Chapter 3

Fractional exhaled Nitric Oxide: a useful adjunct test when assessing asthma control in adult patients in primary care? A cross-sectional exploratory study

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Abstract

Objective Established markers of asthma control, i.e. asthma symptoms and lung function, do not measure underlying bronchial inflammation and their results can contradict each other. Measuring fractional exhaled nitric oxide (FeNO) as a marker of eosinophilic airway inflammation may have added value for primary care asthma management. The aim of this study was to explore the added value of FeNO as an adjunct to symptoms and lung function when assessing asthma control in primary care.

Methods Cross-sectional analysis of two primary care adult asthma cohorts. We measured FeNO levels, lung function, and Asthma Control Questionnaire (ACQ) scores. Pearson correlation coefficients were calculated between FeNO, ACQ, FEV_1%predicted, and reversibility. In a decision tree analysis patients' asthma control was categorized according to the two established control markers, and subsequently with FeNO as an additional marker.

Results We included 307 patients (63% females). Correlations between FeNO, symptoms and lung function were weak (max. r=0.240). In 25.7% of patients all three markers were consistent in their interpretation of asthma control. In 28.1% the two established markers were consistent, but FeNO showed a contradictory result. In 46.3% the two established markers contradicted each other.

Conclusions We observed weak correlations between FeNO, symptoms and lung function in adults with asthma in primary care, which confirms that FeNO is an independent marker of asthma control. In almost half the study population the results of symptoms and lung function contradicted each other; in this group FeNO might fine-tune assessment of asthma control and tailor therapy choices.

Background

Asthma is a prevalent chronic airways disease that is mainly diagnosed and managed in primary care. It is characterised by recurrent respiratory symptoms, airflow obstruction, airway hyperresponsiveness and an underlying airways inflammation. Although airways inflammation varies in intensity, it remains persistent in asthma, even when symptoms are not present. Asthma can place severe limitations on daily life, and may even lead to life-threatening exacerbations. In order to reduce these complications, and to improve prognosis, it is important to achieve control of asthma, which is one of the main targets in asthma management according to different international guidelines [1-4]. On the other hand it is also important to avoid overtreatment and concomitant side-effects as much as possible. Therefore asthma control should be achieved with the lowest possible medication dosage and the choice between different types of asthma medication should be targeted to individual needs.

The management of asthma control in primary care is mainly guided by the severity of clinical symptoms as manifested in experienced limitations and ability to perform everyday life activities. It can be measured using short questionnaires like the Asthma Control Questionnaire (ACQ) [5]. Symptoms assessment is supplemented by spirometric measurement of airway obstruction and its reversibility after administering a bronchodilator [1]. However, both symptoms and lung function do not reflect the severity of the underlying chronic airway inflammation.

For several reasons, measuring airway inflammation and incorporating it as a marker of asthma control in asthmatic patients could be interesting for general practitioners (GPs). Firstly, it provides independent information in the assessment of asthma so it can be considered a separate domain of asthma control, just like symptoms and lung function are [6]. Secondly, asthma symptom control can be achieved with pharmacotherapy while underlying inflammation may still be present but 'masked', which may lead to an increased frequency of exacerbations [7,8]. Finally, airway inflammation is the target for inhaled corticosteroids (ICS), the cornerstone of pharmacotherapy in asthma.

During the last two decades, fractional exhaled nitric oxide (FeNO) has emerged as a more direct marker of eosinophilic airway inflammation [9]. Nitric oxide (NO) is produced in the bronchial epithelial cells as part of the inflammatory process [10]. It is measured in a simple, non-invasive manner in exhaled air and can therefore easily be applied in primary care, especially with the advent of small handheld NO-meters. Several studies have been performed to test the usefulness, accuracy and implications of measuring FeNO in managing asthma. They found that FeNO could predict asthma exacerbations [8] and response to ICS [11], was cost-effective [12] and could aid in optimizing titration of inhaled steroid treatment [12-14]. Besides, FeNO can predict changes in asthma control [15]. Other studies found no additional value when using FeNO [16-19]. These

differences in results might depend on cut-off values for FeNO, study populations, and how influential FeNO results were in therapy management-decisions. Since most studies have been performed in secondary care settings, the added value of FeNO needs to be studied in a primary care population, which is more heterogenous and differs in asthma severity. Furthermore, there is a need to identify how FeNO could aid in the assessment of current asthma control, and which patients could benefit most from a FeNO measurement. Therefore, the aim of this study was to explore the added value of FeNO as an adjunct to symptoms and spirometry when assessing asthma control in primary care patients.

