Performance of two portable exhaled nitric oxide fraction devices compared to a "gold standard" chemiluminescence device

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Shareable abstract (@ERSpublications)
Study with >100 children looking at the performance of portable devices and their applicability to ERS F_{ENO} cut-offs and asthma diagnosis: the devices agree with ERS cut-offs and can be screening tools; they are dependable and user friendly for children https://bit.ly/48nIIor

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Abstract

Background Recent guidelines for the diagnosis of asthma in schoolchildren recommend the measurement of exhaled nitric oxide fraction (F_{ENO}) as part of the diagnostic algorithm. However, implementation may be hampered by the lack of F_{ENO} devices that are affordable and usable in all healthcare settings. We aimed to compare the performance of two portable F_{ENO} devices (Evernoa (EVE) and NObreath (NOB)) to a stationary "gold standard" device (CLD 88 sp (CLD)) in children.

Methods 106 children aged 6–17 years under investigation or monitoring for asthma underwent F_{ENO} measurements using the three devices in randomised order.

Results All devices showed high repeatability across a wide F_{ENO} range (2.5–191.9 ppb). Median (interquartile range) F_{ENO} levels were significantly lower with the portable devices (20.8 (9.5–43.5), 16 (9–36) and 22.8 (13.2–55.2) ppb for NOB, EVE and CLD, respectively; p<0.0001). Despite the proportional bias (−20% (NOB) and −40% (EVE)), both portable devices demonstrated good overall agreement with CLD (>94%) at a cut-off level of 25 ppb but lower agreement for a cut-off of 35 ppb. EVE required a greater number of attempts compared to NOB and CLD to achieve two valid measurements.

Conclusions Both portable devices showed limited interchangeability with the gold standard, making them less applicable for research and disease monitoring purposes. However, good overall agreement at the European Respiratory Society cut-off level (25 ppb) suggests potential as a simple and convenient screening tool in clinical settings for initial asthma diagnosis.

Introduction

Asthma is a frequent and heterogeneous chronic disease [1] characterised by airway inflammation, reversible airway obstruction and bronchial hyperreactivity [2]. Because obstructive respiratory symptoms are very frequent and non-specific, without objective tests asthma misdiagnosis occurs in up to 50% of children presenting asthma-like symptoms [3–7]. Recent guidelines recommend objective tests, including spirometry and the measurement of exhaled nitric oxide fraction (F_{ENO}), in all schoolchildren with suspected asthma, as part of the diagnostic workup [2, 8]. Based on moderate evidence, the European Respiratory Society (ERS) clinical practice guidelines for the diagnosis of asthma in children aged 5–16 years recommend a F_{ENO} value ⩾25 ppb in a child with asthma symptoms as supportive of a diagnosis of asthma (ERS cut-off) [2], whereas the UK National Institute for Health and Care Excellence (NICE) guideline recommends a F_{ENO} value ⩾35 ppb as a positive test (NICE cut-off) [8]. For these guidelines to be successfully implemented in all healthcare settings, relevant barriers have to be taken into consideration. One important barrier is the availability and affordability of F_{ENO} devices. The cost of stationary devices can be up to 16 times higher than that of portable devices (see supplementary material for the exact cost structure). As a result, stationary devices are currently restricted to specialist care and, in

some less affluent countries, are not even accessible in certain tertiary care settings. The availability of easy-to-use and inexpensive devices is a requirement for broader use of F_{ENO} measurements and hence proper asthma diagnosis in primary and secondary care settings. Most of the evidence for F_{ENO} as part of the asthma diagnosis algorithm derives from measurements with chemiluminescence devices [2], which are expensive, bulky and not suitable for broad use. A recent ERS technical standard on Global Lung Function Initiative (GLI) reference values for F_{ENO} concluded that due to different devices and protocols, available F_{ENO} data were too variable to develop a single reference equation [9]. The authors underscored the need for further standardisation of such devices [9]. More portable devices are coming to market, but the data suggest that these devices are not interchangeable, and it is often unclear how they perform in clinical practice over a full range of exhaled NO concentrations. It is important not only to assess their precision around the cut-offs proposed by the recent guidelines but also the applicability of the measurement setups over the full age range of children between 5 and 16 years. Until now, however, there were limited and mixed results in the literature, with some studies demonstrating high correlation of F_{ENO} levels between the methods [10–16], while others report differences up to 60% in F_{ENO} readings between more affordable and "gold standard" methods [17–23]. Additionally, most research focused on the adult or mixed population, with rather limited data on paediatric applications.

In this study we aimed to compare the performance of two novel electrochemical-based portable F_{ENO} analysers with a well-established stationary chemiluminescence analyser as the reference device. Data were collected in a real-world clinical setting with a population consisting exclusively of paediatric patients. Specific emphasis was given to the F_{ENO} cut-off levels for asthma diagnosis defined by the recent guidelines.

Methods

Participants

Between September 2022 and July 2023, a consecutive cohort of 142 children under investigation for asthma, monitoring of their asthma or allergies, was recruited at the respiratory outpatient clinics of the University Children's Hospital Zurich, Zurich, Switzerland. The study was approved by the cantonal ethics committee (KEK 2022-D0043) and written informed consent was obtained for each participant by the legal representative and, where appropriate, from the child. Clinical and demographic characteristics were collected at the time of assessment. Allergy was defined by demonstrating a positive skin prick test and/or specific IgE. Asthma was defined according to the current international guidelines [2].

