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Original Article

Domiciliary Fractional Exhaled Nitric Oxide and Spirometry in Monitoring Asthma Control and Exacerbations

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What is already known about this topic? The use of home spirometry and fractional exhaled nitric oxide (FENO) may facilitate better disease control in people with asthma. However, the lack of compliance may be a major hurdle to its effectiveness.

What does this article add to our knowledge? The compliance with domiciliary use of spirometry and FENO devices varied widely. Despite this, FENO and spirometry parameters were associated with asthma exacerbations and control, making it potentially clinically useful.

How does this study impact current management guidelines? The domiciliary use of spirometry and FENO may assist patients and healthcare professionals in improving asthma outcomes, particularly in patients with moderate to severe disease. This merits further validation in future studies.

BACKGROUND: Domiciliary measurements of airflow obstruction and inflammation may assist healthcare teams and patients in determining asthma control and facilitate self-management.

OBJECTIVE: To evaluate parameters derived from domiciliary spirometry and fractional exhaled nitric oxide (FENO) in monitoring asthma exacerbations and control.

METHODS: Patients with asthma were provided with hand-held spirometry and FENO devices in addition to their usual asthma care. Patients were instructed to perform twice-daily measurements for 1 month. Daily symptoms and medication change were reported through a mobile health system. The Asthma Control Questionnaire was completed at the end of the monitoring period.

RESULTS: One hundred patients had spirometry, of which 60 were given additional FENO devices. Compliance rates for twice-daily measurements were poor (median [interquartile range], 43% [25%-62%] for spirometry; 30% [3%-48%] for FENO); at least 15% of patients took little or no spirometry measurements and 40% rarely measured FENO. The coefficient of variation (CV) values in FEV_1 and FENO were higher, and the mean % personal best FEV_1 lower in those who had major exacerbations compared with those without ($P < .05$). FENO CV and FEV_1 CV were associated with asthma exacerbation during the monitoring period (area under the receiver-operating characteristic curve, 0.79 and 0.74, respectively). Higher FENO CV also predicted poorer asthma control (area under the receiver-operating characteristic curve, 0.71) at the end of the monitoring period.

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Abbreviations used
ACD-6- 6-item Asthma Control Diary
ACQ-6- 6-item Asthma Control Questionnaire
AUROCC- area under the receiver-operating characteristic curve
CV- coefficient of variation
FENO- fractional exhaled nitric oxide
IQR- interquartile range
OCS- oral corticosteroid
OR- odds ratio
Pb%- percent personal best in FEV_1
PEF- peak expiratory flow

CONCLUSIONS: Compliance with domiciliary spirometry and FENO varied widely among patients even in the setting of a research study. However, despite significant missing data, FENO and FEV_1 were associated with asthma exacerbations and control, making these measurements potentially clinically valuable if used. **(J Allergy Clin Immunol Pract 2023;11:1787-95)**

Key words: *Asthma; Monitoring; Home monitoring; Asthma management; Adult asthma*

INTRODUCTION

Asthma is a variable disease whereby patients typically experience periods of controlled and uncontrolled symptoms. Poorly controlled asthma drives substantial disease-related morbidity, mortality, and cost.[1] Maintaining optimal control is the major goal in asthma management, and the ability to predict the level of asthma control may assist patients and healthcare teams in managing disease better.[2,3]

Despite recent advances in technologies and the emergence of portable devices, the peak expiratory flow (PEF) meter, introduced more than 60 years ago, remains the only equipment that is used in the domiciliary setting.[4,5] Although its use is widely promoted in clinical care, data supporting its role in asthma management are sparse.[6-11] PEF is far less sensitive than FEV_1 in detecting clinically meaningful airflow limitation and the correlation between the 2 is poor.[12,13] Hand-held spirometry and in-clinic measurements are highly correlated and have comparable effectiveness in demonstrating asthma treatment response in clinical trials,[14] and therefore is potentially more useful than PEF for disease monitoring. Fractional exhaled nitric oxide (FENO), a breath biomarker of T2 airway inflammation measured by portable devices, has been widely used for asthma diagnosis and monitoring.[15] Suppression of FENO following corticosteroid treatment correlates with improvements in lung function and disease control.[16] The combination of diurnal variations in FENO and Asthma Control Questionnaire score has been useful at predicting uncontrolled asthma, particularly the risk of a future exacerbation.[17]

One of the major challenges in implementing ambulatory monitoring in asthma is lack of compliance.[9,10] Even with regular reinforcement, the adherence to twice-daily PEF measurements may only be 50% to 60% within the first month, beyond which the compliance rate falls further.[9,10] Strikingly, more than a third of patients rarely take any measurements, even when devices are provided.[10] This issue is hardly ever addressed in studies evaluating the usefulness of FEV_1 and FENO parameters derived from domiciliary use in predicting asthma control. Instead, data tend to rely heavily on complete data sets and frequent (diurnal) measurements.[17] This impedes the effective translation of research findings to the clinical setting.

Although domiciliary spirometry and FENO are feasible,[16-18] it is largely unknown whether acquiring twice-daily measurements regime is a realistic ambition, or whether less frequent measurements may still generate sufficient data to reflect and predict asthma outcomes both during and following a monitoring period.

The myAirCoach mHealth system was an app-based platform to facilitate data collection and asthma self-management.[2] Here, we report on the analysis of the physiological and behavioral data of domiciliary use of spirometry and FENO in patients with asthma from the EU-Horizon 2020 myAirCoach study. We investigated the compliance rate with twice-daily measurement of home spirometry and FENO in patients with asthma. We further explored which parameter(s) (taking into account missing data) was associated with and/or predictive of disease-related outcomes (asthma control, medication use, exacerbations) during and after the monitoring period.

