Predictive value of exhaled nitric oxide in the management of asthma: a systematic review

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ABSTRACT   The clinical value of measuring fractional exhaled nitric oxide (F_{e}NO) in asthma is not clear. We aimed to assess whether F_{e}NO can reliably predict clinical outcomes in asthma treated with inhaled corticosteroids (ICS). We also evaluated whether its predictive role is influenced by different inflammatory phenotypes of asthma.

We conducted a systematic review focusing on five clinically relevant questions. Two authors independently screened search results, extracted data and assessed quality of the included studies. Data were synthesised by qualitative methods.

12 prospective studies were included, answering partly three of the five questions. In steroid-naïve asthma, a high F_{e}NO level probably predicts good response to ICS. In ICS-treated asthmatics, a low F_{e}NO level probably predicts low risk of exacerbation, and the patient is unlikely to benefit from increasing ICS dose. There were scarce data to conclude whether F_{e}NO predicts exacerbations when ICS treatment is stopped in well-controlled asthma. Only one study reported results separately in different asthma phenotypes.

The current evidence on the predictive value of F_{e}NO and its role in the management of asthma is incomplete. Future studies should focus on clinically meaningful questions and probably target only eosinophilic phenotypes where F_{e}NO is best associated with the activity of airway inflammation.

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Introduction

Asthma is characterised by chronic inflammation of the airways, bronchial hyperresponsiveness and recurrent symptoms. The degree and type of airway inflammation vary between individuals and multiple asthma phenotypes have been identified [1]. Eosinophilic inflammation is particularly pronounced in atopic asthma, but can be present in nonatopic phenotypes as well. Adult-onset asthma is sometimes characterised by neutrophilic inflammation or by almost nonexistent granulocyte activity [2]. Although inflammation is important in asthma, the diagnosis and follow-up of asthma are mainly based on symptoms and measures of lung function.

Measurement of exhaled nitric oxide

Airway inflammation is related to asthma symptoms and exacerbations [3, 4], but it is difficult to measure directly the level and nature of inflammation in clinical practice. Fractional exhaled nitric oxide (F_{eNO}) is particularly associated with eosinophilic airway inflammation [5–9]. Nitric oxide (NO) is an important cellular signalling molecule that regulates pulmonary blood flow, mucus production, ciliary activity and inflammation. Under normal circumstances NO is produced at very low concentrations by constitutive NO synthases (endothelial NOS and neuronal NOS). In cases of airway inflammation pro-inflammatory cytokines upregulate inducible NOS, producing higher levels of NO [10].

Using online methods, it is practically possible to measure F_{eNO} in children aged ⩾5 years. In children, NO values are directly correlated with height, hence height-adjusted reference values are needed [11]. It is not known whether height significantly affects NO values in adults [12]. Active smoking reduces F_{eNO} and corrupts the results. Atopic individuals have significantly elevated F_{eNO} irrespective of asthma, both in children and adults [10], probably reflecting lower airway inflammation in the absence of airway hyperresponsiveness and clinical asthma. Other factors that influence F_{eNO} values are respiratory infections, high dietary nitrate concentration, bronchial obstruction and, possibly, physical exercise [13].

There are international guidelines for F_{eNO} measurement and interpretation [12, 13]. As F_{eNO} values vary with exhalation flow rate, it is generally recommended to measure F_{eNO} during an exhalation of ⩾6 s using 50 mL·s^{-1} flow rates and 5–20 cmH$_2$O of back pressure. F_{eNO} levels <25 ppb in adults and <20 ppb in children are considered to be low, whereas with F_{eNO} >50 ppb in adults and >35 ppb in children the likelihood of eosinophilic inflammation is increased [12]. The same equipment and measurement procedures should be used for subsequent recordings and follow-up [13].

What is the added value of F_{eNO} measurement in asthma treatment?

Asthma is a complex disease of the airways causing variable airflow obstruction and is associated with different types and intensities of airway inflammation [1]. Since there are no unequivocal and easily accessible methods for quantifying the inflammation *per se*, asthma diagnosis is mainly based on lung function measurements and identification of variable or reversible bronchoconstriction. F_{eNO} measurement cannot supplant lung function tests, but as a marker of inflammation it might provide additional information for asthma diagnosis and estimating disease phenotype and activity. Since the basis of asthma therapy is to alleviate airway inflammation, F_{eNO} could also predict or assess responsiveness to anti-inflammatory therapy.

