years	Normal	ND	No current smoker (subgroup)	Inhaled corticosteroid naïve (subgroup)	ND	ND	Normal pulmonary auscultation

Abbreviations: FEV1, forced expiratory volume in 1 second; RTI, respiratory tract infection; ND, not described.

Table 3. Characteristics related to inhaled corticosteroid treatment responsiveness

Study[ref]	Criteria for prescribing ICS	ICS dose and duration	Definition of ICS responsiveness	ICS responder (%)	Baseline FeNO levels among responder (ppb)	Baseline FeNO levels among non-responder (ppb)
Hahn 2007[17]	Clinical judgement (specific criteria was not described)	Mean FP 419-445 mcg/day for median 5-6 months	All of the following criteria: (1) physician-documented significant improvement in cough, (2) no further diagnostic studies ordered for assessment of cough, and (3) no alteration in ICS dose	59%	Mean 51.25 ± SD 20.1 ppb	Mean 26.0 ± SD 16.5 ppb
Prieto 2009[18]	Prescribed to all participants by study	FP 100 mcg bid for 4 weeks	Reduction of >50% in mean daily cough	44%	Geometric mean 23.2 (95% CI 17.5-30.7)	Geometric mean 18.6 (95% CI 14.7-24.0)

	protocol		symptom score			
Hsu 2013[19]	Clinical judgement (prescribed when cough persisted after initial symptomatic treatment and if FeNO level was ≥30 ppb, if there was borderline to positive BHR, or if baseline FEV1%/FVC<70%)	FP 250 mcg bid for > 2 weeks	Complete control of cough (determined by physician)	50%	NA	NA
Koskela 2013[20]	Prescribed to all participants by study protocol	Budesonide 400 mcg bid for 12 weeks	Improvement in Leicester Cough Questionnaire score ≥ 1.3 points (minimal important change)	77%	Mean 19.7 (median 15.7, IQR 9.2-22.1)	Mean 9.8 (median 9.6, IQR 5.5-13.2)
Watanabe 2014[21]	Clinical judgement (decided	Practical dose of ICS for ≥ 3 months	Significant improvement in	54.5%	Mean 54.5 ± SE 7.1 ppb	Mean 21.1 ± SE 1.6 ppb

	comprehensively with history or data of patients by physicians)		cough with ICS for more than 3 months (declared by the patients and confirmed by physician)			
Watanabe 2014[21] (steroid naïve sample)	Clinical judgement (decided comprehensively with history or data of patients by physicians)	Practical dose of ICS for ≥ 3 months	Significant improvement in cough with ICS for more than 3 months (declared by the patients and confirmed by physician)	41%	Mean 60.6 ± SE 14.1 ppb	Mean 22.2 ± SE 2.3 ppb

Abbreviations: ICS, inhaled corticosteroid; FeNO, fractional exhaled nitric oxide; FP, fluticasone propionate; SD, standard deviation; 95% CI, 95% confidence interval; BHR, bronchial airway hyper-responsiveness; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; SE, standard error