F_{ENO} *measurements*

Children underwent F_{ENO} measurements using a single-breath online technique at an expiratory flow of 50 $mL \cdot s^{-1}$ with the following devices: CLD 88 sp (CLD) (Eco Medics, Duernten, Switzerland), Evernoa (EVE) (Eversens, Pamplona, Spain) and NObreath (NOB) (Bedfont, Maidstone, UK). To minimise any potential bias related to the sequence of device usage, we randomised the order in which the devices were used for each subject. Two-point calibration was made daily for the CLD analyser, while the NOB and EVE analysers were pre-calibrated. Prior to each measurement the environmental NO level was measured using the corresponding device. F_{ENO} measurements were performed in the sitting position by qualified lung function personnel and were completed within a 30-min window during the child's visit at the clinic. The measurements were conducted at various times throughout the day between 08:00 and 19:00, reflecting real-world conditions. For every assessment, two technically acceptable measurements were acquired according to the latest American Thoracic Society (ATS)/ERS guidelines [24]. Exhaled NO levels of each of the two measurements were recorded and their mean calculated per device for subsequent analysis. If two acceptable measurements were not achieved within a maximum of eight attempts on each device, the measurement was considered as failed and not included in the analysis. Standard mode was used on the two portable devices as recommended by the manufacturer, resulting in a 12-s exhalation duration for the NOB device and a 10-s duration for the EVE device. Exhalations on the CLD device were conducted until reaching a NO plateau of 2 s for subjects aged <12 years and a NO plateau of 3 s for subjects aged ⩾12 years. These procedures align with the operating instructions for the devices and the latest ATS/ERS guidelines [24]. To prevent room air containing NO in the exhalations, subjects inhaled NO-free air through a mouthpiece (Denox 88; Eco Medics) for the CLD device. For NOB and EVE, the dead space portion of the exhaled air was automatically subtracted by the devices. Each device had an exhalation flow control with audio and/or visual feedback to maintain flow rates at 50±5 $mL \cdot s^{-1}$. Spirometry and other diagnostic procedures were always conducted after the measurements of F_{ENO}.

Statistical analysis

Continuous variables were summarised as medians and interquartile ranges (IQRs) unless otherwise stated, while categorical variables were reported as counts or relative frequencies. Spearman's rank correlation coefficient was used to assess the association between F_{ENO} levels measured by NOB and CLD as well as

EVE and CLD. The Wilcoxon signed-rank test was applied to compare F_{ENO} levels between the portable devices and CLD. The agreement between NOB and CLD and between EVE and CLD was assessed using Bland–Altman plots [25] and Passing–Bablok regression [26]. Bland–Altman plots compared the means of the two methods on the *x*-axis with the differences between the two methods (NOB–CLD and EVE–CLD) on the *y*-axis. Passing–Bablok regression was used to estimate slope and intercept, capturing both proportional and systematic differences between the methods. Systematic bias was defined if the 95% confidence interval of the intercept did not contain the value 0 and proportional bias was defined if the 95% confidence interval of the slope did not contain the value 1. The applicability of the Passing–Bablok procedure was verified using the Cusum test. Furthermore, the ERS [2] and NICE [8] recommended F_{ENO} cut-off limits for asthma diagnosis in children (25 and 35 ppb, respectively) were introduced as categorical variables (</⩾25 and </⩾35 ppb, respectively) for calculating positive percent agreement (PPA), negative percent agreement (NPA) and overall agreement between the methods. Internal consistency of repeated measurements for each instrument was assessed using intraclass correlation coefficients (ICCs) [27]. The success rate to achieve valid measurements was calculated and, among valid measurements, the efficiency on each device to achieve acceptable measurements was evaluated. Only participants with valid measurements from all three devices were included in the analysis. All data were analysed using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of the 142 subjects recruited, 106 (75%) successfully completed measurements on all three devices. 30 (21%) individuals were unable to achieve two acceptable measurements on one of the three devices, with the majority of the failed measurements (21 out of 30) associated with the EVE device. Additionally, six subjects needed to be excluded due to technical issues with the instruments. Baseline characteristics of the population included in the analysis (n=106) are presented in table 1.

F_{ENO} levels spanned a wide range of values from 2.5 to 191.9 ppb. There was a high level of repeatability, with mean±SD ICCs of 0.98±4.60 for NOB, 0.99±1.72 for EVE and 0.99±3.39 for CLD.

Spearman's rank correlation coefficients revealed strong positive associations between the F_{ENO} levels measured by the portable devices and the CLD reference device (NOB: r=0.961; EVE: r=0.972; both p<0.0001). The median (IQR) concentrations were 20.8 (9.5–43.5) ppb for NOB, 16 (9–36) ppb for EVE and 22.8 (13.2–55.2) ppb for CLD. Both portable devices showed significantly lower F_{ENO} values compared to CLD (Wilcoxon signed-rank test, p<0.0001) (figure 1a and 1b). Similarly, the trellis plot [28], illustrating the individual F_{ENO} measurements for each device and subject, revealed a noticeable separation between the CLD and handheld devices, particularly at higher F_{ENO} values (figure 1c).