METHODS

Study design

This was an international, multicenter, observational study described in detail previously.[19] Briefly, patients with doctor-diagnosed asthma were recruited from outpatient clinics and general practices. Participants had documented history of either (1) improvement in FEV_1 by greater than or equal to 12% or 200 mL following administration of a bronchodilator medication, or (2) evidence of PEF variability over 1 week, or (3) positive bronchial provocation challenge. All included patients were prescribed a minimum of daily inhaled corticosteroids (ie, British Thoracic Society treatment step 2 and above) and were at least 18 years old.

In addition to participants' usual asthma care, hand-held spirometry (nSpire Health, PIKO-1, Longmont, CO) was provided. Patients received training to use the device before an unsupervised monitoring period during which they were asked to perform twice-daily (diurnal) spirometry at home for 1 month. A subset of patients (n = 60) was trained and asked to perform twice-daily FENO (Aerocrine, NIOX VERO, Sweden) in addition to home spirometry.

Participants reported FEV_1 and FENO measurements, daily medication use, and subjective symptoms score (using the 6-item Asthma Control Diary [ACD-6][20]) via a mobile health system.[19] The 6-item Asthma Control Questionnaire (ACQ-6)[21] was administered at baseline and then at the end of the twice-daily monitoring period.[19] Daily measurements and symptoms reporting were not reinforced by reminders. Because it was an observational study, patients were not prompted to any action based on any of the outcomes of these measurements.

Because the study aim was to assess whether a wide variety of parameters, alone, or in combination, were associated with/able to predict the occurrence of either uncontrolled asthma or asthma exacerbations during the monitoring period, an appropriate *a priori* sample size calculation could not be performed.

All participants provided written informed consent. The study protocol was approved by the Local Research Ethics Committees

TABLE I. Baseline characteristics of all recruited population

Baseline characteristics	Total (n = 97)*	Spirometry only (n = 37)	FENO and spirometry (n = 60)	*P* value
Age (y), mean ± SD, n = 97	43.3 ± 12.8	43.6 ± 14.3	43.1 ± 11.9	.853
Sex: male, n (%), n = 97	25 (25.8)	13 (35.1)	12 (20.0)	.157
Ethnicity (White), n (%)	69 of 89 (77.5)	26 of 35 (74.3)	43 of 54 (79.6)	.631
Previous asthma-related hospital admission ever, n (%)	53 of 89 (59.6)	17 of 33 (51.5)	36 of 55 (65.5)	.564
Asthma-related hospitalization during past year, n (%)	20 of 53 (37.7)	4 of 17 (23.5)	16 of 36 (44.4)	.225
Smoking history, n (%)				
Nonsmoker	72 of 90 (80.0)	24 of 35 (68.6)	48 of 55 (87.3)	.055
Ex-smoker	13 of 90 (14.3)	7 of 35 (20.0)	6 of 55 (10.9)	
Current smoker	5 of 90 (5.5)	4 of 35 (11.4)	1 of 55 (1.8)	
Baseline FEV_1 (L), median (IQR), n = 97†	2.45 (1.79-3.11)	2.68 (1.94-3.24)	2.40 (1.75-2.95)	.184
Baseline FEV_1 % predicted (%), median (IQR), n = 87†	81 (63-96)	81 (66-95)	76 (61-95)	.543
Baseline FENO† (ppb), median (IQR), n = 58	18.5 (12.3-34.5)	—	—	—
Baseline ACQ-6 score, median (IQR), n = 74†	1.7 (1.0-2.5)	1.3 (0.8-2.0)	1.8 (1.3-2.7)	.138

ppb, Parts per billion.
*With at least 1 successfully logged FENO/spirometry measurement.
†Reported within the first week of the monitoring period.

(The Leiden University Medical Center and National Health Service Ethics services).

Definitions of asthma-related outcomes

1. Daily asthma control using self-reported ACD-6 score, defined as (1) well controlled (ACD-6 score $\leq$ 0.75); (2) partially controlled (0.75 < ACD-6 score $\leq$ 1.5); (3) uncontrolled (ACD-6 score > 1.5).
2. Treatment escalation, defined as any increase in medication usage (increased salbutamol *or* inhaled corticosteroid use *or* use of oral corticosteroids [OCSs] *or* hospital attendance).
3. Major exacerbation during the 1-month monitoring period, defined as the need of OCS or hospital attendance at least once. Patients were assumed to have no major exacerbations on unreported days.
4. Asthma control at end of the monitoring period using the ACQ-6 score: (1) well controlled (ACQ-6 score $\leq$ 0.75); (2) partially controlled (0.75 < ACQ-6 score $\leq$ 1.5); (3) uncontrolled (ACQ-6 score > 1.5).

Statistical analysis

Clinical and demographic data were summarized using descriptive statistics. To estimate the compliance rate of diurnal measurements and variability, same-session FENO measurements (defined as <2 hours apart) were averaged and regarded as a single data point; for within-session spirometry measurements, the best FEV_1 was obtained and regarded as a single data point. Repeated-measures correlation function was used to assess the relationship between intrapersonal objective test measures and subjective symptoms. We used mixed-effect models to account for repeated measurements in individuals (random effects) and investigated the relationship between test measurements (fixed effects) and same-day symptoms/treatment escalations.

The intraindividual relative variability in measurements was defined as coefficient of variation (CV) (calculated as SD/mean), a measure of the spread of data around the mean and expressed as %; the higher the CV, the more the variability. To evaluate mean and CV, patients who rarely performed any measurements (defined as $\leq$7 data points over the monitoring period) or missing the end ACQ-6 score (the outcome of interest) were excluded from the analysis. Univariate and multivariate regression models were used to explore the relationship between variability parameters and asthma control/exacerbation levels. The area under the receiver-operating characteristic curve (AUROCC) was used to describe the discriminative ability of key parameters in determining exacerbations and asthma control.

Missing data were excluded to mimic clinical settings. Extreme outliers, which were likely due to input errors, were excluded from this analysis. All analyses were performed using R version 4.1 (RStudio 1.4.1106).