Figure 1. PRISMA for study selection

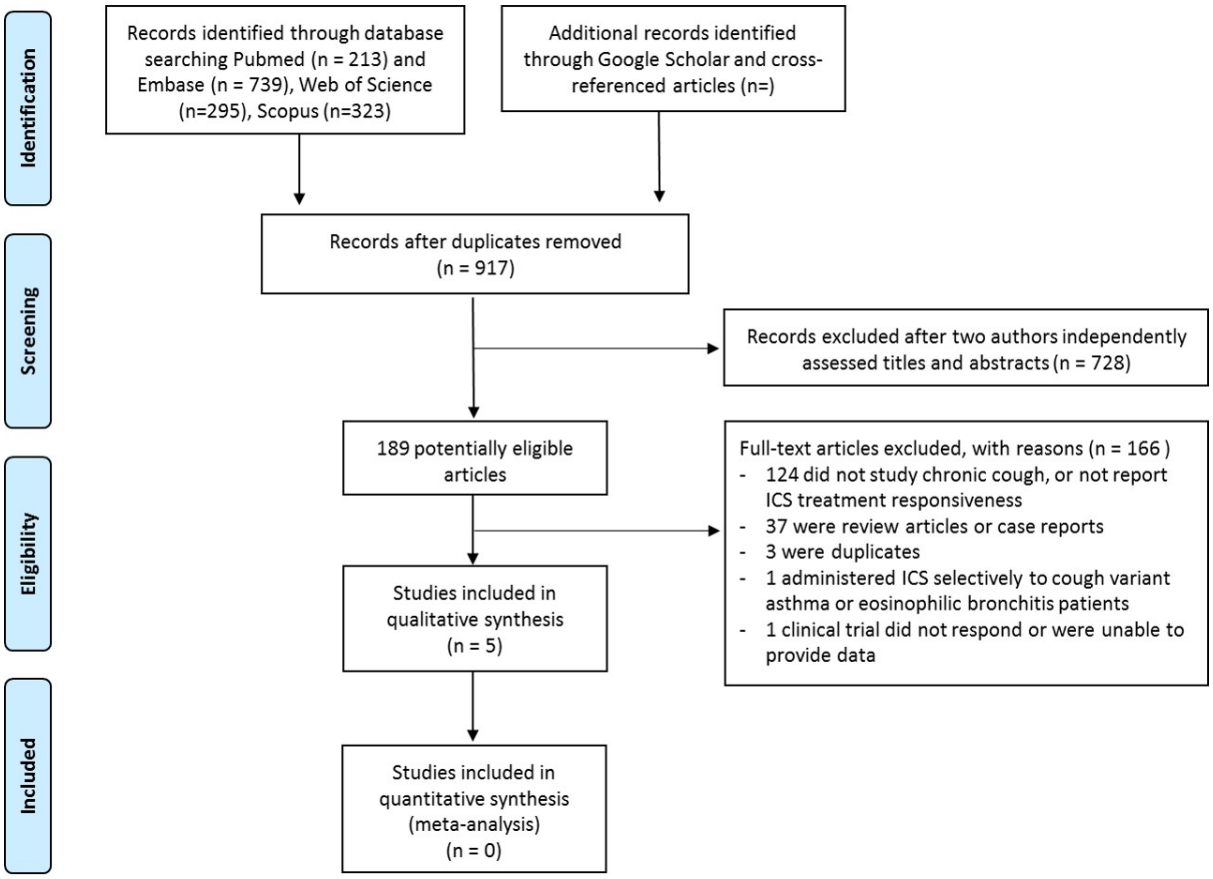
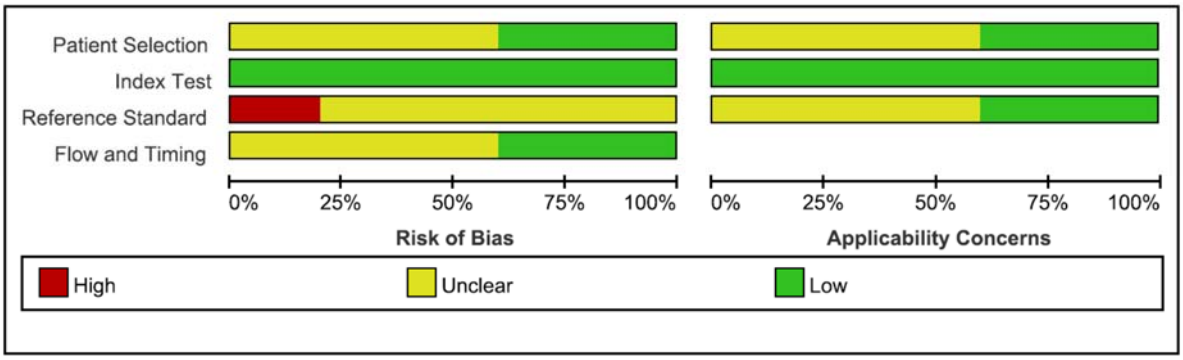


Figure 2. QUADAS-2 quality assessment of the included studies. (A) Graph showing the risk of bias and concerns regarding applicability: review of authors' judgements in each domain, presented as percentages across the included studies. (B) Risk of bias and concerns regarding applicability summary: review of authors' judgements in each domain for all included studies.