Study questions

Previous reviews focusing on using F_{eNO} in the diagnosis of asthma or in adjusting individual corticosteroid treatment have been published [14, 15]. The aim of this review was to assess the predictive value of F_{eNO} measurements in asthma treated with inhaled corticosteroids (ICS). Concurrent use of other medication was allowed, but its effect was not evaluated.

We addressed five clinically relevant questions concerning the predictive utilisation of F_{eNO} measurement:

1) Since glucocorticoids reduce eosinophilic inflammation more effectively than other types of inflammation [2], could high F_{eNO} predict a favourable response to ICS treatment in steroid-naïve asthmatics?
2) During maintenance treatment, ICS dose should be kept as low as possible [1]. Could elevated F_{eNO} identify those patients who are at risk of exacerbation?
3) During regular stable ICS treatment, could elevated F_{eNO} identify those patients who would benefit from augmented glucocorticoid treatment?
4) If the patient is asymptomatic for a prolonged period of time with normal lung function, it is recommended to step-down controller treatment [1]? Does a low level of F_{eNO} predict that ICS therapy could be successfully discontinued?
5) After cessation of ICS therapy, does an elevated F_{eNO} predict the reactivation of the disease and hence the need for anti-inflammatory therapy?

As the predictive ability of F_{e}NO may depend on the inflammatory phenotype of asthma, in each of the study questions we addressed whether the inflammatory phenotype was defined and if the prognostic value of F_{e}NO was assessed separately in different inflammatory phenotypes.

Methods

Criteria for including studies

Types of studies and participants

We included only prospective studies where the subjects were aged ⩾5 years (for reliable online F_{e}NO measurement) and asthma was diagnosed based on reversible or variable airway obstruction [1]. The criteria for anti-inflammatory medication depended on the study question. Question 1: subjects had to be steroid-naïve; question 2: subjects had to be on regular stable ICS and additional oral glucocorticoids were allowed; question 3: subjects had to be on regular stable glucocorticoid treatment at baseline; and questions 4 and 5: at baseline subjects had to have good asthma control on low-dose ICS for ⩾3 months.

Comparison of intervention and prognostic factors

We included studies where high F_{e}NO was compared to low F_{e}NO; F_{e}NO had to be measured using an online technique and measured at a healthcare unit excluding serial home measurements. Cut-off values for high and low F_{e}NO were taken from each original study instead of setting predetermined values.

Types of outcome measures

The prognostic accuracy of F_{e}NO to the following clinical outcomes had to be reported. 1) asthmatic symptoms, lung function or exacerbations of asthma (questions 1, 3, 4 and 5); and 2) exacerbations of asthma (question 2).

Search strategy

We searched the following six electronic databases up to September 24, 2015 to track down systematic reviews and individual trials: Medline (OVID), US National Library of Medicine PubMed, the Cochrane Database of Systematic Reviews and the Centre for Reviews and Dissemination (Health Technology Assessment Database, the NHS Economic Evaluation Database and the Database of Abstracts of Reviews of Effects). Search strategies are presented in online supplementary appendix 1. In addition to searching the electronic databases, we screened the reference lists from the already identified studies and review articles for any additional relevant studies.

There were no language restrictions. If the information in the report was insufficient to make the final assessment of inclusion or exclusion, we contacted the authors of the studies to obtain additional information.

Data extraction and quality assessment

At least two authors independently screened search results, extracted data and assessed risk of bias of the included studies. The following information was extracted from the included studies: study design, follow-up time, numbers of patients at baseline and analysed, age, sex, allergy, if asthma inflammatory phenotype was assessed, severity of asthma, forced expiratory volume in 1 s (FEV_1) at baseline, exhalation flow rate ($mL·s^{-1}$) used in F_{e}NO measurement, F_{e}NO level at baseline and funding.

Assessments of the risk of bias in the studies were made by using the quality in prognostic studies (QUIPS) assessment tool [16]. We assessed the following six methodological domains: representativeness of study population; adequateness of follow-up period and attrition; appropriateness of prognostic factor (F_{e}NO) measurement; appropriateness of outcome measurement; adequateness of statistical analysis (including confounding factors) and reporting; and conflict of interests (detailed criteria for judgements are presented in online supplementary appendix 2). If the information in the report was insufficient to extract detailed data, we contacted the authors of studies to obtain additional information.