RESULTS

Compliance

Of 100 patients, 97 had at least 1 spirometry measurement successfully recorded. Key baseline and/or monitoring data from 3 patients were absent, likely due to a technical failure of the mobile app platform and therefore were excluded from the compliance analysis (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org; Table I). All patients (n = 60) who were given a FENO device had at least 1 FENO measurement successfully logged via the mobile app platform during the 4-week monitoring period and therefore were included in the FENO compliance assessment.

Compliance with twice-daily spirometry and FENO measurements was poor and highly variable (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). The median (interquartile range [IQR]) number of spirometry data points for each patient during the monitoring period was 24 (14-36) (of a total of 56 possible data points over 28 days), corresponding to a 43% (25%-62%) compliance rate. The compliance with FENO was lower (18 [2-27] data points, 30% [3.3%-48%]). Only one-third of the total measurements were taken at the frequency of at least twice-daily (Table II). The overall monitoring frequency for spirometry and FENO dropped over time (see Figures E3 and E4 in this article's Online Repository at www.jaci-inpractice.org). Compliance was not associated with patient factors such as sex, internet experience, education, or general health (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). The

TABLE II. Compliance with home FEV_1 and FENO monitoring

Measurement	Data points per patient, median (IQR)	No. of measurements n (% of total data points available)			
		Once daily	Twice daily	Three times daily	Four times daily
FEV_1	24 (14-36)	1119 (64.9)	563 (32.6)	42 (2.4)	1 (0.1)
FENO	18 (2-27)	551 (66.6)	261 (31.6)	14 (1.7)	0

compliance rate of once-daily symptom reporting and ACD-6 were 14 (7-22) and 15 (7-22) recordings over 28 days, corresponding to 50% (25%-79%) and 54% (25%-79%). The patient-reported daily medication use data were obtained in 93 participants on 18 (10-25) days over the monitoring period. The frequency of controller medication usage reporting correlated with lung function ($r = 0.56$; $P < .001$) and FENO ($r = 0.41$; $P < .001$) compliance.

Symptoms and treatment escalation

FENO, FEV_1, and ACD-6 versus self-reported symptoms. Using repeated-measures correlation, it was found that FEV_1 weakly correlated with ACD-6 scores ($r = -0.21$ [-0.25 to -0.17]; $P < .001$). A decreased FEV_1 was associated with increased ACD-6 score in univariate mixed-effect linear models ($\beta = -0.47$ [-0.55 to -0.38]; $P < .001$). Although the percent personal best FEV_1 (Pb%, defined as FEV_1/highest personal FEV_1 during the monitoring period) was lower during periods of poor control than of better control, substantial overlap was noted (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). On 67% of occasions where the FEV_1 was less than 60% of personal best, participants did not report increased symptoms; on occasions where participants reported increased symptoms, 65% had good FEV_1 (>80% of personal best). FENO was not correlated with ACD-6 scores or with FEV_1 measurements.

FENO, FEV_1, and ACD-6 score versus treatment escalation on the same day. Daily FEV_1, FENO, and ACD-6 score during treatment escalation are summarized in Table E3 in this article's Online Repository at www.jaci-inpractice.org. Approximately 12% of occasions when the recorded Pb% was more than 80% were associated with escalation of asthma treatment (increased inhaler use, OCS/hospital attendance). A Pb% of 70% or less was associated with treatment escalation on the same day (increased inhaler use or OCS/hospital attendance) using mixed-effect logistic regression (odds ratio [OR], 1.63 [1.03-2.58]; $P = .037$). Despite the statistical significance of this association, only 7% of patients with a recorded Pb% of less than 70% used OCS or needed hospital attendance on the same day. An increase in ACD-6 score was associated with treatment escalation on the day (OR, 19.5 [12.9-29.5]; $P < .001$). FENO was not associated with escalation of treatment (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

Associations with asthma outcomes

FEV_1, FENO, and ACD-6 score were associated with major exacerbations during the monitoring period. A total of 73 (75.3%) patients were included in the spirometry analysis and 36 (60%) in FENO analysis (Figure E1). Of 72 (98.6%) who reported medication usage and hospital attendance during the monitoring period, most (n = 59 [81.9%]) patients were classified as "no major exacerbations" throughout, and 13 had major exacerbations. FENO CV and FEV_1 CV were higher and mean Pb% lower in those with major exacerbations than in those without (Figure 1; Table III). The median (IQR) daily usage of controller medication in patients who had major exacerbations was 4.5 (3.2-5.4) puffs and 5.1 (4.6-5.9) puffs in those without ($P = .178$). No participant had an average use of controller medication of less than 2 puffs per day. The mean FEV_1, mean FENO, FEV_1 CV, and FENO CV were not correlated with daily controller medication use. The median (IQR) of total reliever medication use over the monitoring period was 67 (31-96) puffs in patients with major exacerbation and 30 (11-62) puffs in those without ($P = .084$). The total reliever medication use was correlated with FEV_1 CV ($r = 0.25$; $P = .034$) but not with mean FEV_1, mean FENO, or FENO CV.

The baseline ACQ-6 scores, FEV_1, FEV_1 % predicted, FENO, and compliance rate of FENO or spirometry use were not different between those who subsequently had or did not have major exacerbations.

Using logistic regression, FEV_1 CV, mean Pb%, and FENO CV were found to be associated with major exacerbations during the monitoring period in the univariate analysis (Table IV); in backwards multivariate regression, FEV_1 CV and FENO CV remained significant (Table IV). Increased mean ACD-6 scores during the monitoring period were associated with major exacerbations (OR, 2.94; 95% CI, 1.50-6.71; $P = .004$).