Methods

Design and study population

The study was a cross-sectional analysis of two available primary care cohorts of adult patients with asthma in the Netherlands. Cohort A consisted of patients who were referred by their GP for lung function testing in a primary care diagnostic centre in the period October 2008 until July 2010. Cohort B consisted of patients who were recruited from 128 general practices between June 2009 and July 2010 to participate in a longitudinal multicentre trial (Clinical Trial number: NTR1756)[20]. Table 3.1 shows the inclusion and exclusion criteria for both cohorts.

All patients underwent FeNO measurement, followed by spirometry. The ACQ [5] was completed during the same session. Several patient characteristics that may influence FeNO levels were recorded: gender, age, height, smoking status, allergy status, and upper respiratory infection in the previous week. Both studies were approved by our local ethics committee and all subjects gave informed consent.

Measurement of asthma control markers

Asthma symptom control

Symptom control was measured using the six-item ACQ [5], a validated questionnaire that uses a 7-point scale (0=totally controlled, 6=severely uncontrolled). The ACQ has been shown to be an effective instrument to measure asthma control in general practice [21]. The six items comprise: nocturnal symptoms; symptoms when waking up; limitations of daily activity; shortness of breath; wheeze; and use of bronchodilator rescue medication. Level of asthma symptom control was categorized as *controlled* (mean ACQ score ≤0.75) or *uncontrolled* (mean ACQ score >0.75) [22].

Table 3.1. Inclusion and exclusion criteria for the two asthma cohorts

	Cohort A	Cohort B
Source	Consecutive patients with asthma referred to primary care diagnostic centre for lung function testing as a periodical control or because of asthma symptoms	Trial population
Inclusion criteria	Selection of patients: GPs diagnosis of asthma according to patients history OR at least once ≥12% reversibility according to available database in diagnostic centre	Selection of patients: diagnosis asthma according to medical records GP AND ICS use at least three months within past year AND No exacerbation within one month before entry AND No serious comorbidity such as end-stage disease or inability to visit GP
	16-40 years	18-50 years
Exclusion criteria	No successful FeNO-measurement or spirometry	No successful FeNO-measurement or spirometry
	No available information about height, smoking status, allergy status, upper respiratory infection preceding week	No available information about height, smoking status, allergy status, upper respiratory infection preceding week

GP: general practitioner
ICS: inhaled corticosteroids
FeNO: fractional exhaled nitric oxide

Lung function

Spirometry was performed in accordance with international guidelines [23]. Reversibility was assessed after administration of 400 micrograms of aerosolized salbutamol and expressed as the percentage increase in FEV_1. A cut-off of ≥12% was used for presence of reversibility. Airway obstruction was defined as prebronchodilator FEV_1 % predicted <80% [1].

Fraction exhaled nitric oxide

FeNO was measured with a portable NIOX MINO® Airway Inflammation Monitor (Aerocrine AB, Solna, Sweden). Patients exhaled 10 seconds at a flow rate of 50 ml/s, in accordance with international recommendations [24]. FeNO levels were corrected for gender, height, smoking, allergy and recent upper respiratory infection by applying appropriate factors for adjustment [25]. A FeNO level of ≤25 parts per billion (ppb) was regarded as normal, >25 FeNO ≤50 ppb as intermediate, and FeNO >50 ppb as high (26]. In this study we defined FeNO >25 ppb as an indicator of uncontrolled asthma.

Analysis

First, correlations between FeNO, ACQ, percentage reversibility, and prebronchodilator FEV_1 (forced expiratory volume in one second) percentage of predicted were calculated.

