



Use of exhaled nitric oxide in the diagnosis and monitoring of childhood asthma: myth or maxim?

Anna Fraser^{1,2}, Ruairaidh Simpson^{1,2} and Steve Turner ¹

¹Child Health, Women and Children's Division, NHS Grampian, Aberdeen, UK. ²Joint first authors.

Corresponding author: Steve Turner (s.w.turner@abdn.ac.uk)



Shareable abstract (@ERSpublications)

Guidelines recommend F_{ENO} as a second-line test for diagnosing asthma in children. F_{ENO} -guided treatment is associated with reduced odds of exacerbation, but it is unclear how F_{ENO} should be incorporated into pathways of asthma care. <https://bit.ly/3roh6hG>

Cite this article as: Fraser A, Simpson R, Turner S. Use of exhaled nitric oxide in the diagnosis and monitoring of childhood asthma: myth or maxim? *Breathe* 2023; 19: 220236 [DOI: 10.1183/20734735.0236-2022].

Copyright ©ERS 2023

Breathe articles are open access and distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0.

Received: 25 Aug 2023
Accepted: 14 Sept 2023

Abstract

Asthma is a common condition in children. This review describes the evidence from the literature and international asthma guidelines for using fractional exhaled nitric oxide (F_{ENO}) in the diagnosis and monitoring of childhood asthma. The accuracy of F_{ENO} measuring devices could be further improved, the difference in F_{ENO} results between devices are equivalent to what is considered a clinically important difference. For diagnosing asthma no guideline currently recommends F_{ENO} is used as the first test, but many recommend F_{ENO} as part of a series of tests. A cut-off of 35 ppb is widely recommended as being supportive of an asthma diagnosis, but evidence from children at risk of asthma suggests that a lower threshold of 25 ppb may be more appropriate. Nine randomised clinical trials including 1885 children have added F_{ENO} to usual asthma care and find that exacerbations are reduced when care is guided by F_{ENO} (OR for exacerbation compared to usual care 0.77, 95% CI 0.62–0.94). What is not clear is what cut-off(s) of F_{ENO} should be used to trigger a change in treatment. After 30 years of intensive research there is not sufficient evidence to recommend F_{ENO} for routine diagnosing and monitoring asthma in children.

Educational aims

- To give the reader an overview of literature that supports and does not support the role of F_{ENO} in diagnosing asthma in children.
- To give the reader an overview of literature that supports and does not support the role of F_{ENO} in monitoring asthma in children.
- To give the reader an understanding of the role of F_{ENO} in international guidelines for diagnosing and monitoring asthma in children.

Introduction

Childhood asthma is a condition with complex underlying mechanisms and is characterised by symptoms of cough and wheeze and difficulty in breathing [1]. The aetiology of asthma remains uncertain and seems likely to involve interactions between genetic and environmental factors, resulting in a spectrum of different clinical presentations with common symptoms and which respond to similar treatment [2]. Asthma affects millions of children around the world [3, 4], causes morbidity by disrupting sleep and limiting activities, and can be life-threatening when symptoms are severe during an asthma exacerbation. There is no cure for asthma, but there are effective treatments to prevent symptoms and exacerbations. Despite being so common, there is no universally accepted definition of asthma and no single test for diagnosing or monitoring symptoms.



Childhood-onset asthma is associated with diagnoses of eczema, hayfever and food allergies, and individuals with childhood-onset asthma characteristically have an immune system where T-helper type 2 (Th2) cells [5] predominate. These Th2 cells preferentially release mediators, including interleukin (IL)-4, IL-5 and IL-13, which are implicated in causing the pathological findings seen in the airways of children with asthma, *e.g.* airway eosinophilia.

Airway eosinophilia is considered a key feature of childhood asthma, and therefore a potential objective outcome which could support asthma diagnosis, monitoring and treatment. Airway eosinophilia is determined from airway biopsy or from induced sputum, but neither of these is readily available in children, which severely limits their application to routine clinical practice. Fractional exhaled nitric oxide (F_{ENO}) is positively correlated to airway eosinophilia in both airway mucosal biopsies [6] and induced sputum [7–9], can be measured in the clinical setting, without discomfort to the patient, results are available within a minute and all at a reasonable price [10].