For major exacerbation during the monitoring period, FENO CV had the highest AUROCC of 0.79 (95% CI, 0.64-0.95). FEV_1 CV had an AUROCC of 0.74 (0.56-0.93) and mean Pb% of 0.69 (0.52-0.85) (Figure 2). Mean ACD-6 score during the monitoring period had an AUROCC of 0.76 (0.60-0.92).

FEV_1 and FENO parameters in predicting asthma control at end of the monitoring period. The median (IQR) of end of monitoring period ACQ-6 score was 1.50 (0.83-2.33) points, with 24.7% classified as well controlled, 31.5% partially controlled, and 43.8% uncontrolled. In ACQ-6 score–defined patients with uncontrolled asthma, the FEV_1 CV and FENO CV during the monitoring period were higher, and the mean Pb% lower than those who were well or partially controlled (Figure 3). The total reliever medication usage was significantly higher (median [IQR], 66.5 [34.5-98] puffs) in those with uncontrolled asthma compared with those without (20 [6-41] puffs, $P < .001$) during the monitoring period, but no difference was found in controller medication use.

FENO CV (OR, 1.08 [1.02-1.17]; $P = .040$), FEV_1 CV (OR, 1.09 [1.02-1.17]; $P = .016$), and mean Pb% (OR, 0.95 [0.92-0.99]; $P = .019$) were predictive of ACQ-6 score–defined "uncontrolled" asthma in univariate logistic regression model, but mean FENO and mean FEV_1 were not. The total reliever medication usage over the monitoring period was also predictive of uncontrolled asthma (OR, 1.03 [1.02-1.05]; $P < .001$). The

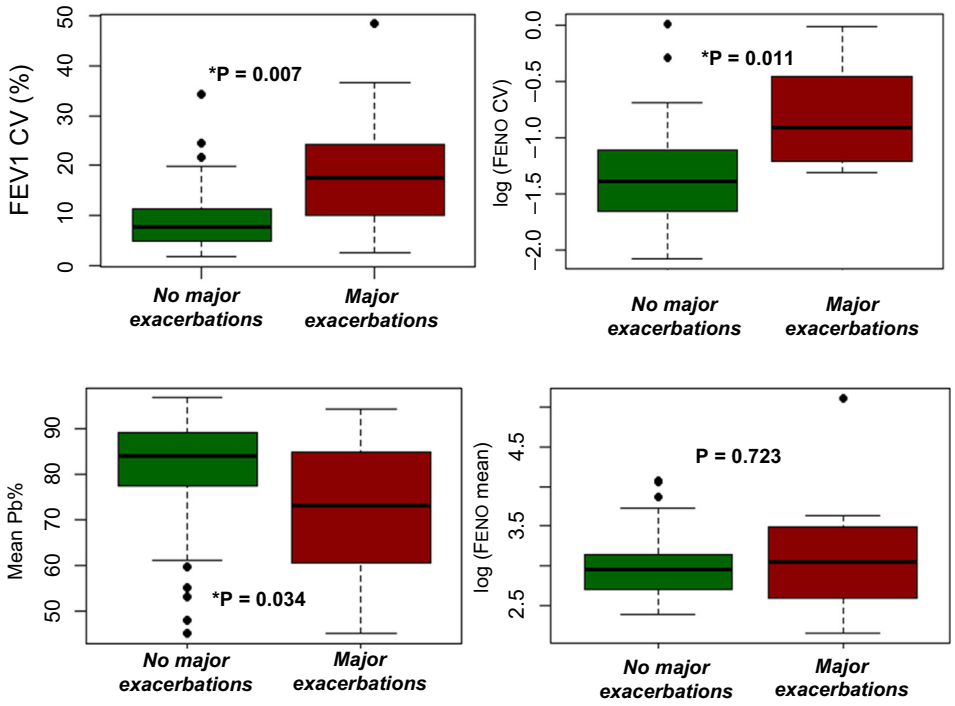

FIGURE 1. Increased FEV_1 CV and FENO CV and decreased mean Pb% were observed in patients with major exacerbations. Log (FENO mean) and log (FENO CV) were used for better visualization.

TABLE III. The median (IQR) of parameters by exacerbation level

Parameters	No. of patients	Median (IQR)	*P* value
FEV_1 mean (L)			
Major exacerbation	13	1.9 (1.7-2.7)	.447
No major exacerbation	59	2.5 (1.7-2.9)	
FEV_1 CV (%)			
Major exacerbation	13	17.6 (10.0-24.3)	**.007**
No major exacerbation	59	7.7 (4.8-11.3)	
Mean Pb% (%)			
Major exacerbation	13	73.4 (60.7-85.0)	**.034**
No major exacerbation	59	84.1 (77.5-89.2)	
Mean FENO (ppb)			
Major exacerbation	8	21.0 (16.8-30.9)	.723
No major exacerbation	28	19.1 (15.6-23.2)	
FENO CV (%)			
Major exacerbation	13	40.3 (31.0-60.7)	**.011**
No major exacerbation	59	24.9 (19.3-32.4)	

ppb, Parts per billion.
Bold indicates *P*-value < .05.

compliance rates with FENO and spirometry monitoring were not associated with poor control at the end of the monitoring period.

For the determination of uncontrolled asthma at the end of the monitoring period, FENO CV had an AUROCC of 0.71 (0.53-0.89). FEV_1 CV had an AUROCC of 0.66 (0.53-0.79) and mean Pb% of 0.68 (0.55-0.81) (Figure 4). The mean ACD-6 score had the highest AUROCC of 0.91 (0.84-0.98). With a FENO CV of more than 40% during the previous month, all patients (n = 7) had uncontrolled asthma defined by ACQ-6 score, accounting for 22% of patients with uncontrolled asthma. Similarly, with an FEV_1 CV of more than 20%, 78% (7 of 9) had uncontrolled asthma, and with a mean Pb% of less than 60%, 78% (7 of 9) had uncontrolled asthma.