To draw conclusions about the overall risk of bias within a study, we decided to classify the studies into three categories: studies with low, unclear or high risk of bias. If all the domains within a study were graded as having low risk of bias, the overall judgement was low risk of bias, and if even one of the domains was assessed as having high risk of bias, the overall risk of bias for a study was graded as high risk of bias.

Data synthesis

The combined qualitative result for each research question is based on the similarity of the results of the individual studies and their overall assessments of risk of bias. Quantitative analyses were not made due to heterogeneity across the included studies at each research question regarding *e.g.* outcome measures.

Results

Search results

In total 1846 records were identified from the electronic searches after removing duplicates. We discarded 1744 records as irrelevant to this review on the basis of abstract or title. We obtained the remaining 102 reports in full-text and among those we found 12 eligible prognostic accuracy studies (13 reports). No additional studies were identified by screening reference lists from the already identified studies and review articles. The processing of search results is presented as a flow chart in figure 1 according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement [17]. The exclusion of the 89 full-text reports was decided in two stages: at the first stage, 81 reports were excluded mainly because studies considered only asthma diagnostics, or the design or research question of studies clearly did not fulfill the inclusion criteria of this review; at the final stage, eight further studies were excluded. Detailed reasons for their exclusion are presented in online supplementary appendix 3.

Characteristics of included studies

Detailed characteristics of the 12 included studies are provided in online supplementary appendix 4. All study designs were prospective cohort studies related to $F_{e}NO$ measurement. The number of participants included in the analyses of prognostic accuracy varied from 21 to 169 in adults (nine studies in adults), and from 28 to 111 in children (three studies in children). The mean or median age ranged from 30 years to 56 years in adults, and was on average 11 years in children. Studies in adults included participants with asthma of varying severity from mild to severe, but not all the studies reported the severity of asthma. Most of the studies measured $F_{e}NO$ using the recommended flow rate of 50 mL·s^{-1}, but one study used a higher flow rate of 100 mL·s^{-1} and two did not report the flow rate used. There was marked variation in baseline $F_{e}NO$ between the studies, reflecting differences in factors affecting $F_{e}NO$ such as age, use of anti-inflammatory medication and possibly differences in phenotypes of asthma. Seven out of the 12
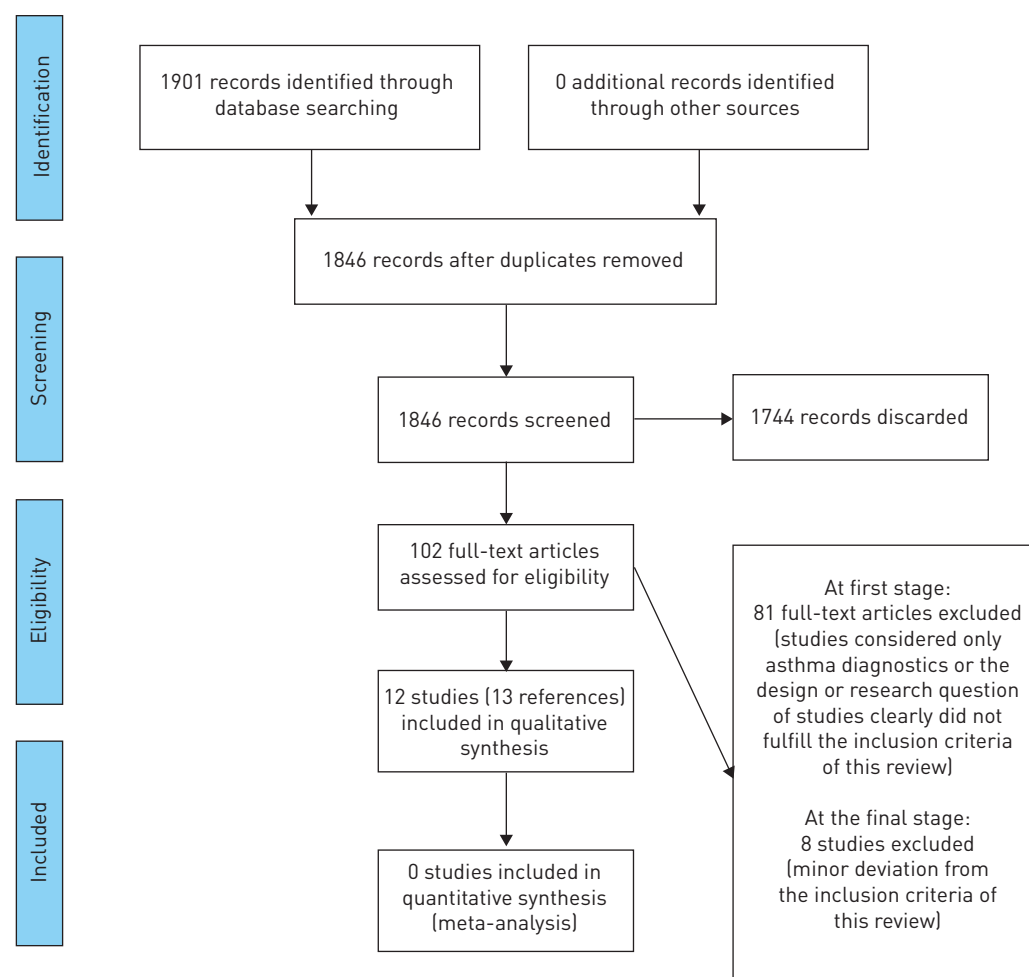