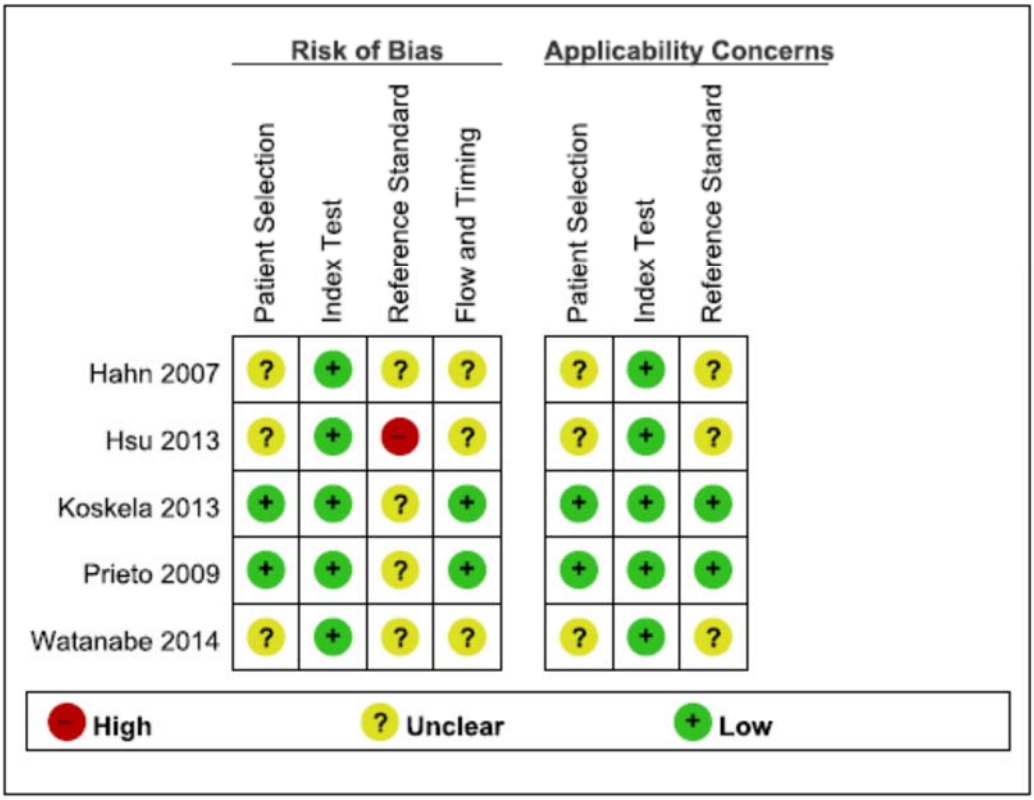


Figure 3. Forest plot summarising the findings of each study regarding the usefulness of fractional exhaled nitric oxide (FeNO) tests for predicting inhaled corticosteroid (ICS) response in chronic cough patients. The study of Watanabe 2014 indicates the results from steroid-naïve samples.