DISCUSSION

We found that the compliance with twice-daily domiciliary spirometry and FENO monitoring in people with asthma is poor. Despite this, we highlighted that the variability parameters in both FENO and FEV_1 can reflect asthma exacerbations and predict control. The included population is representative of patients with moderate to severe disease and would be an important patient group for which a home monitoring system is needed.

Compliance

Adherence to PEF monitoring is problematic and can be as low as 16%.[9,10,22] We found that without reinforcement, 15% of patients took no or very few spirometry measurements, and this was even higher for domiciliary FENO use (40%). Although this could be due to poor device adaptation for home use, only a minority of patients gave unsatisfactory feedback regarding the FENO device on the after-scenario questionnaire (see Figure E5 in this article's Online Repository at www.jaci-inpractice.org). Huang et al[23] reported a home spirometry compliance rate of 70% for twice-daily use in 12 patients. However, adherence was reinforced during the study period.[23] Kupczyk et al[18] have shown that most patients can be compliant with infrequent FEV_1 monitoring over short period of time (3 readings over any 7-day period over 3 weeks). However, variability in compliance was high,[18] suggesting that home monitoring is a suitable option for some patients but not all. We observed the same heterogeneity in compliance rate. It is also important to note that the

TABLE IV. Relationships between FEV_1 and FENO parameters and major exacerbations during the monitoring period using logistic regression

	Univariate analysis			Multivariate analysis		
Parameters	**OR***	**95% CI**	***P* value**	**OR***	**95% CI**	***P* value**
FEV_1 CV (%)†	1.12	1.05-1.23	**.003**	1.65	1.17-3.13	**.031**
Mean FEV_1 (L)	0.73	0.34-1.51	.405	—	—	—
Mean Pb% (%)†	0.95	0.91-1.00	**.034**	1.14	0.97-1.43	.185
FENO CV (%)†	1.04	1.00-1.08	**.050**	1.06	1.01-1.13	**.044**
Mean FENO (ppb)	1.02	0.99-1.06	.221	—	—	—
Total reliever medication use over the monitororing period (n)	1.01	1.00-1.02	.096	—	—	—
Average daily controller medication use (n)	1.05	0.84-1.27	.624	—	—	—

ppb, Parts per billion.
Bold indicates *P*-value < .05.
*Major exacerbation compared with those without major exacerbations.
†Included in the multivariate ordinal regression.

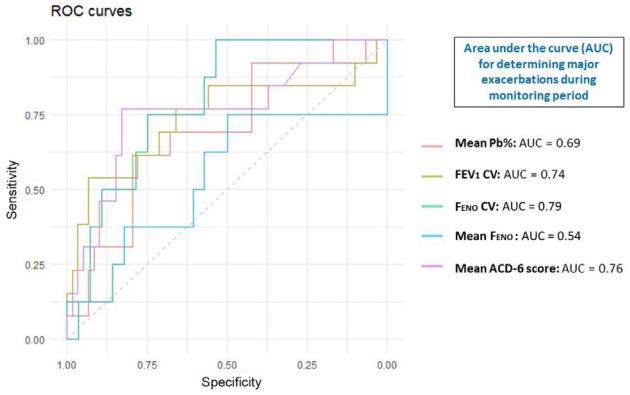

FIGURE 2. ROC curves for the determination of major exacerbation during the monitoring period.

domiciliary spirometry and FENO monitoring and symptoms reporting were among other tasks participants were asked to perform on the myAirCoach platform, including the manual input of all test data.[19] Better compliance may be possible if a reduction in patients' burden was achieved by using devices with functions of automated data logging and reduction of the number of tasks, and this should be the subject of future research. Establishing the minimum required monitoring frequency and the optimal timing of spirometry and FENO measurements should also be investigated as the next step.

Discordance between lung function and perceived symptoms

The discordance between FEV_1 measurements and perceived symptoms and treatment escalations indicates that interpretation of unsupervised domiciliary FEV_1 in the absence of clinical context should be avoided. It is apparent that in the current study, treatment escalation was primarily guided by patients' perceived symptoms (ACD-6 score). Although patients' perception of symptoms alone may not fully reflect the underlying physiological changes, it is also possible that the discordance between objective measures of lung function and symptoms is due to, at least partly, the lack of quality check assurance in the device used. Like PEF monitoring, FEV_1 is highly effort- and technique-dependent. The lack of quality validation in such tests may raise doubts in the reliability of results reported. Indeed, Kupczyk et al[18] had demonstrated that only 56% of home spirometry measurements were of acceptable standard even with adequate training and inbuilt validation system. The device used in the current study does not have an inbuilt quality check function, but whether such a system would improve the clinical usefulness of domiciliary spirometry is unknown. Furthermore, it is possible that FEV_1 is not sufficiently sensitive in reflecting changes in small airway function, and the domiciliary use of more sensitive techniques, such as impulse oscillometry, should be the subject of further research.[24,25]

Variability parameters

We have confirmed that the variability (measured using the CV) in FEV_1 and FENO may be useful in reflecting exacerbations during the monitoring period and predicting asthma control following the monitoring period. The defining feature of asthma is variable symptoms with variable airflow limitation over time.[26] Indeed, Delgado-Eckert et al[27] demonstrated that the fluctuations in twice-daily lung function measurement in patients with obstructive airway diseases were larger in patients who had more exacerbations, and diminished bronchodilator response. Increased airflow variability also predicts risk of asthma control and effectiveness of treatment.[28] Furthermore, patients with high variations in sputum eosinophils had increased exacerbation rates and greater health care utilization.[29] Van der Valk et al[30] performed a *post hoc* analysis in 27 children with moderate to severe exacerbations and found that the geometric mean of FENO or maximum FENO was not associated with risk of exacerbation but the increased FENO CV was. Stern et al[31] also found that increased random fluctuations in daily FENO were associated with increased exacerbation risk and poor control in children with asthma. Saito et al[17] investigated the domiciliary use of FENO in determining asthma control before the monitoring period, and found that the day-to-day (and diurnal) variations in FENO can be a useful marker for uncontrolled asthma. Furthermore, the diurnal variation in FENO was also associated with early treatment response.[32] Although long-term compliance to diurnal measurements may not be feasible in practice, we have demonstrated