Table 3.2. Patient characteristics for cohorts A, B, and overall. Numbers are means (SD) unless stated otherwise

	Cohort A	Cohort B	Overall
n (%)	147 (100%)	160 (100%)	307 (100%)
Females, n (%)	77 (52.4%)	115 (71.9%)	192 (62.5%)
Age, years [a]	29.7 (7.0)	40.7 (9.1)	35.4 (9.8)
Current smokers[a], n (%)	44 (29.9%)	21 (13.1%)	65 (21.2%)
Allergic symptoms, n (%)	118 (80.3%)	129 (80.6%)	247 (80.5%)
Asthma medication use, n (%)			
None	26 (17.7%)	16 (10.0%)	42 (13.7%)
Bronchodilator only	31 (21.1%)	11 (6.9%)	42 (13.7%)
ICS only	9 (6.1%)	12 (7.5%)	21 (6.8%)
ICS and bronchodilator	81 (55.1%)	121 (75.6%)	202 (65.8%)
Mean ACQ-score [b]	1.00 (0.33-1.83)	0.67 (0.33-1.33)	0.83 (0.33-1.67)
Controlled (mean ACQ ≤ 0.75)	58(39.5%)	81 (50.6%)	139(45.3%)
Uncontrolled (mean ACQ >0.75)	89 (60.5%)	79 (49.4%)	168 (54.7%)
FEV_1 % predicted [a]	77.7 (13.6)	86.3 (17.9)	82.2 (16.5)
Obstruction (<80%)	85 (57.8%)	42 (26.2%)	127 (41.4%)
Reversibility, % [b]	6.8 (3.6-14.1)	4.0 (1.4-9.5)	5.43 (2.3-10.9)
Reversibility (≥12%), n (%)	42 (28.6%)	29 (18.1%)	71 (23.1%)
Uncorrected FeNO values, ppb [b]	12.0 (8.0-22.0)	16.0 (12.0-27.0)	15.0 (9.0-26.0)
Normal level (≤25 ppb), n (%)	111 (75.5%)	81 (50.6%)	192 (62.5%)
Intermediate level (25<FeNO≤50 ppb)	21 (14.3%)	51 (31.9%)	72 (23.5%)
High level (>50 ppb)	15 (10.2%)	28 (17.5%)	43 (14.0%)
Corrected FeNO values, ppb [b d]	18.9 (10.0-43.0)	25.6 (14.9-48.2)	22.4 (11.9-44.9)
Normal level (≤25 ppb), n (%)	87 (59.2%)	76 (47.5%)	163 (53.1%)
Intermediate level (25<FeNO≤50 ppb)	31 (21.1%)	49 (30.6%)	80 (26.1%)
High level (>50 ppb)	29 (19.7%)	35 (21.9%)	64 (20.8%)

[a] Parametric data: mean and standard deviation (SD)

[b] Non-parametric data: median and interquartile range (IQR)

[c] Ex-smokers were regarded as non-smokers if they had stopped at least four weeks before the date of the measurements

[d] For smokers FeNO levels were corrected by multiplying by 0.627, for males by 1.174, for allergic symptoms by 1.496, for upper respiratory infection by 1.235 and for height by $1.113^{(\text{height in cm}-170)/10}$

FEV_1: forced expiratory volume in one second

ACQ: asthma control questionnaire

ppb: parts per billion

Because FeNO values were not normally distributed according to a histogram and Kolmogorov-Smirnov test, they were $\log_{10}$-transformed for this part of the analysis. Pearson correlation coefficients were calculated with $\log_{10}$-FeNO levels for the two cohorts separately. Next, patients were categorized according to their level of asthma control using the established markers of asthma control (i.e., symptom control and lung function),