FIGURE 1 Flow chart of search results.

studies were supported by national or academic sources without or with equipment support by a manufacturer, and one study was supported by a manufacturer which did not participate in the data collection, analysis or writing of the manuscript. The other four studies did not provide information on funding or support.

10 (83%) out of the 12 studies showed unclear or high risk of bias in at least one domain, often because of a high drop-out rate or incomplete blinding of the outcome measurement or a follow-up time too short for an outcome. Thus, only two studies were assessed as having low overall risk of bias [18, 19]. Detailed results of the risk of bias assessments are provided in online supplementary appendix 5.

Predictive accuracy

Does increased F_{eNO} predict a favourable response to ICS in steroid-naïve asthmatics?

In steroid-naïve patients with asthma, increased F_{eNO} probably predicts favourable response to ICS (two studies in adults and one in children; one with low risk and two with high risk of bias; the results are similar between the studies).

In a 24-week study (n=21) by SzEFLER et al. [20] in 2002, the baseline F_{eNO} was significantly higher in those adult asthmatics in whom treatment with ICS increased FEV1 ⩾15% compared to those in whom FEV1 increased <5% (median (interquartile range (IQR)) 17.6 ppb (16.1–23.0 ppb) versus 11.1 ppb (7.9–14.2 ppb); exhalation flow rate not reported). In another study in adult asthmatics (n=88), CowAN et al. [18] reported that high baseline F_{eNO} (>33 ppb, flow rate 50 mL·s^{-1}) predicted better symptom alleviation during ICS treatment of ⩾4 weeks in eosinophilic asthma and decrease of bronchial hyperresponsiveness in both eosinophilic and noneosinophilic asthma. A further subanalysis of the same study focusing on different inflammatory markers confirmed the results on the predictive ability of F_{eNO} [21].

In another study by SzEFLER et al. [22] in 2005, 40% of asthmatic children (n=111, mean age 11 years), responded to ICS treatment lasting 8 weeks, response defined as improvement in FEV1 of ⩾7.5%. Univariable analysis with dichotomised predictors revealed that one of the significant predictors of a response to ICS treatment included baseline F_{eNO} >25 ppb (flow rate 50 mL·s^{-1}) (OR 2.8, p<0.05).

Does increased F_{eNO} predict risk of exacerbation in asthmatic patients on regular stable ICS treatment?

Based on three studies in adults (one with high risk of bias and the other two with unclear risk) there is indication that low F_{eNO} in an asthmatic subject on regular ICS treatment predicts a low risk of exacerbation, while high F_{eNO} predicts a high risk of exacerbation.

GELB et al. [23] studied whether high F_{eNO} predicted exacerbations during the forthcoming 18 months in stable nonsmoking adult asthmatic patients (n=44) on regular ICS plus long-acting β-agonist treatment. Half the patients (22 out of 44) had at least one exacerbation during follow-up, and 59% of these (13 out of 22) had baseline F_{eNO} ⩾28 ppb. In subjects with baseline F_{eNO} >28 ppb (flow rate 100 mL·s^{-1}), 77% had an exacerbation (positive predictive value (PPV) 77%), while in subjects with F_{eNO} <28 ppb, 87% did not have an exacerbation (negative predictive value (NPV) 87%).