The Cusum test for linearity confirmed the applicability of the Passing–Bablok regression for both portable devices (p>0.05). Analysis using the coefficients of Passing–Bablok regression revealed the presence of proportional bias (figure 2a and b). More precisely, both portable devices exhibited slopes significantly lower than 1 (NOB 0.8 (95% CI 0.73–0.86) and EVE 0.61 (95% CI 0.56–0.65)), showing that as the F_{ENO} levels measured by CLD increased, the portable devices increasingly underestimated these levels. The

TABLE 1 Baseline characteristics of the study population

Participants	106
Female	40 (37.7)
Age (year)	12.9±2.7
Height (cm)	158.5±15.9
Weight (kg)	51.4±16.4
FVC (L)	3.5±1.2
FVC (z-score)	0.2±1
FEV_1 (L)	2.9±1
FEV_1 (z-score)	−0.3±1.1
Allergic asthma	73 (68.9)
Non-allergic asthma	13 (12.3)
Allergy[#]	75 (70.8)
Others[¶]	11 (10.4)

Data are presented as n, n (%) or mean±SD. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s. [#]: clinically relevant allergic sensitisation to airborne allergens either by skin prick test and/or specific IgE and allergic symptoms; [¶]: chronic cough, wheezing, exercise intolerance (neither asthma subjects nor allergy sufferers).

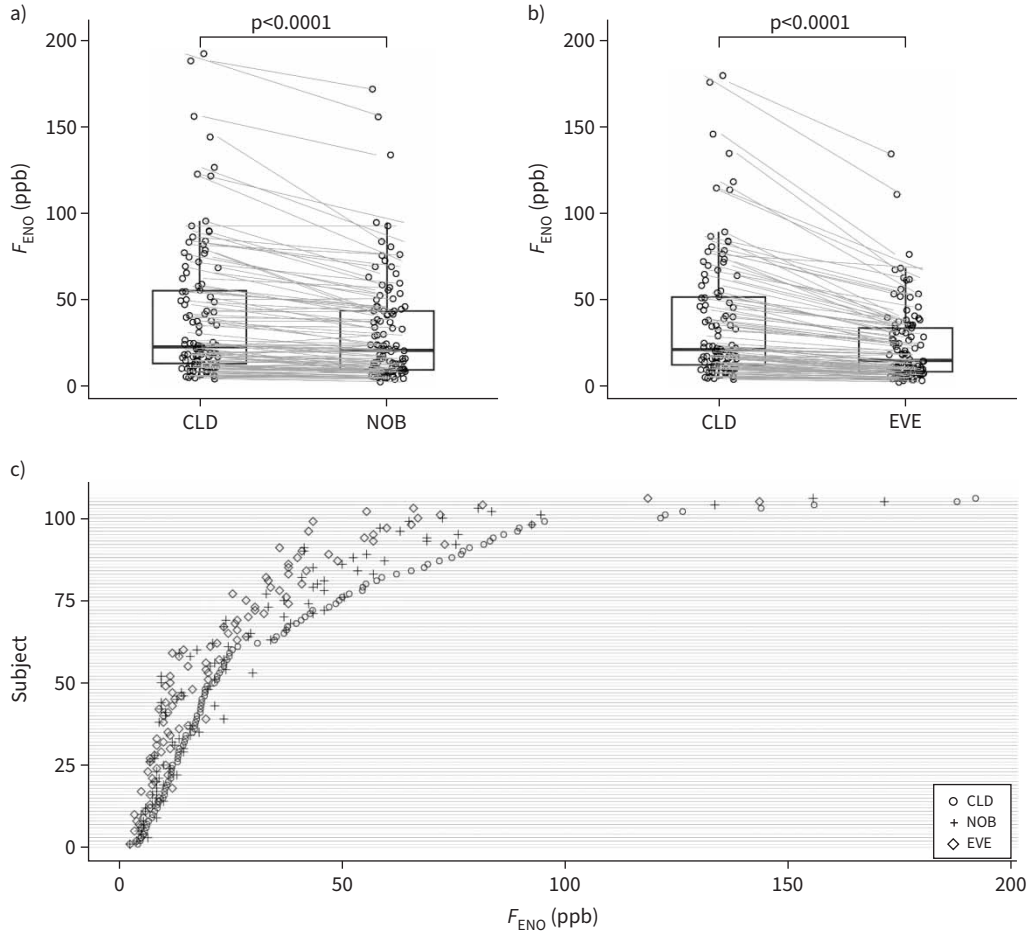

FIGURE 1 Comparison between measured exhaled nitric oxide fraction (F_{ENO}) levels of the handheld devices (NObreath (NOB) and Evernoa (EVE)) and CLD 88 sp (CLD). a, b) Box plots comparing F_{ENO} measurements between a) NOB and CLD and b) EVE and CLD. c) Trellis plot showing individual F_{ENO} measurements (*x*-axis) for each subject (*y*-axis) across the three devices (NOB, EVE and CLD), with subjects ordered by average F_{ENO} values across the three devices. Horizontal grey lines connect the measurements for each subject (n=106).