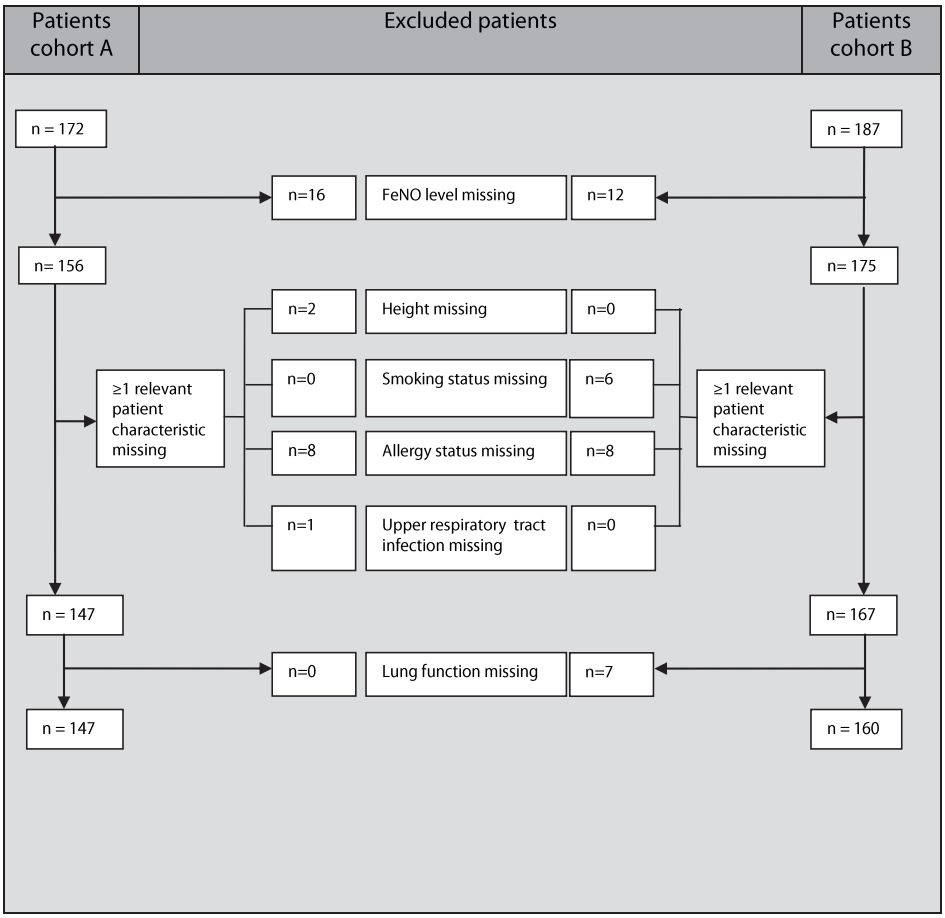

Figure 3.1. Flow diagram of the study population

with FeNO added as a third marker. This resulted in eight categories (see Figure 3.2). In the analysis of the flow diagram, the two cohorts were combined. Sensitivity analyses were performed using uncorrected instead of corrected FeNO values and using less strict cut-off values for uncontrolled symptom score (mean ACQ >1.50) and for uncontrolled FeNO level (FeNO>50ppb). The Statistical Package for the Social Sciences (SPSS) version 16.0 was used for the statistical analyses. P-values <0.05 indicated statistical significance.

Results

Patient characteristics

147 patients in cohort A and 160 in cohort B could be analysed (Figure 3.1). Table 3.2 describes characteristics for both cohorts. Most characteristics showed different distri-

Table 3.3. Pearson correlation coefficients for the established markers of asthma control and FeNO for both cohorts

	ACQ (score)		**Reversibility** (%)		**log_{10}-FeNO** (ppb)**	
	Cohort A (n=147)	*Cohort B (n=160)*	*Cohort A (n=147)*	*Cohort B (n=160)*	*Cohort A (n=147)*	*Cohort B (n=160)*
ACQ (mean)	1	1			0.15 p=0.07	−0.04 p=0.61
Reversibility %	0.28 p=0.001*	0.17 p=0.036*	1	1	0.16 p=0.05	0.24 p=0.002*
FEV_1%pred	−0.31 p<0.001*	0.01 p=0.94	−0.63 p<0.001*	−0.50 p<0.001*	−0.02 p=0.85	−0.21 p=0.009*

As the correlation coefficient is a standardized ratio, its interpretation is independent whether variables are log-transformed or not.

*= correlation is statistically significant at the 0.05 level (2-tailed)

**= log_{10}-FeNO level corrected for gender, height, smoking, allergy and upper respiratory infection

butions for the two cohorts. In both cohorts the majority of patients were treated with ICS (61.2% in cohort A and 83.1% in cohort B, respectively).

Correlations between markers of asthma control

Table 3.3 shows that correlations between log_{10}-FeNO values and ACQ scores, FEV_1 values, and reversibility were weak (maximum of r=0.24 for correlation between log_{10}-FeNO and % reversibility in cohort B; p=0.002). The two spirometric markers of asthma control (i.e., % FEV_1 predicted and % reversibility) showed moderate correlation (r= −0.63 and −0.50 in the respective cohorts; p<0.001).