OziER et al. [24] studied whether F_{eNO} can be used to predict maintenance of good asthma control during a 3-week follow-up in 55 adults with well-controlled asthma (41 on ICS, 14 without ICS). A low baseline F_{eNO} <31 ppb (flow rate 50 mL·s^{-1}) was a good predictor of not losing good asthma control (NPV 95.3%), but high F_{eNO} >31 ppb was only a modest predictor of loss of asthma control (PPV 66.7%).

KupczyK et al. [25] followed 169 adult asthmatics on regular ICS (76 mild-to-moderate asthmatics on a low-to-medium dose of ICS and 93 severe asthmatics on high doses of ICS with or without oral glucocorticoids) for 1 year. 104 exacerbations were recorded in severe asthmatics and 18 in mild-to-moderate asthmatics. Baseline F_{eNO} >45 ppb was associated with an increased risk of having at least two exacerbations in the whole group (OR (95% CI) 4.32 (1.02–18.31), p=0.047; adjusted for age, sex, smoking, asthma severity and atopy) and in the severe asthma group (OR (95% CI) 5.98 (1.28–27.99), p=0.023; adjusted for age, sex, smoking and atopy).

Does increased F_{eNO} in asthmatic patients on regular stable ICS treatment predict further benefit from augmenting the glucocorticoid treatment?

We found four studies addressing this question. Two of these studies [19, 26] reported that increased F_{eNO} in asthmatic subjects on regular ICS predicts further benefit from enhancing the glucocorticoid treatment, but this was not supported by the other two studies [27, 28]. However, all four studies reported that low F_{eNO} in asthmatics on regular ICS implies that enhancing the glucocorticoid dose would not result in improvement of asthma (one study with high risk of bias, one with low risk and two with unclear risk of bias).

Pérez-de-Llano et al. [26] found that among 102 asthmatics with poor control of their disease, baseline F_{eNO} >30 ppb (flow rate 50 mL·s^{-1}) predicted that the patient gained from enhancing glucocorticoid treatment by increasing the dose of ICS and, if further needed, by adding oral glucocorticoids (PPV 87.5%), while F_{eNO} <30 ppb predicted no improvement (NPV 90.6%).

Little et al. [19] started oral prednisolone (20 mg per day) on 37 asthmatics (36 already on ICS) for 2 weeks. Baseline F_{eNO} >10 ppb (flow rate not reported) predicted that the subject would gain an increase >15% in FEV1 (PPV 83%), while F_{eNO} <10 ppb probably excluded such an increase (NPV 72%).

In 2013 Kupczyk et al. [27] provided results for this study question based on the same study population as in their study described earlier [25], but drop-outs were excluded from the analyses in this report. This report included subjects with severe (n=84) and mild-to-moderate (n=62) asthma who were treated for 2 weeks with oral prednisolone in addition to their regular treatment. In subjects with severe asthma, baseline F_{eNO} <45 ppb (flow rate 50 mL·s^{-1}) excluded a favourable response (defined as improvement of ⩾12% in FEV1; NPV 92.0%), but high F_{eNO} >45 ppb was not a reliable predictor of favourable response (PPV 31.2%). In mild-to-moderate asthma, baseline F_{eNO} was not a significant predictor of response in FEV1.

Michils et al. [28] studied 82 asthmatics with poor asthma control on regular ICS treatment of ⩾500 μg of beclometasone (25 also used leukotriene receptor antagonists (LTRAs) and six were on oral prednisolone). Baseline F_{eNO} <35 ppb (flow rate 50 mL·s^{-1}) probably excluded the symptomatic benefit (NPV 88%) of increasing the ICS dose (13 subjects were started on LTRA simultaneously and one with oral prednisolone), but F_{eNO} >35 ppb was not a reliable predictor of favourable response (PPV 42%).

If an asthmatic patient on low-dose ICS has good asthma control for ⩾3 months, does low baseline F_{eNO} predict successful withdrawal of ICS without asthma relapse?

There are insufficient data to conclude whether or not low F_{eNO} predicts that the patient could be weaned off ICS without risk of activation of asthma (one small study in children with unclear risk of bias).

Pijnenburg et al. [29] followed 37 asthmatic children (mean (range) age 12 (7–17) years) without asthmatic symptoms during the prior 6 months while on regular ICS treatment (100–400 μg budesonide or equivalent per day). F_{eNO} was measured at baseline and at control visits 2, 4, 12 and 24 weeks after discontinuing the treatment. Nine children had a relapse (median (range) 36 (14–141) days after discontinuation). There was no significant difference in baseline F_{eNO} between those who relapsed and those who did not (geometric mean 14.8 ppb versus 10.5 ppb; ratio (95% CI) 1.4 (0.7–2.8), p=0.32). The mean age and height of the children with and without relapse were similar.