Nitric oxide (NO) is a diatomic molecule which was considered as an air pollutant until the 1980s when it was recognised as having multiple key roles in both health and illness, most notably as being synonymous with “endothelial derived relaxing factor” and explaining why glycerine trinitrate was an effective treatment for angina. By the time NO was voted molecule of the year in 1992 it was seen as being key to multiple roles in health and disease including causing vasodilation, smooth muscle hypertrophy and reducing platelet adhesion. A family of enzymes called nitric oxide synthases (NOS) produce NO; constitutional NOS produces NO for physiological purposes and NO associated with diseases such as asthma arises from the action of inducible NOS [11]. Gaseous NO was identified in exhaled breath in 1993 [12], prompting 30 years of research into the potential use of F_{ENO} in asthma diagnosis, monitoring and treatment.

Measuring F_{ENO}

Exhaled NO concentrations are inversely proportional to expiratory flow and by consensus are measured at $50 \text{ mL}\cdot\text{s}^{-1}$ [13]. The flow dependence of F_{ENO} has been used to derive alveolar NO and central airway NO flux; these flow-dependent parameters are not discussed further in this article and the interested reader is referred elsewhere [14]. Despite standardisation of flow to measure F_{ENO} , there are marked differences in F_{ENO} measurements when analysers made by different manufacturers are used by the same person [15], meaning that measurements from different analysers are not directly comparable.

F_{ENO} analysers have visual/audio aids to encourage the patient to exhale at the correct flow; this is particularly useful in paediatrics. F_{ENO} can only be measured passively in infants [16], but children aged ≥ 5 years can exhale into apparatus for F_{ENO} measurements to be obtained [17]. The apparatus is very transportable and this allows F_{ENO} measurements to be made in children in community and hospital settings [17, 18].

This article reviews the current evidence for F_{ENO} being a useful tool to diagnose and monitor asthma in children aged ≥ 5 years. A related article reviews the relevant literature for the role of spirometry in diagnosing and monitoring asthma in this age group [19].

Exhaled NO to diagnose asthma

What is the evidence that F_{ENO} may help diagnose asthma?

For >25 years, children with asthma have been known to have higher F_{ENO} concentrations compared to children without asthma [20]. However, the relationship between asthma and elevated F_{ENO} is not exclusive [21]; for example children without asthma but who have allergy and/or bronchial hyperresponsiveness also have elevated F_{ENO} [22]. There are many non-asthma-related and non-allergy-related factors associated with elevated F_{ENO} values [13, 23] including increasing age [13] and height [13], ingestion of food or drink containing arginine [24] and caffeine [25]. F_{ENO} values vary through the day (in adults this diurnal variation may be clinically useful [26]) and are reported to differ between ethnic groups [27]. Exposures that may be associated with reduced F_{ENO} include upper respiratory tract infection, active and passive smoking [13] and doing spirometry [28]. Many of the associations described here are not replicated in all populations and the magnitude of difference in F_{ENO} is generally small, *e.g.* <5 ppb, meaning that these individual factors may not be relevant to clinical interpretation. However, these factors might combine to have a “clinically meaningful” effect in F_{ENO} values, *e.g.* make F_{ENO} values “high” or result in a “significantly different” change in repeated F_{ENO} measurements.

The best level of evidence for F_{ENO} as a diagnostic tool comes from a small number of studies where children with undifferentiated respiratory symptoms had F_{ENO} measured and then were categorised as either having asthma or not having asthma. A recent European Respiratory Society (ERS) task force [29] identified five studies with this design and found that there was a relationship between increasing F_{ENO}

concentrations and increasing likelihood of asthma; additionally, decreasing F_{ENO} concentrations were associated with a decreasing likelihood of asthma.

What cut-off value in F_{ENO} defines abnormality?

There is no consistency in which cut-off should be used when considering with a diagnosis of asthma in children. The most commonly used values of <20 ppb being “normal” and >35 ppb being “elevated” [13] comes from normative data within a cross-sectional whole-population study [30]. This cut-off of >35 ppb is defined as positive by both UK asthma guidelines [31, 32] and also the National Asthma Education and Prevention Program (United States of America) [33]. The American Thoracic Society (ATS) states that values >35 ppb identify a child whose symptoms are steroid responsive [34]. The assumption that a cut-off based on normative data within the general population can be extrapolated to a cut-off for diagnosing asthma is not unreasonable, but elevated F_{ENO} is present in children without asthma [21, 22]. The previously mentioned ERS task force used data from children presenting with possible asthma symptoms and found that values >25 ppb had best sensitivity and specificity for diagnosing asthma and values <19 ppb for excluding an asthma diagnosis [29].