Classification of asthma control levels

Figure 3.2 depicts the distribution of patients according to the two established markers of asthma control (i.e., ACQ and lung function), with FeNO as an additional marker. In total 144 (46.9%) patients were considered to be uncontrolled in terms of airway inflammation. In 25.7% of patients (13.0% in category 1 and 12.7% in category 8) all three control markers were consistent in their interpretation of asthma control. Furthermore, in 28.1% of patients, the two established markers were consistent in their interpretation of asthma control, but FeNO was contradicting (13.4% in category 2 and 14.7% in category 7). In category 3 until 6 of figure 3.2 the results of the two established markers showed disagreement: asthma was controlled according to one marker and uncontrolled according to the other. This comprised 46.3% of the total study population (142/307).

Sensitivity analyses

Using uncorrected FeNO values, only 25.7% of patients had uncontrolled FeNO levels. More patients ended up in categories 1 and 5, less in categories 2 and 6 (see footnote

d in figure 3.2). Adopting 50 ppb as the cut-off for uncontrolled FeNO led to only 20.9% of patients being considered uncontrolled. More patients ended up in categories 1, 3, 5, and 7, and less in categories 2, 4, 6, and 8 (see footnote e). Use of a less strict ACQ score cut-off (1.50 instead of 0.75) led to more patients ending up in categories 1, 2, and 3 but fewer patients in categories 5, 6, and 7 (see footnote f). Irrespective of these different

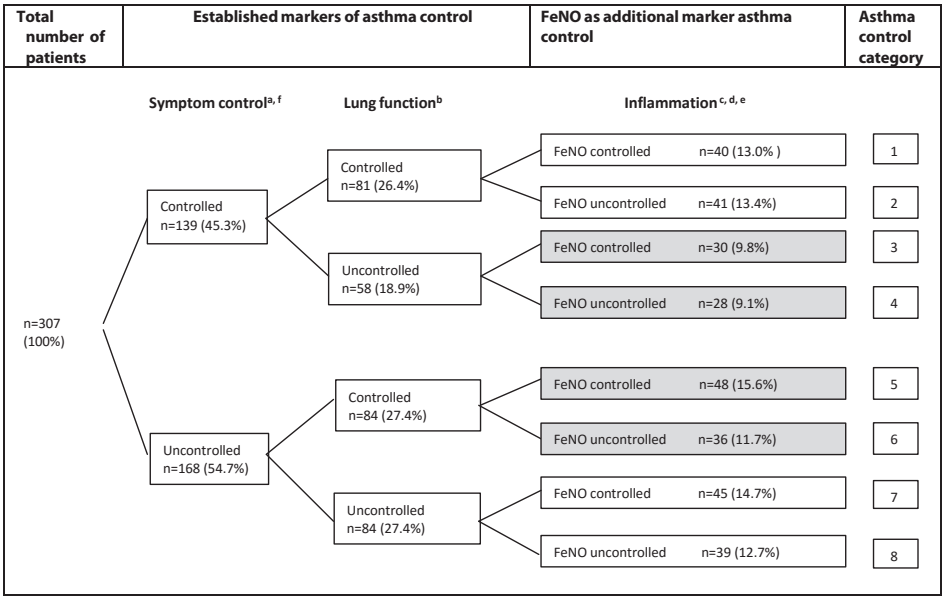

Figure 3.2. Flow diagram for classification of asthma control based on the established markers, with FeNO as an additional, independent marker

Marked boxes indicate patients with conflicting asthma control according the two GINA markers.

[a] Being controlled= mean ACQ ≤0.75; being uncontrolled= mean ACQ >0.75

[b] Being controlled= no obstruction or reversibility; being uncontrolled= obstruction and/or reversibility. Obstruction= FEV_1 <80% predicted;

Reversibility = (FEV_1-postbronchodilator minus FEV_1-prebronchodilator)/ FEV_1-prebronchodilator ≥12%

[c] Being controlled= FeNO ≤25; being uncontrolled= FeNO >25 (corrected FeNO)

[d] Sensitivity analyses: uncorrected FeNO levels lead to the following % in the 8 categories: 19.5%; 6.8%; 13.0%; 5.9%; 23.1%; 4.2%; 18.6%; 8.8%, respectively

[e] Sensitivity analyses: being controlled= FeNO ≤50; being uncontrolled= FeNO >50 (corrected FeNO) lead to the following % in the 8 categories: 21.2%; 5.2%; 14.3%; 4.6%; 24.1%; 3.3%; 19.5%; 7.8%

[f] Sensitivity analyses: being controlled= mean ACQ <1.50; being uncontrolled= mean ACQ ≥1.50 lead to the following % in the 8 categories: 22.8%; 19.2%; 15.0%; 12.7%; 5.9%; 5.9%; 9.4%; 9.1%

percentages of patients ending up in the separate categories, in all sensitivity analyses the overall percentages of patients with either three consistent markers of control, two consistent established markers but contradicting FeNO, or two contradicting established markers remained more or less the same.