intercepts were 0.17 (95% CI −0.6–0.98) for NOB and 1.06 (95% CI 0.31–1.82) for EVE, with the intercept for EVE showing a significant positive systematic bias but of small magnitude. To further illustrate the underestimation of F_{ENO} levels by the portable devices, bias was estimated from the Passing–Bablok regression model by $\text{bias}_{(\text{NOB or EVE})}=\text{intercept}_{(\text{NOB or EVE})}+(\text{slope}_{(\text{NOB or EVE})}-1)\times F_{ENO(CLD)}$. For instance, at a decision value of 25 ppb, NOB exhibited a bias of −4.8 (95% CI −6.1– −3.8) ppb and EVE of −8.6 (95% CI −9.4– −8) ppb against CLD. Bias for both portable devices as a function of F_{ENO} levels measured by CLD is displayed in figure 2c and d, with further numerical examples provided in table 2. For a simultaneous illustration, the Passing–Bablok regressions for both portable devices (NOB and EVE) against the reference device (CLD) are shown in a single plot in supplementary figure S1a.

Bland–Altman difference plots illustrated a relationship between measurement differences and F_{ENO} magnitude for both NOB and EVE (figure 3a and b). A simultaneous illustration of the Bland–Altman differences for both devices is presented in supplementary figure S1b. When analysing $\log_{10}$-transformed data, Bland–Altman plots revealed an offset for both portable devices, indicating underestimation on the log scale (figure 3c and d). By back-transforming (antilog) for better interpretability, the geometric mean ratio of the measured levels was 0.79 (95% limits of agreement 0.50–1.25) for NOB and CLD, and the geometric mean ratio for EVE and CLD was 0.66 (95% limits of agreement 0.44–1). This implies that in 95% of the cases NOB measurements might deviate by up to 50% lower to 25% higher than those from the CLD device, while EVE measurements could range from 56% lower to equalling those from the CLD device.