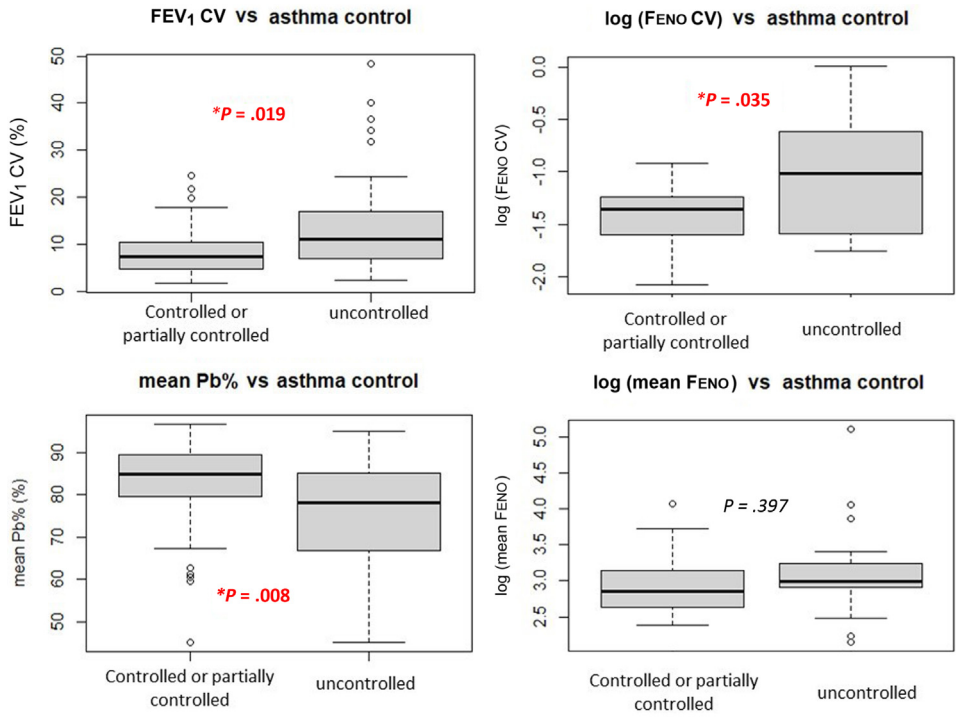

FIGURE 3. The differences in test parameters between ACQ-6 score–defined asthma control categories. Log (FENO mean) and log (FENO CV) were used for better visualization.

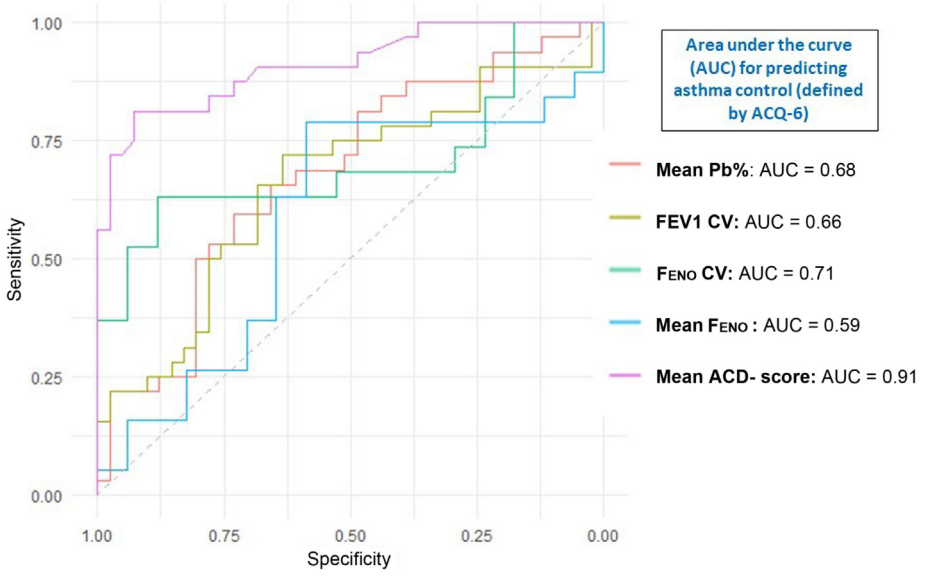

FIGURE 4. ROC curves for the prediction of asthma control at the end of the monitoring period.

that the variability parameters derived from much less frequent monitoring may still provide useful information and warrants further validation.

Practical challenges and limitations

Although the lack of compliance is a major hurdle in implementing asthma home monitoring, we have demonstrated that even with significant missing data, home spirometry and FENO measurements may still provide useful clinical information. Therefore, it may be that a much less frequent monitoring regimen could be used, and is likely to improve adherence and acceptability. Future research should explore the optimal frequency and timing of measurements (ie, time of the day, baseline vs time of exacerbation) that balances compliance and

performance. It is also important to note that it is possible participants had experienced increased symptoms and/or exacerbations that were unreported during the monitoring period. This could potentially create observational bias and have resulted in misclassification (and underestimation) of major exacerbations. The behavioral patterns of long-term home monitoring in asthma are unclear and should be the subject of future research. Patients may be more motivated to perform home monitoring during periods when they are poorly controlled and less motivated for "routine" checks, although in the current study, patients with uncontrolled asthma and major exacerbations during the monitoring period did not perform significantly more tests than those with better asthma control.