If an asthmatic patient on low-dose ICS has good asthma control for ⩾3 months and the ICS is withdrawn, does increased F_{eNO} level during the follow-up predict asthma relapse?

There are insufficient data to conclude whether or not increased F_{eNO} level after discontinuing ICS treatment predicts asthma relapse (two small studies in children with conflicting results; both with unclear risk of bias).

In the study by Pijnenburg et al. [29] described earlier, F_{eNO} levels measured 2 and 4 weeks after discontinuing ICS were higher in those children who relapsed than in those who did not (geometric mean F_{eNO} at 2 weeks 35.3 ppb (n=8) versus 15.7 ppb; ratio (95% CI) 2.3 (1.2–4.1), p=0.01; at 4 weeks 40.8 ppb (n=7) versus 15.9 ppb, ratio (95% CI) 2.6 (1.3–5.1), p=0.009). However, even among children with increasing F_{eNO}, the majority of children did not relapse in 24 weeks of follow-up.

Ferrer et al. [30] recruited asthmatic children (mean (range) age 11 (6–14) years) in whom regular asthma treatment had been stopped 1–12 months previously and who had good asthma control (their previous asthma medication is not reported). F_{eNO} was measured and the children were divided into two groups having F_{eNO} either above or below 49 ppb. After 6 months follow-up, five out of 15 children with baseline F_{eNO} <49 ppb had relapsed, while only one out of 13 children with baseline F_{eNO} >49 ppb relapsed. The difference in risk of relapse between the groups was not statistically significant (risk ratio (95% CI) 0.2 (0.03–1.72)). The cut-off value was based on the median F_{eNO} value in this study and on the results reported by Pijnenburg et al. [29]. Due to the relatively small sample size, this cut-off value cannot be considered very reliable. However, the predictive value of F_{eNO} in the present study would have been roughly the same even with different cut-off levels, as the F_{eNO} values in children with a relapse were widely scattered (13, 14, 25, 33, 34 and 60 ppb).

The predictive ability of F_{eNO} in different inflammatory phenotypes

Out of the 12 studies included, six reported some measures of inflammatory activity and type (e.g. sputum or blood eosinophils) and three of these studies categorised subjects into eosinophilic or noneosinophilic phenotypes (online supplementary appendix 4). However, only one study (Cowan et al. [18]) assessed the

predictive value of FeNO separately in different inflammatory phenotypes (discussed earlier). The rest of the studies did not take inflammatory phenotype into account in the analysis.

Discussion

There is increasing interest in noninvasive measures of inflammation to guide asthma management. Prognostic studies analysed in this review measure the accuracy of FeNO to predict clinical outcomes and not the benefit in patient management directly. Based on these data, it seems that in steroid-naïve patients, high FeNO levels predict good response to ICS treatment. A low level of FeNO in adult patients on regular ICS therapy is associated with reduced likelihood of exacerbation, and these patients are less likely to benefit from increased doses of ICS, regardless of possible symptoms. Currently, there are not enough data to conclude whether or not FeNO can predict the risk of exacerbation after ICS reduction or cessation in well-controlled asthma.

The number of included studies in each research question in this review was small and, hence, it is difficult to draw firm conclusions. Furthermore, although we included only prospective designs, the information was mainly of poor quality with studies having small samples and unclear or high overall risk of bias. In addition, the studies comprised different designs, medication protocols, FeNO cut-off values, visit intervals, lengths of follow-up, definitions of asthma exacerbation and inclusion criteria of patients. Furthermore, it has been shown that in children FeNO values are related to age and height and increase linearly between 6 and 14 years of age in females and between 6 and 16 years of age in males [11, 31]. This is an important factor that may have influenced the ability of FeNO to predict outcomes in children, as the studies in this review included children of quite wide age ranges.