While F_{ENO} is usually expressed in parts per billion, attempts have been made to standardise concentrations, similar to percentage predicted or z-score values of forced expiratory volume in 1 s (FEV_1). One group standardised F_{ENO} for height using data from two UK populations and found that concentrations above the 90th centile (equivalent to 25 ppb in a 10-year-old boy of average height) has 59% sensitivity, 96% specificity, 97% positive predictive value and 50% negative predicted value [35].

Recognising that factors such as age, sex, height and ethnicity are associated with different F_{ENO} concentrations, it would be desirable to have predicted normal values for F_{ENO} , similar to those that we have for spirometry. An ERS task force has attempted to apply Global Lung Initiative methodology [36] to produce individualised “norms” for F_{ENO} , but has found it was not able to derive age-, gender- and ethnic-specific normative values [37]. This was because the variation in F_{ENO} measurements between centres contributing data was too wide, even when a subgroup of centres who used the same device was considered. In the meantime, the cut-off values of >25 ppb and >35 ppb remain the most pragmatic way of determining “high” or “low” values. In summary, there is no agreed cut-off value of F_{ENO} to support a diagnosis of asthma in children. All guidelines emphasise that asthma is a clinical diagnosis which is primarily based on the presence of episodic cough and wheeze and difficulty in breathing, and that one (or ideally two) objective tests can usefully support a diagnosis (or help exclude a diagnosis). So the absence of an agreed cut-off does not prevent a diagnosis being made. A very high or very low F_{ENO} can be useful to clinicians, but both can occur in children with asthma and without asthma.

Where does F_{ENO} sit in the diagnostic hierarchy?

Due to the lack of precision of F_{ENO} for asthma, no guideline recommends F_{ENO} as the first-line diagnostic test. Figure 1 shows that spirometry is the first-line test recommended by all guidelines. F_{ENO} is recommended by the ERS task force [29] and the UK National Institute for Health and Care Excellence [32] where lung function is normal. F_{ENO} is also recommended for diagnosis by the Scottish Intercollegiate Guidelines Network/British Thoracic Society [31] after lung function testing and bronchodilator reversibility, if there is an intermediate probability of asthma. The Global Initiative for Asthma says that “ F_{ENO} has not been established as useful for ruling in or ruling out a diagnosis of asthma...it is also elevated in non-asthma conditions” [1].

How do these guidelines perform in real life?

A study of 514 children aged 5–17 years where F_{ENO} was measured and in whom an asthma diagnosis was subsequently given in 357 has reported sensitivities and specificities for different F_{ENO} cut-offs (table 1) [38]. A second whole-population study of 630 13–16-year-old children, including 34 on regular inhaled corticosteroids (ICS) has also reported the relationship between increasing F_{ENO} cut-offs for diagnosed asthma (table 1) [39]. Table 1 presents sensitivities and specificities of different F_{ENO} cut-offs for asthma from three different sources [29, 38, 39].

At cut-off values of >24 or >25 ppb, the sensitivity (*i.e.* precision for ruling out asthma) of F_{ENO} is lower for children at a higher risk of asthma [29, 38] and the specificity (*i.e.* precision for ruling in asthma) is higher compared to children selected from the general population [39] (table 1). Applying a cut-off of >35 ppb, the sensitivity of F_{ENO} remains lower in children at higher risk of asthma [29] compared to a group not selected for asthma [39], but the specificity is the same (table 1). This suggests that a lower cut-off (*e.g.* >25 ppb) than the currently recommended concentration of >35 ppb may be more useful in children where a diagnosis of asthma is being considered.