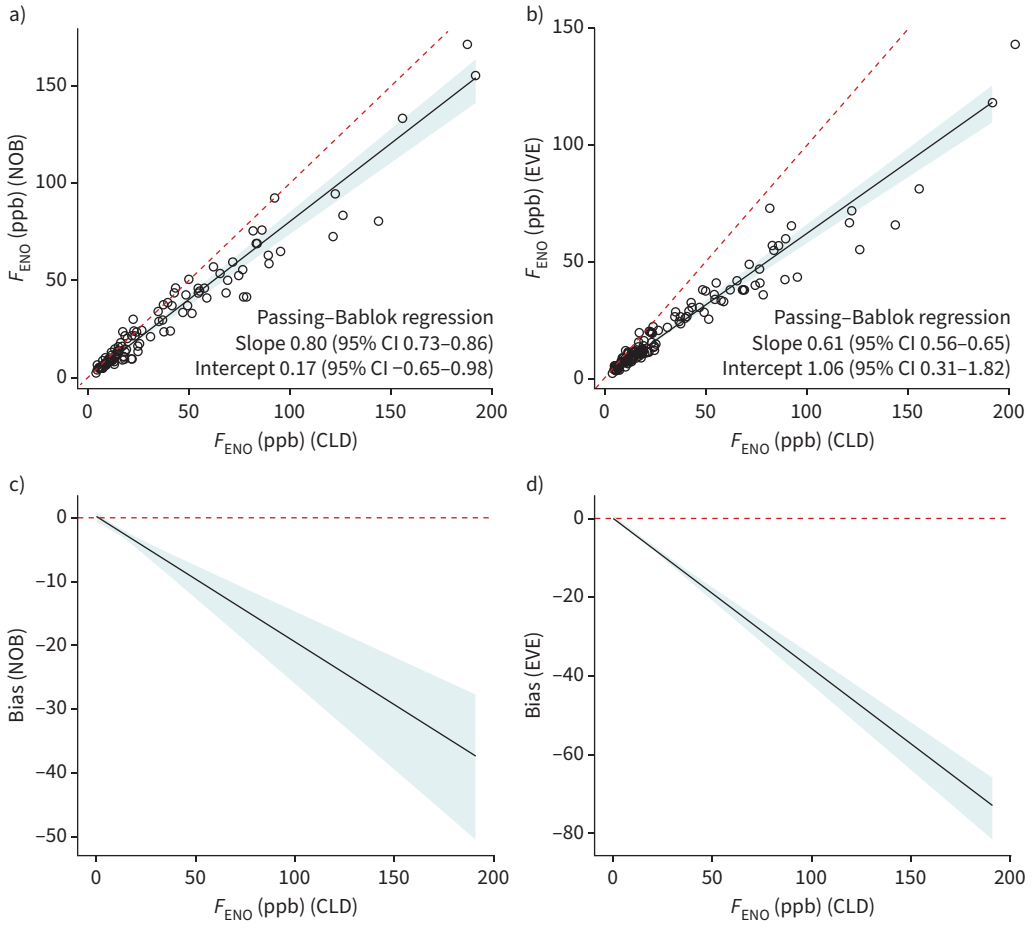

FIGURE 2 Passing–Bablok regression and bias plots. a, b) Passing–Bablok regression. Exhaled nitric oxide fraction (F_{ENO}) values from CLD 88 sp (CLD) (*x*-axis) *versus* F_{ENO} values from a) NObreath (NOB) and b) Evernoa (EVE). The solid black line is the estimated regression line by the Passing–Bablok method, with the red dashed line representing the line of perfect agreement ($y=x$). The shaded area represents the 95% confidence band around the regression line. c, d) Bias plots. The *x*-axis represents F_{ENO} values obtained from the CLD device. The *y*-axis represents the bias for c) NOB and d) EVE. The solid black line represents the estimated bias from the Passing–Bablok model. The shaded area represents the 95% confidence band calculated with the bootstrap quantile method. The red dashed line represents zero bias.

Applying the ERS threshold of 25 ppb, the comparison between NOB and CLD demonstrated an overall agreement of 94.3% (95% CI 88.2–97.4%) with a PPA of 89.4% (95% CI 77.4–95.4%) and a NPA of 98.3% (95% CI 91–99.7%) (table 3). Similarly, comparing EVE to CLD resulted in an overall agreement of 95.3% (95% CI 89.4–98%), with a PPA of 89.4% (95% CI 77.4–95.4%) and a NPA of 100% (95% CI 93.9–100%) (table 3).

With the NICE cut-off threshold of 35 ppb, the comparison between NOB and CLD showed an overall agreement of 94.3% (95% CI 88.2–97.4%) with a PPA of 86% (95% CI 72.7–93.4%) and a NPA of 100%

TABLE 2 Estimated bias (95% CI) for NObreath (NOB) and Evernoa (EVE) from the Passing–Bablok regression model at different exhaled nitric oxide fraction (F_{ENO}) levels

	F_{ENO}			
	25 ppb	**35 ppb**	**50 ppb**	**70 ppb**
Bias by NOB	−4.7 (−6.1– −3.8)	−6.7 (−8.7– −5.3)	−9.7 (−12.5– −7.5)	−13.6 (−17.7– −10.4)
Bias by EVE	−8.6 (−9.4– −8)	−12.5 (−13.8– −11.6)	−18.3 (−20.1– −16.6)	−26.1 (−28.6– −23.5)