When first reports of increased FeNO in subjects with asthma were published more than 20 years ago [32, 33], our understanding of asthma was not as broad as it is nowadays. Asthma was mainly divided into intrinsic and extrinsic types and both were largely considered as eosinophilic [34]. It is well established that FeNO increases most markedly in T-helper type 2 lymphocyte-driven eosinophilic airway inflammation [35], and that this elevation can be readily reduced by ICS therapy. Therefore, FeNO was studied as a potential "inflammometer" in asthma in general and not in certain subtypes of asthma. However, a wide spectrum of different phenotypes of asthma have been recognised [2], some of which are characterised by neutrophilic rather than eosinophilic inflammation, while others may not have mucosal inflammation at all. These noneosinophilic phenotypes of asthma are probably not associated with FeNO level. In the present systematic review, only half of the studies assessed inflammatory activity and phenotype in some way and a quarter of the studies assessed the proportion of subjects with eosinophilic asthma in their sample. Furthermore, only one study evaluated the ability of FeNO to predict responsiveness to ICS separately in eosinophilic and noneosinophilic asthma [18]. In that study, elevated baseline FeNO predicted improvement of asthma control only in eosinophilic asthma, but alleviation of bronchial hyperresponsiveness in both eosinophilic and noneosinophilic asthma. One reason for inconsistence between the results of different studies might be that the studies did not focus on certain NO-related asthma phenotypes, but recruited asthmatics in general. FeNO might be suitable for "FeNO-typing" asthma and it might be more useful for clinical decision making if applied only in eosinophilic phenotypes that are usually associated with higher FeNO.

We found that a low level of FeNO in adult patients on regular ICS therapy is associated with reduced likelihood of exacerbation, and these patients are less likely to benefit from increased doses of ICS. These results suggest that FeNO could be used in tailoring individual ICS dosage and help in directing ICS to those subjects with active steroid-sensitive eosinophilic inflammation. This clinical issue has been addressed by several studies and the information has been summarised (*e.g.* in a recently published *Health Technology Assessment* report [14] and in a meta-analysis [15]). According to these reports the evidence is inconclusive, although consistent with FeNO use resulting in fewer exacerbations, with a small or zero reduction in ICS use in adults and a possible increase in ICS use in children or patients with more severe asthma. In a way, our research questions on the predictive ability of FeNO are a part of this broader question of using FeNO as a monitoring tool. However, none of the studies assessing the ability of FeNO to guide individual ICS dose adjustment focused on FeNO-related asthma types, but instead asthmatics in general were included. In addition to differences in treatment algorithms and cut-off values, this heterogeneity of asthma phenotypes is likely to be a confounding factor, possibly weakening the clinical benefit of FeNO measurements. In treatment-tailoring studies, FeNO should probably not be evaluated as a replacement for symptom assessment and lung function measurement, but rather as a complementary tool.

The utility of FeNO in the diagnosis of asthma was not evaluated in the current review. As long as the definition of asthma remains tightly linked to the detection of variable or reversible airway obstruction, markers of inflammation cannot replace lung function measurements, but they could be augmenting tools providing information on the other major aspect of asthma pathophysiology. Now that new markers of type and activity of airway inflammation are available and new biological treatments focus on certain

mediators of inflammation, it may be that the whole concept of asthma needs to be revised. Currently, suitable patients for ICS treatment in the clinic are mainly identified based on symptoms and variable lung function, but revision of the diagnostic label "asthma" might help us to better aim ICS at subjects with steroid-sensitive inflammation, and also ultimately to identify subjects in whom the treatment should be based on other drug classes. High F_{e}NO has been associated with better response to treatment with anti-IgE or anti-interleukin-13 antibodies [36, 37].

Measuring F_{e}NO is technically simple, relatively economical and safe. However, there might be a risk of under- or overtreatment of asthma if clinical decisions rely too heavily on F_{e}NO values.

Based on this review, it is not possible to provide clear recommendation about the use of F_{e}NO in asthma management. It is difficult to provide exact cut-off values for clinicians due to heterogeneity of cut-off values and exhalation flow rates used across studies. It is possible that instead of predetermined absolute cut-off levels, individual values relative to personal best value might be more useful. How frequently F_{e}NO should be measured; how far in time we can extrapolate F_{e}NO values measured at a certain time point; and which patient groups are more likely to benefit from F_{e}NO measurements also remain uncertain.

In conclusion, there is a lack of good-quality data to draw firm conclusions on the predictive role of F_{e}NO in asthma. It seems that in steroid-naïve patients high F_{e}NO predicts a good response to ICS, while low F_{e}NO in adult patients on regular ICS predicts reduced likelihood of exacerbation and no benefit from increased doses of ICS regardless of possible symptoms. Very little is known about how the predictive ability of F_{e}NO depends on the inflammatory phenotype of asthma.

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