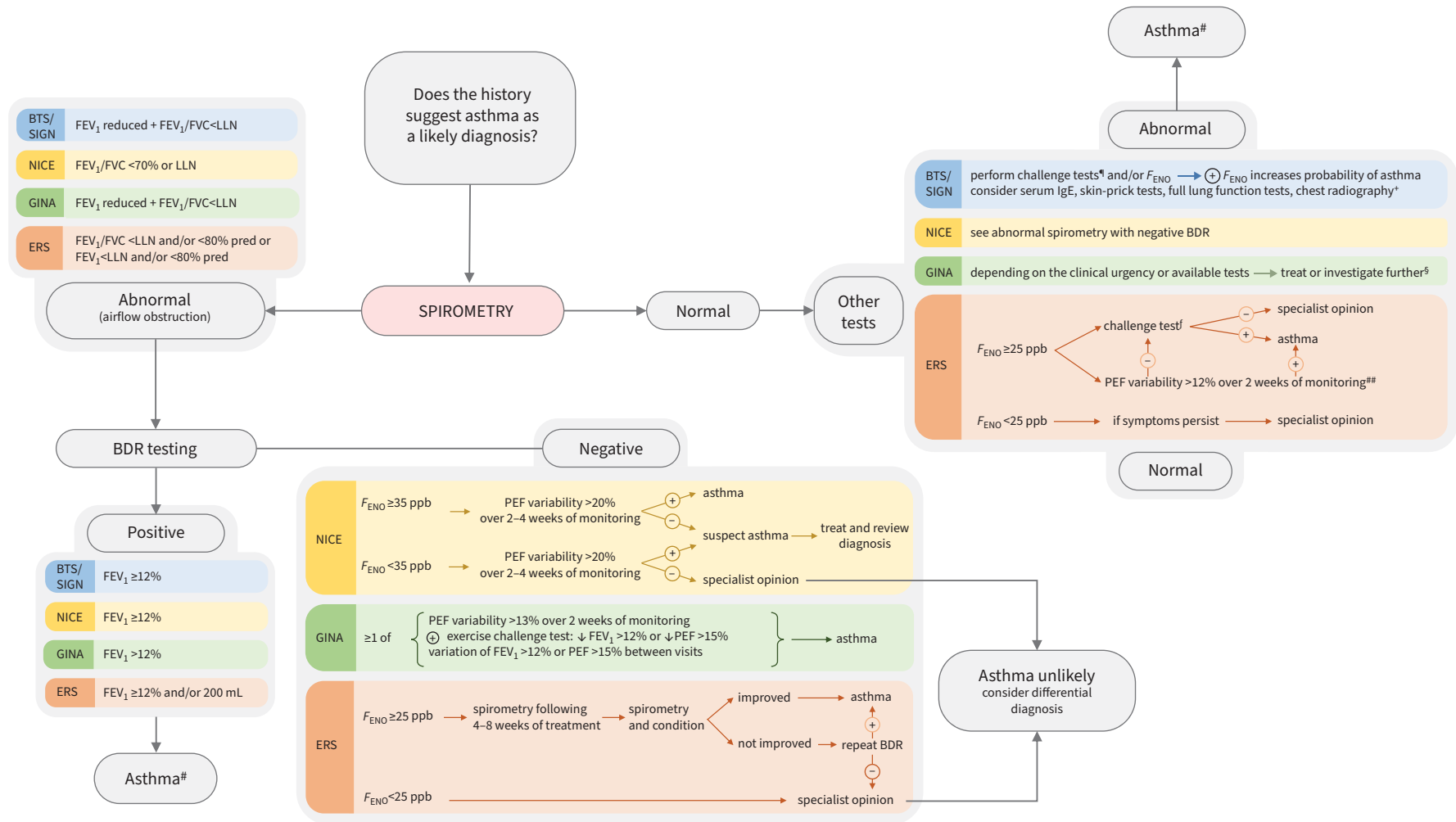


FIGURE 1 A summary of the place of spirometry in diagnostic algorithms from current guidelines. BTS: British Thoracic Society; SIGN: Scottish Intercollegiate Guidelines Network; NICE: National Institute for Health and Care Excellence; GINA: Global Initiative for Asthma; ERS: European Respiratory Society; FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; LLN: lower limit of normal; F_{ENO}: fractional exhaled nitric oxide; BDR: bronchodilator responsiveness; PEF: peak expiratory flow; ⊕: positive; ⊖: negative. [#]: BTS/SIGN uses high probability/intermediate/low probabilities of asthma as part of the diagnostic algorithm. A patient in the high-probability category has an increased probability of having asthma if spirometry shows airflow obstruction reversible to bronchodilator; a child who is in the intermediate category can have asthma diagnosis confirmed if spirometry is abnormal and has significant responsiveness to bronchodilator; [†]: direct challenge tests (methacholine challenge test positive if provocative concentration causing a 20% fall in FEV₁ ≤ 8 mg·mL⁻¹; mannitol test positive if fall in FEV₁ ≥ 15% at cumulative dose of ≤ 635 mg), indirect challenge test (exercise challenge positive range: 8–20% fall in FEV₁); [‡]: indicated for children with severe disease or clinical suspicion of other conditions; [§]: GINA guideline provides two options in case the patient is on controller treatment and requires asthma diagnosis confirmation: in case there are variable respiratory symptoms but spirometry is normal, the recommendation is to consider repeating spirometry either when withholding bronchodilator or the patient is symptomatic. In case there are lesser respiratory symptoms and spirometry is normal, bronchodilator testing can be repeated when symptomatic or when temporarily stopping bronchodilator; ^f: direct bronchial challenge test with methacholine or indirect bronchial challenge tests by using either a treadmill, bike or both; ^{##}: PEF variability would be an inferior choice to challenge tests and could be used if challenge tests are not available.