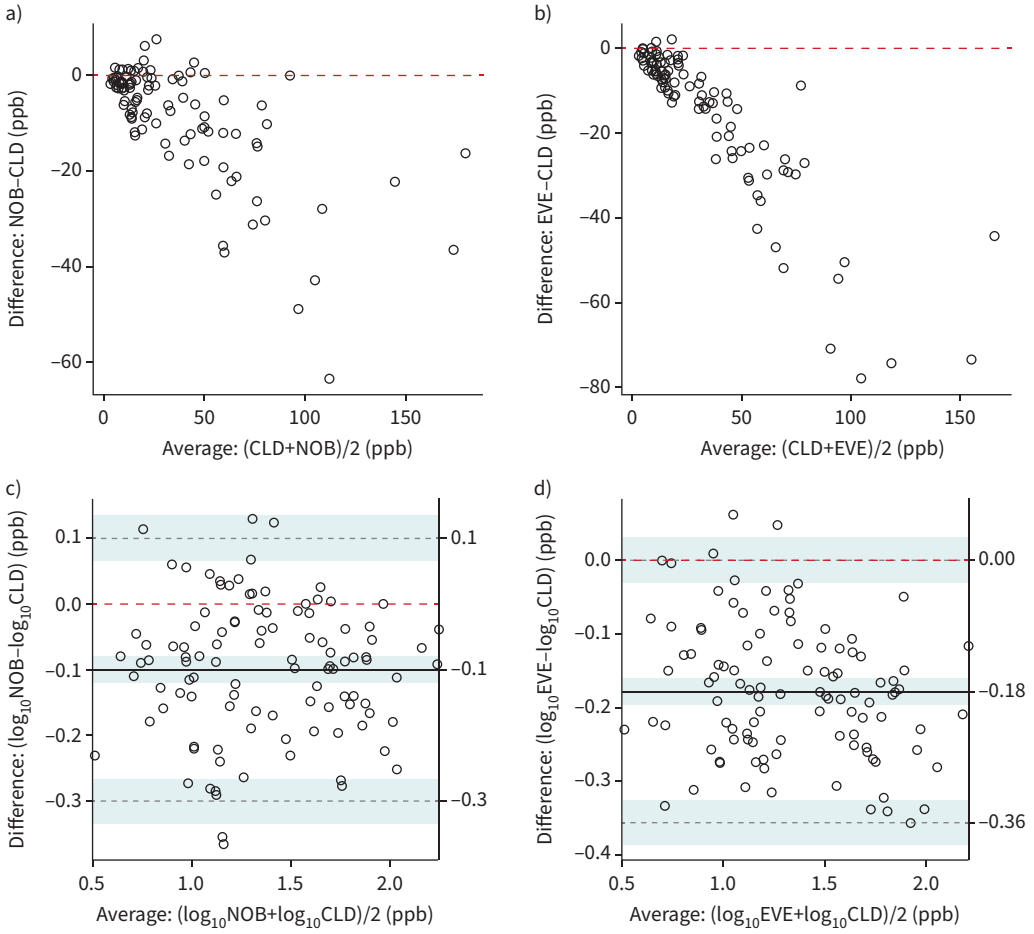

FIGURE 3 Bland–Altman plots. a, b) Mean exhaled nitric oxide fraction (F_{ENO}) values (*x*-axis) and the difference in F_{ENO} values (*y*-axis) between a) NObreath (NOB) and CLD 88 sp (CLD) and b) Evernoa (EVE) and CLD. The dashed red line indicates perfect agreement. c, d) Mean $\log_{10}$-transformed F_{ENO} values (*x*-axis) and the difference in $\log_{10}$-transformed F_{ENO} values (*y*-axis) between c) NOB and CLD and d) EVE and CLD. The solid black line represents the estimated bias, the dashed lines represent the 95% limits of agreement and the shaded areas represent the 95% confidence bands. The dashed red line indicates perfect agreement.

TABLE 3 Contingency tables comparing NObreath (NOB) and CLD 88 sp (CLD) and Evernoa (EVE) and CLD exhaled nitric oxide fraction measurements using the European Respiratory Society recommended threshold of 25 ppb for children (values ⩾25 ppb are assumed to be positive) [2]

	CLD		Total	Overall agreement	Positive percent agreement	Negative percent agreement
	⩾25 ppb	<25 ppb				
NOB				100/106=94.3% (95% CI 88.2–97.4%)	42/47=89.4% (95% CI 77.4–5.4%)	58/59=98.3% (95% CI 91–99.7%)
⩾25 ppb	42	1	43			
<25 ppb	5	58	63			
Total	47	59	106			
EVE				101/106=95.3% (95% CI 89.4–98%)	42/47=89.4% (95% CI 77.4–95.4%)	59/59=100% (95% CI 93.9–100%)
⩾25 ppb	42	0	42			
<25 ppb	5	59	64			
Total	47	59	106			

TABLE 4 Contingency tables comparing NObreath (NOB) and CLD 88 sp (CLD) and Evernoa (EVE) and CLD exhaled nitric oxide fraction measurements using the National Institute for Health and Care Excellence recommended threshold of 35 ppb for children (values ⩾35 ppb are assumed to be positive) [8]

	CLD		Total	Overall agreement	Positive percent agreement	Negative percent agreement
	⩾25 ppb	<25 ppb				
NOB				100/106=94.3% (95% CI 88.2–97.4%)	37/43=86% (95% CI 72.7–93.4%)	63/63=100% (95% CI 94.3–100%)
⩾35 ppb	37	0	37			
<35 ppb	6	63	69			
Total	43	63	106			
EVE				91/106=85.8% (95% CI 78–91.2%)	28/43=65.1% (95% CI 50.2–77.6%)	63/63=100% (95% CI 94.3–100%)
⩾35 ppb	28	0	28			
<35 ppb	15	63	78			
Total	43	63	106			

(95% CI 94.3–100%) (table 4). The comparison between EVE and CLD yielded an overall agreement of 85.8% (95% CI 78–91.2%) with a PPA of 65.1% (95% CI 50.2–77.6%) and a NPA of 100% (95% CI 94.3–100%) (table 4).

The recorded ambient NO levels ranged from 0.1 to 40 ppb, with a median (IQR) of 12 (3–15.36) ppb. No significant correlation was found between the ambient NO readings and the respective measured levels by the three instruments. Similarly, factors such as forced expiratory volume in 1 s (z-score), forced vital capacity (z-score) and gender showed no significant influence. However, age demonstrated a significant correlation with F_{ENO} readings across all three instruments ($p<0.05$), but of a modest and similar magnitude per device (Spearman's rank correlation: NOB, r=0.26; EVE, r=0.27; CLD, r=0.27; all $p<0.01$).

The secondary outcome assessed the efficiency to obtain two acceptable measurements out of a maximum of eight attempts on each device. Among the 106 participants who completed the study, the median number of attempts was two for both NOB and CLD (IQR 2–2.3 and 2–3, respectively). However, participants using the EVE device required a greater number of attempts, with a median of three attempts per participant (IQR 2–5). In particular, 90% of the participants needed a maximum of three attempts to achieve two successful measurements with the NOB and CLD devices, while only 57% of the participants achieved the same with the EVE device.

Discussion

This study investigated the agreement of two portable F_{ENO} devices (EVE and second-generation NOB) with the reference chemiluminescence analyser (CLD). To the best of our knowledge, this is the first such comparison in a paediatric population to date, particularly for the relatively new EVE device. All three instruments showed a high level of repeatability (ICC 0.98–0.99) over a wide range of F_{ENO} values (2.5–191.9 ppb) and consequently it could be suggested that a single technically valid F_{ENO} measurement may be sufficient to determine a valid F_{ENO} value.

Passing–Bablok regression demonstrated the presence of proportional bias, indicating that the portable devices were not interchangeable with the reference device. In estimate, F_{ENO} measurements obtained using NOB were ~20% lower, while measurements obtained with EVE were ~40% lower than those obtained with CLD. Prior comparative studies conducted with the NOB device have led to inconsistent results concerning the interchangeability of F_{ENO} levels, but none of these studies reported that a second-generation NOB device was used for data collection [11, 13, 20, 29]. For the relatively new EVE device, no conclusion can be drawn about the comparability with other analytical devices as there is only one study conducted with the EVE device [30].