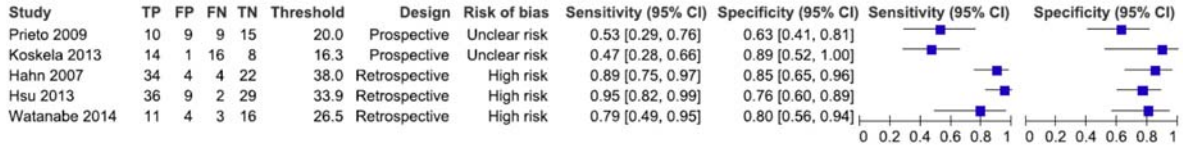
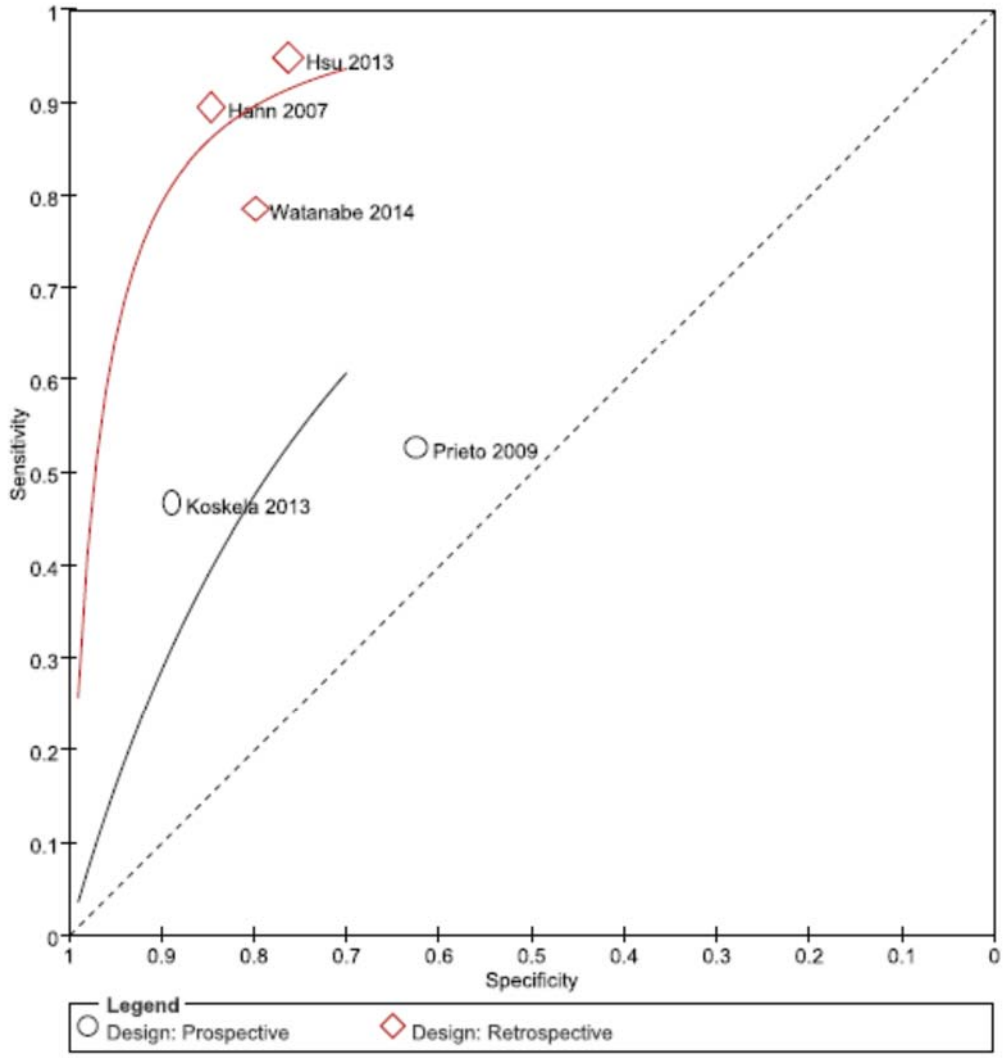


Figure 4. Summary receiver operating characteristics curve for FeNO tests with respect to prediction of ICS responsiveness among patients with chronic cough, subgrouped by study design. The study of Watanabe 2014 indicates the results from steroid-naïve samples.



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