The devices used required patients' manual input of data via the mobile app platform. Therefore, missing data entry may have been due to (1) noncompliance, (2) technical failure of logging results via mobile app platform, (3) device failures/loss, or (4) test failure despite attempts (although unlikely because all patients underwent training). To circumvent some of these problems in the compliance analysis, we included patients who had successfully logged results at least once to eliminate the possibility of technical failure. Although highly unlikely, it is also possible that the devices were lost or damaged during this period. We also note that manual input of data (for both spirometry and FENO) is prone to errors (as for the widely used written peak flow charts). Although it was clear that some data points were due to error and could be reliably discarded, it is possible that more subtly incorrect data could not be identified. Newer generations of spirometry devices allow full reports to be uploaded automatically, potentially circumventing some of the challenges we experienced. Nevertheless, a fully automated and user-friendly platform integrating lung function, breath biomarkers, and other asthma-related outcomes is needed.

Our study was limited by a fairly small sample size. The predictive efficiency using AUROCC demonstrate a wide 95% CI, indicating significant uncertainty in sensitivity and specificity of the parameters. Therefore, it is imperative to externally validate our findings in a larger group of patients. Although hand-held spirometry is becoming more affordable, domiciliary FENO may be less scalable due to high cost. Nevertheless, our finding highlights the importance of monitoring variability in airway inflammation in asthma and supports future development in this area.

CONCLUSION

Despite poor adherence to home monitoring, we have shown that markers of airflow obstruction and inflammation are associated with asthma exacerbations and can be useful in predicting asthma control. However, poor compliance during the monitoring period can pose a significant challenge in data interpretation and results in observational bias; this should be acknowledged and addressed in future research. Unsupervised spirometry needs to be interpreted with caution, and clinical context must be taken into account. Future research should be aimed at establishing the optimal frequency and timing of measurements to maximize compliance and clinical usefulness.

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TABLE E1. Compliance and associated factors

Patient factors	Median (IQR) of data points available	*P* value
Spirometry compliance		
Sex		
Male (n = 24)	24 (12.2-29.5)	.501
Female (n = 72)	25 (14.8-38.5)	
Internet experience*		
No experience (n = 1)	11	.638
A little experience (n = 5)	20 (19-24)	
A reasonable amount (n = 26)	26.5 (12-40.2)	
A lot of experience (n = 51)	25 (15-40)	
Education†		
University or college or equivalent (n = 44)	22 (13.2-36.5)	.122
Intermediate between secondary level and university (n = 13)	25 (22-47)	
Secondary school (n = 18)	27.5 (19.5-40.8)	
Primary school (n = 4)	29 (23.8-36.2)	
General health‡		
Excellent (n = 3)	41 (38.5-48.5)	.293
Very good (n = 14)	19.5 (15-26.5)	
Good (n = 35)	24 (8-39.5)	
Fair (n = 27)	25 (19-35)	
Bad (n = 4)	25.5 (21.5-27.2)	
Depression		
Present (n = 10)	25 (15-40)	.374
Absent (n = 73)	19 (7.3-33.8)	
FENO compliance		
Sex		
Male (n = 12)	25 (19.5-31.5)	.134
Female (n = 48)	10 (1-27.2)	
Internet experience*		
A little experience (n = 2)	21 (19.5-22.5)	.308
A reasonable amount (n = 20)	23 (5-42.5)	
A lot of experience (n = 29)	20 (7-28)	
Education†		
University or college or equivalent (n = 26)	7.5 (2-24.8)	.180
Intermediate between secondary level and university (n = 9)	6 (1-24)	
Secondary school (n = 13)	25 (14-44)	
Primary school (n = 3)	27 (18-43.5)	
General health‡		
Excellent (n = 3)	1 (1-21.5)	.592
Very good (n = 9)	5 (2-20)	
Good (n = 22)	22.5 (4.5-31.2)	
Fair (n = 14)	16 (2-24.8)	
Bad (n = 3)	25 (17-25.5)	
Depression		
Present (n = 4)	19 (1.5-28.5)	.672
Absent (n = 47)	7.5 (4-12.8)	

*Self-reported patient characteristics based on questionnaires: "How much experience have you got with the internet?"
†Self-reported patient characteristics based on questionnaires: "What is your highest form of education?"
‡Self-reported patient characteristics based on questionnaires: "How would you rate your health in general?"

TABLE E2. The median (IQR) of Pb% within different levels of asthma control

Asthma control and medication escalation parameters	Median (IQR) Pb%
ACD-6 score–defined asthma control	89 (81-94)
Well controlled (n = 931 measurements)	
Partially controlled (n = 650 measurements)	88 (80-93)
Poorly controlled (n = 688 measurements)	82 (70-90)
Medication escalation	
No medication change (n = 1879 measurements)	87 (79-93)
Increased inhaler use (n = 240 measurements)	84 (75-91)
Use of OCS or hospital attendance (n = 75 measurements)	77 (63-92)

TABLE E3. FEV_1, FENO, and ACD-6 score during escalation of medications

Lung function, FeNO and asthma control parameters	No medication change	Increased inhaler use	OCSs or hospital attendance
FENO* (ppb) [n of data points]	18 (13-27) [887]	17 (13-23) [134]	11 (7.5-23.5) [51]
FEV_1 (L)† [n of data points]	2.36 (0.92) [1879]	2.40 (0.85) [240]	2.0 (0.86) [75]
ACD-6 score* [n of data points]	0.83 (0.33-1.5) [1977]	1.83 (1.33-2.5) [247]	3.42 (2.33-4.63) [78]

ppb, Parts per billion.
*Median (IQR).
†Mean ± SD.

TABLE E4. Univariate mixed-effect logistic regression model to predict same-day treatment escalation (increase in inhalers, OCSs, or hospital attendances).

Lung function, FeNO and asthma control	OR (95% CI)	*P* value
Pb% of <70% personal best*	1.63 (1.03-2.58)	.037
FENO (ppb)	1.00 (0.99-1.02)	.557
ACD-6 score (points)	19.5 (12.9-29.5)	<.001

*As categorical variable.