Discussion

Main findings

We aimed to explore the added value of FeNO as an adjunct to symptoms and spirometry when assessing asthma control in primary care. We observed only weak cross-sectional relationships between symptoms, lung function (the two established markers of asthma control) and FeNO. This lack of correlation confirmed that FeNO can be considered to be an independent marker of asthma control in primary care patients. The analysis of the flow chart in figure 3.2 revealed that in 46.3% of the adult asthma patients in primary care, symptoms and lung function yielded contradicting results regarding the interpretation of asthma control. FeNO might serve as a third decisive marker of asthma control in those instances, since it is an independent marker measuring airways inflammation, which is the central process to airway obstruction and hyperresponsiveness and the target for inhaled corticosteroid therapy. In 28.1% of patients the two established markers were consistent in their interpretation, but FeNO was contradictory.

Strengths and limitations of this study

This is the first study executed in a large heterogenous primary care sample where the added value of FeNO when assessing asthma control was examined for individual patients. By combining two primary care cohorts of patients, data from a larger study population could be analysed. As the cohorts consist of heterogeneous populations, including smokers, patients with recent upper respiratory infections, ICS use and allergies, this greatly enhances generalizability of the results. Cohort A consisted of a more heterogeneous group of asthma patients, including milder asthmatics and some patients who had been referred for spirometry by their GP because of worsening of their symptoms. This might explain the lower ICS use and the lower lung function values in this cohort. In cohort B the ACQ was completed not solely by the patient him- or herself, but together with a practice nurse [27]. Despite the differences between both cohorts, we combined them in our analysis, to assess the additional value of measuring FeNO when assessing asthma control in all types of asthma and in different circumstances. Final limitations are our cross-sectional design (i.e., we could not study the utility of FeNO when monitoring asthma), and the fact that our data did not contain detailed information about the dose of asthma medication for all patients, which would have

enabled us to look at possible modifications of pharmacotherapy in the patients in the respective asthma control categories when FeNO is added to their assessment.

It is not easy to define an 'uncontrolled' or increased FeNO in a particular patient. Although some prefer using a 'personal best' value [28], using fixed cut-off points is more widely accepted. Several studies have been performed in the general population [29,30] as well as in specialist care settings [31], to generate normal values. Based on these studies, we chose to use the 25 ppb cut-off. We are aware of the problem that, as shown in our sensitivity analysis, we might overestimate the percentage of patients being uncontrolled compared to using the less strict 50 ppb cut-off, which is also mentioned as a justified cut-off in the literature [26]. To date it is unclear what the longitudinal consequences of normalizing FeNO are; therefore it is difficult to predict whether it is most important to demonstrate controlled disease by using a lower cut-off (and to avoid under treatment), or to prove uncontrolled disease by using a higher cut-off (and to avoid over treatment). However, even when using the less strict 50 ppb cut-off, the proportion of patients where FeNO provided additional information remained similar.

A final limitation of using FeNO in primary care are the high costs when purchasing a device, which currently has a refractory life of three years only, and the need of acquiring a new costly sensor every twelve months. However, Honkoop et al have shown that due to decreased medication usage and costs, adding FeNO is a cost-effective strategy [12].

Interpretation of findings in relation to previously published work

Most studies on FeNO have analysed whether FeNO could be used as a replacement for conventional asthma control markers. Only few studies have been performed about the relation between FeNO and other asthma control markers, and their results are inconsistent. Some studies indicate that increased FeNO levels are associated with uncontrolled asthma [32] or are significantly related to changes in ACQ scores over time [33]. On the other hand, one study showed that FeNO was not associated with ACQ scores [34]. In the primary care setting, one study found a modest correlation between FeNO and a non-validated symptom score ($r=0.4$, $p<0.05$) [35] which disappeared when treatment with ICS was taken into account. In this same study the correlation between FeNO and FEV_1 was weak ($r=0.2$, $p=0.03$). Another study found very weak correlations between FeNO, the ACQ and lung function, cross-sectional as well as longitudinal [36]. Finally, Hewitt et al showed that by adding FeNO to conventional markers they were able to lower ICS usage [18].