Bias plots and the estimated bias at different F_{ENO} values can be used to calculate the mean deviation of the F_{ENO} values measured with the portable devices from the reference device. This makes it possible to approximately assign the F_{ENO} values measured with the NOB or EVE instrument to the reference values measured with the CLD instrument. We show that the F_{ENO} values measured with the portable devices can

deviate from those of the CLD device over a wide range (95% CI −50 to +25% for NOB and 95% CI −56 to +0% for EVE, respectively). Consequently, a single device model may be used in one clinic, and for individual patients the same device should be used over time [15, 22].

Contingency tables using the ERS recommended threshold of 25 ppb for asthma diagnosis in children demonstrated an overall agreement of 94.3% between NOB and CLD and an overall agreement of 95.3% between EVE and CLD [2]. Agreement decreased with higher F_{ENO} values and therefore agreement was lower at the cut-off recommended by the NICE guidelines (35 ppb) [8].

Our study revealed differences in terms of usability between devices. 30 individuals were unable to perform two acceptable measurements on each device, with 21 of the failed measurements being associated with the EVE instrument. Similarly, among the successful measurements, a median of one more attempt was required to achieve at least two acceptable measurements with EVE compared to NOB and CLD. We used the standard mode with both portable devices and still claim that this fact is not related to the stated success rate. In child mode, exhalation time could be reduced from 12 to 10 s by NOB and from 10 to 6 s by EVE. Instead, we observed that children struggled with the audio-visual feedback loop of the EVE instrument, regardless of exhalation time. Its response to flow deviations from the target flow (50 $mL \cdot s^{-1}$) was very sensitive, resulting in failed attempts needing to be repeated. In addition, preparation time for the EVE instrument was required after each acceptable measurement. Such a delay could be inconvenient in an occupational setting, particularly because corrective instructions have to be implemented immediately.

To prevent room air containing NO from biasing the measurements, the different extraction methods were equally effective in our investigation. Despite different extraction methods, we found no clinically relevant bias of ambient NO on the F_{ENO} levels on any device, even for high ambient NO levels.

To obtain successful measurements on all devices, the children had to attempt multiple measurements. While it is possible that the number of attempts may have influenced the results, the randomised order of device usage minimises the likelihood of any systematic bias. We did not observe a trend for F_{ENO} values with measurement attempts; however, the study was not specifically designed to investigate this effect.

There are several limitations to this study. First, the more validated standard application mode was used to collect F_{ENO} data because the majority of our individuals counted two acceptable measurements even with the standard mode. Nevertheless, the comparability and usability of different application modes of NOB and EVE would be another interesting aspect to focus on. Second, our investigation cannot make any statement about the performance of F_{ENO} levels over time, for which longitudinal studies would be necessary. Thus, further studies are needed to address these limitations. The recent ERS technical standard on GLI reference values for F_{ENO} found important heterogeneity between the study sites and F_{ENO} devices [9]. It was not possible to derive a single all-age reference equation for F_{ENO} in healthy individuals. Most data were collected using the NIOX MINO device. Some sites used the NOB device (first generation) and a few used chemiluminescence techniques in addition to others. This underscores the conclusion that different devices may not be interchangeable and there is need for further standardisation [9].

In conclusion, our data confirm that F_{ENO} values measured with the two portable devices were not interchangeable in comparison with the reference device. Contingency tables using the ERS recommended threshold of 25 ppb for asthma diagnosis in children demonstrated a high overall agreement between the two portable devices and the reference device. Therefore, if individuals have elevated F_{ENO} levels of >25 ppb when measured with the portable devices, it is very likely that these F_{ENO} levels would also be >25 ppb when measured with the reference device. Consequently, this suggests potential for both portable devices to be used as a practical tool in clinical settings for the initial diagnosis of asthma. In terms of ease of use, the chance of obtaining valid measurements was higher using NOB and CLD than using EVE, and even valid measurements were achieved in a lower number of attempts. According to our assessment, a feasible feedback loop is a key requirement for children to obtain valid measurements.

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Ethics statement: The study was approved by the cantonal ethics committee (KEK 2022-D0043) and written informed consent was obtained for each participant by the legal representative and, where appropriate, from the child.

Conflict of interest: The authors have no conflicts of interest to declare.