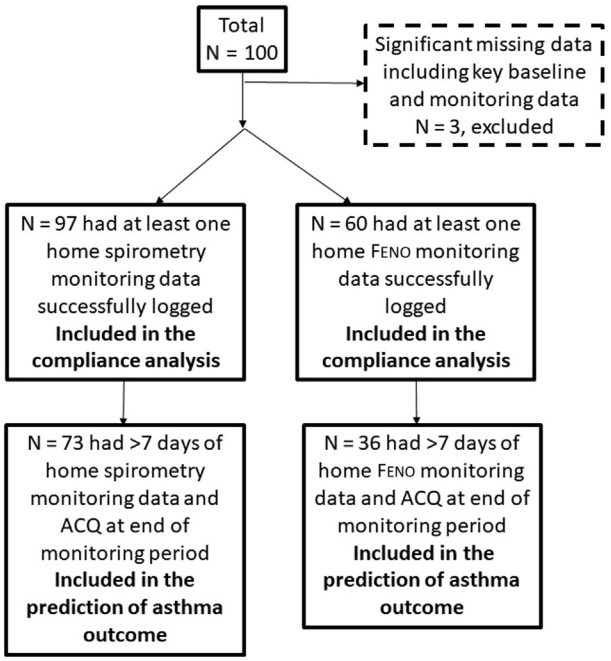

FIGURE E1. Inclusion and exclusion of population and measurements.

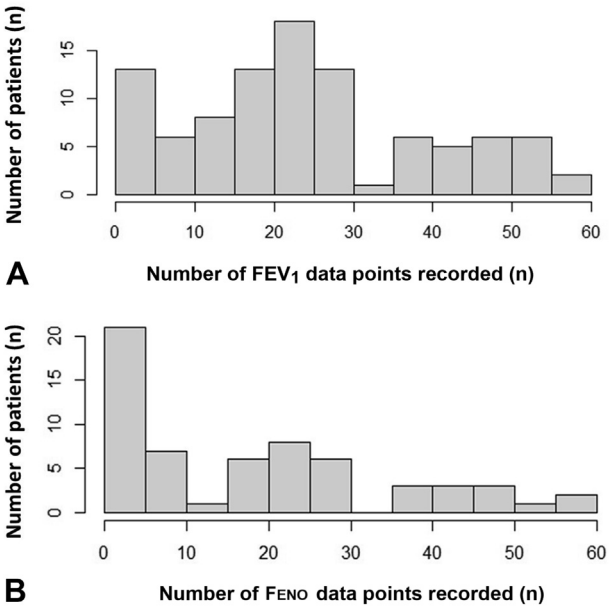

FIGURE E2. Histogram of (**A**) FEV_1 and (**B**) FENO data points during the monitoring period.

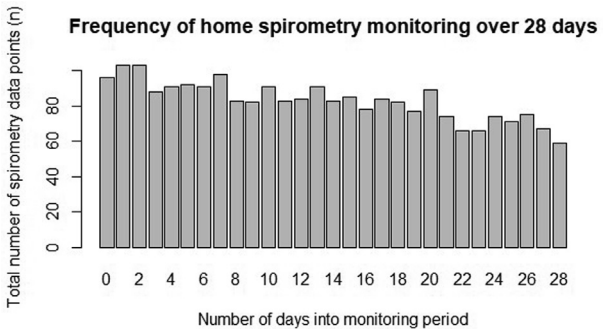

FIGURE E3. Frequency of spirometry monitoring over the 4 weeks.

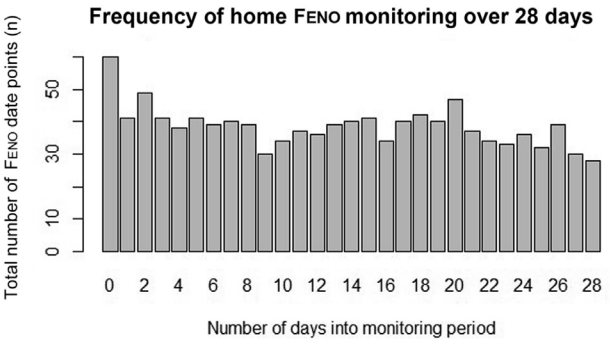

FIGURE E4. Frequency of FENO monitoring over the 4 weeks.

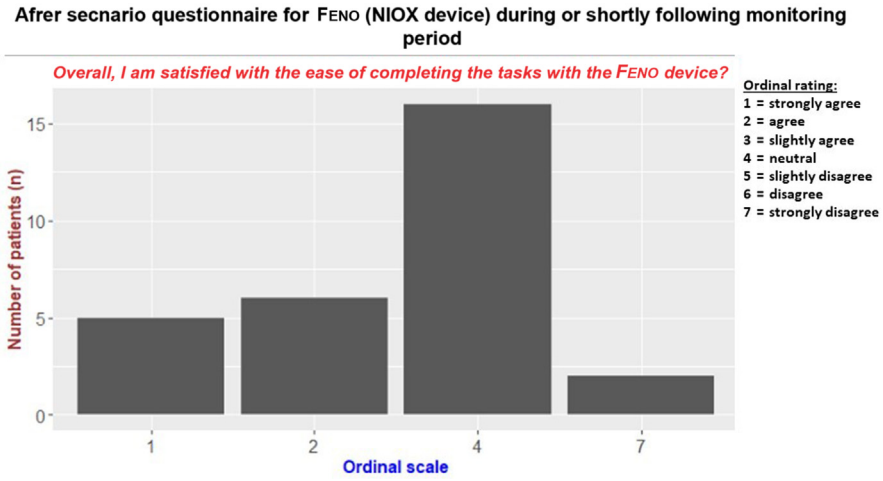

FIGURE E5. After-Scenario Questionnaire for domiciliary FENO use.