Our finding of only weak cross-sectional associations confirms that FeNO might serve as an independent, distinctive marker when assessing asthma control [37]. This weak cross-sectional association on its own is naturally no conclusive proof of added value. However, combined with results from previous longitudinal studies where the additional use of FeNO resulted in lower ICS usage [12,14,18], this points towards its added value

in the assessment of asthma control. In other words, FeNO does indeed seem to reflect another domain of asthma control than the current markers do: underlying inflammation rather than symptoms or (reversible) airway obstruction.

Implications for future research, policy and practice

Since asthma has a multi-dimensional nature, FeNO could provide GPs with additional information, especially in those patients where symptoms and lung function provide conflicting results. GPs might in the future define asthma control not only by symptoms and spirometry, but also by level of inflammation.

As presented in the flow chart analysis in figure 3.2, in a substantial percentage of patients (46.3%) the GP will be confronted with patients whose asthma is controlled according to one of the established markers (e.g. symptoms) but uncontrolled according to the other (lung function), or vice versa. Although currently clinical symptoms are considered to be more important than lung function when assessing asthma control [1], it may still confuse the GP when these two markers contradict each other. In these patients, adding FeNO as a third marker could be decisive when judging the patient's asthma control. In another 28.1% it is FeNO that gives contradicting results compared to the two established markers. As to date it is unclear which of the three markers should be the dominant one and future research should focus on establishing an order. The ultimate goal of improving the assessment of a patient's asthma control level by adding FeNO are the therapeutic consequences. With this additional measurement, decisions regarding treatment could be guided on the actual pathophysiology. For instance, in circumstances where both symptoms and lung function show uncontrolled asthma and FeNO is controlled, patients should be prescribed LABAs, whereas ICS would be preferred if FeNO is uncontrolled. On the other hand, when symptoms are controlled, a GP might be more reluctant to prescribe high-dosed ICS when there is no sign of active bronchial inflammation. In case of uncontrolled FeNO and after checking compliance and inhaler technique, ICS could be started or increased as the risk of exacerbation should be considered [8]. Follow up of the patient remains necessary though, as not all elevated FeNO levels seem to respond to ICS [38]. Also, if symptoms and lung function are uncontrolled, it could be harmful for the patient to stop or reduce (ICS-) treatment in response to normal FeNO levels, as there are phenotypes of asthma that never have an increased FeNO level.

If FeNO is to be used as a new marker of asthma control in primary care, some important barriers remain. One important issue is whether FeNO testing is 'robust' enough to be applicable for all patients and in all circumstances. Levels of FeNO appear to be gender, age, and height dependent [25,29], which hampers interpretation of FeNO results in individual patients. Furthermore, raised FeNO levels are not exclusively due to asthma, but are also seen in atopic subjects [29], in patients with an upper respiratory

infection [39], after bronchodilation [40] and after a nitrate rich meal [41]. Conversely, levels are reduced by smoking [42], ICS use [43], and spirometry manoeuvres [40]. More recent studies concluded therefore that FeNO should be corrected for its main influencing factors, gender, height, smoking, allergy and recent upper respiratory infection [25,29,30]. Therefore, we chose to correct FeNO using the established adjustments for these influencing factors [25]. In our sensitivity analysis, however, we showed that results of categorizing patients differed only slightly if FeNO values are not corrected.

Conclusions

In conclusion, our cross-sectional study of adult patients with asthma in primary care demonstrated that FeNO correlates weakly with respiratory symptoms and lung function, which confirms that it might serve as an independent marker for assessing asthma control. If, in the future, FeNO would be incorporated as a marker of asthma control in primary care, it will enable 'fine-tuning' when categorizing asthma control in almost half of the patients. Although for the time being measuring FeNO is rather impractical and provides additional work, it is likely that these obstacles will resolve over time, especially since FeNO has been shown to be cost-effective. Prospective research on the impact of the additional use of FeNO in the subgroup of patients with conflicting symptom and lung function results on long-term results such as asthma control and exacerbation rate is needed, to be able to tailor asthma management in primary care.

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