References

1 van den Akker-van Marle ME, Bruil J, Detmar SB. Evaluation of cost of disease: assessing the burden to society of asthma in children in the European Union. *Allergy* 2005; 60: 140–149.
2 Gaillard EA, Kuehni CE, Turner S, *et al.* European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5–16 years. *Eur Respir J* 2021; 58: 2004173.
3 Danvers L, Lo DKH, Gaillard EA. The role of objective tests to support a diagnosis of asthma in children. *Paediatr Respir Rev* 2020; 33: 52–57.
4 Aaron SD, Boulet LP, Reddel HK, *et al.* Underdiagnosis and overdiagnosis of asthma. *Am J Respir Crit Care Med* 2018; 198: 1012–1020.
5 Lai CKW, Beasley R, Crane J, *et al.* Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009; 64: 476–483.
6 Looijmans-van den Akker I, van Luijn K, Verheij T. Overdiagnosis of asthma in children in primary care: a retrospective analysis. *Br J Gen Pract* 2016; 66: e152–e157.
7 Yang CL, Simons E, Foty RG, *et al.* Misdiagnosis of asthma in schoolchildren. *Pediatr Pulmonol* 2017; 52: 293–302.
8 National Institute for Health and Care Excellence. Asthma: Diagnosis, Monitoring and Chronic Asthma Management. NICE Guideline NG80. 2021. www.nice.org.uk/guidance/ng80 Date last accessed: 26 December 2024.
9 Högman M, Bowerman C, Chavez L, *et al.* Global Lung Function Initiative reference values for exhaled nitric oxide fraction (F_{ENO50}). *Eur Respir J* 2024; 63: 2300370.
10 Korn S, Wilk M, Voigt S, *et al.* Measurement of fractional exhaled nitric oxide: comparison of three different analysers. *Respiration* 2020; 99: 1–8.
11 Antus B, Horvath I, Barta I. Assessment of exhaled nitric oxide by a new hand-held device. *Respir Med* 2010; 104: 1377–1380.
12 Pisi R, Aiello M, Tzani P, *et al.* Measurement of fractional exhaled nitric oxide by a new portable device: comparison with the standard technique. *J Asthma* 2010; 47: 805–809.
13 Yune S, Lee JY, Choi DC, *et al.* Fractional exhaled nitric oxide: comparison between portable devices and correlation with sputum eosinophils. *Allergy Asthma Immunol Res* 2015; 7: 404–408.
14 Schiller B, Hammer J, Barben J, *et al.* Comparability of a hand-held nitric oxide analyser with online and offline chemiluminescence-based nitric oxide measurement. *Pediatr Allergy Immunol* 2009; 20: 679–685.
15 Boot JD, de Ridder L, de Kam ML, *et al.* Comparison of exhaled nitric oxide measurements between NIOX MINO electrochemical and Ecomedics chemiluminescence analyzer. *Respir Med* 2008; 102: 1667–1671.
16 Olaguíbel JM, Parra A, Alvarez MJ, *et al.* Measurements of fractional exhaled nitric oxide with 2 portable electrochemical sensors: a comparative study. *J Investig Allergol Clin Immunol* 2011; 21: 322–323.
17 Brooks CR, Brogan S-BM, van Dalen CJ, *et al.* Measurement of exhaled nitric oxide in a general population sample: a comparison of the Medisoft HypAir FE_{NO} and Aerocrine NIOX analyzers. *J Asthma* 2011; 48: 324–328.
18 Endo Y, Shirai T, Akamatsu T, *et al.* Comparison of fractional exhaled nitric oxide levels measured using the NIOX VERO and NOA 280i. *Ann Allergy Asthma Immunol* 2017; 119: 383–385.
19 Korn S, Telke I, Kornmann O, *et al.* Measurement of exhaled nitric oxide: comparison of different analysers. *Respirology* 2010; 15: 1203–1208.
20 Kapande KM, McConaghy LA, Douglas I, *et al.* Comparative repeatability of two handheld fractional exhaled nitric oxide monitors. *Pediatr Pulmonol* 2012; 47: 546–550.
21 Borrill Z, Clough D, Truman N, *et al.* A comparison of exhaled nitric oxide measurements performed using three different analysers. *Respir Med* 2006; 100: 1392–1396.
22 Saito J, Kikuchi M, Fukuhara A, *et al.* Comparison of fractional exhaled nitric oxide levels measured by different analyzers produced by different manufacturers. *J Asthma* 2020; 57: 1216–1226.
23 Tanabe Y, Harada N, Ito J, *et al.* Difference between two exhaled nitric oxide analyzers, NIOX VERO electrochemical hand-held analyzer and NOA280i chemiluminescence stationary analyzer. *J Asthma* 2019; 56: 167–172.

24 American Thoracic Society/European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005; 171: 912–930.

25 Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999; 8: 135–160.

26 Passing H, Bablok. A new biometrical procedure for testing the equality of measurements from two different analytical methods. Application of linear regression procedures for method comparison studies in clinical chemistry, part I. *J Clin Chem Clin Biochem* 1983; 21: 709–720.

27 Armitage P, Berry G, Matthews JNS. Statistical Methods in Medical Research. Malden, Blackwell, 2001.

28 Choudhary PK, Nagaraja HN. Measuring Agreement: Models, Methods, and Applications. Hoboken, Wiley, 2017.

29 Kang S-Y, Lee SM, Lee SP. Measurement of fractional exhaled nitric oxide in adults: comparison of two different analyzers (NIOX VERO and NObreath). *Tuberc Respir Dis* 2021; 84: 182–187.

30 Olaguibel A, Oleaga M, Iraola A, *et al.* Exhaled nitric oxide (eNO) measurements with the new Evernoa device are valid and reproducible through an extended range of eNO levels. *J Investig Allergol Clin Immunol* 2020; 30: 147–149.