TABLE 1 Sensitivity and specificity of fractional exhaled nitric oxide (F_{ENO}) for diagnosing asthma from three studies

	F_{ENO} ppb	Sensitivity %	Specificity %
MURRAY <i>et al.</i> [39]	$\geq 24^{\#}$	63 [#]	73 [#]
	≥ 35	52	83
	≥ 40	46	87
DE JONG <i>et al.</i> [38]	≥ 20	52	77
	≥ 21	50	80
	≥ 23	48	87
	$\geq 25^{\#}$	46 [#]	88 [#]
ERS task force [29]	>15	75	61
	>20	58	68
	>25 [#]	57 [#]	81 [#]
	>30	44	79
	>35	36	81

The study by MURRAY *et al.* [39] was based on a population not selected for asthma, whereas the remaining studies used data from children referred to hospital with possible asthma. ERS: European Respiratory Society. #: at values of 24 or 25 ppb, the sensitivity of F_{ENO} is lower and the specificity is higher for children at a higher risk of asthma compared to children in the general population.

Why might F_{ENO} be useful to monitor asthma?

What is the evidence?

There is persuasive evidence that F_{ENO} should be a useful measurement to support monitoring of asthma, including making treatment decisions, in order to reduce exacerbations.

- 1) F_{ENO} concentrations rose after reducing ICS dose in a study of 40 children [40]: the results suggest that odds of ICS reduction being successful were six times higher when F_{ENO} was ≥ 22 ppb compared to < 22 ppb.
- 2) F_{ENO} concentrations rose before symptoms relapsed after stopping ICS in one study of 40 children [41]; a F_{ENO} of ≥ 49 ppb has the best combination of sensitivity and specificity for predicting relapse. This finding was not replicated in a second study of 32 children [42].
- 3) F_{ENO} concentrations fall after treatment with oral corticosteroids for an asthma exacerbation [43, 44].
- 4) F_{ENO} concentrations fell by 35% in 11 children after commencing treatment with leukotriene receptor antagonist (LTRA) and rose when LTRA was stopped [45].
- 5) F_{ENO} levels fell by 40% after starting anti-IgE biological treatment [46].

To balance this convincing evidence, there are some results which need to be considered when evaluating the role of F_{ENO} in monitoring asthma:

- 1) Combined data from eight randomised clinical trials found no evidence that F_{ENO} -guided asthma treatment improves asthma control [47].
- 2) A trial of 55 children found no evidence that sputum eosinophil count (the physiological characteristic which F_{ENO} is a proxy for) was a useful guide for asthma treatment in children [48].
- 3) F_{ENO} values remain high in some individuals despite high-dose ICS treatment [49].
- 4) F_{ENO} is not sensitive to ICS adherence in children. One study of 130 children found no relationship between F_{ENO} values and adherence to ICS adherence [50], and a second, of 93 children with severe asthma, found a weak relationship between poor ICS adherence and elevated F_{ENO} [51].
- 5) One study of 1112 children, using data from six clinical trials whose intervention was to add F_{ENO} to usual care to guide asthma treatment, found that rising F_{ENO} over a 3-month period was not associated with risk of subsequent exacerbations [52].
- 6) At the time of writing there are no clinical trials which have described the use of F_{ENO} in children within a primary care setting.

Despite any concerns about the role of F_{ENO} in guiding asthma treatment in children, a Cochrane review of 1279 participants from eight clinical trials found that the odds ratio for asthma exacerbation was 0.62 (95% CI 0.49–0.80) when care was delivered by symptoms plus F_{ENO} compared to symptoms only [53]. When data from a ninth recently published trial [54] are added to the Cochrane analysis, the odds ratio for exacerbation is 0.77 (95% CI 0.62–0.92), as shown in figure 2. There is no evidence that F_{ENO} -guided treatment improves asthma control [53]. The mechanism for F_{ENO} reducing exacerbations is likely to involve optimal titration of the child's ICS dose (equivalent to an increase in ICS dose of 60–100 μg budesonide equivalent) [23, 55].

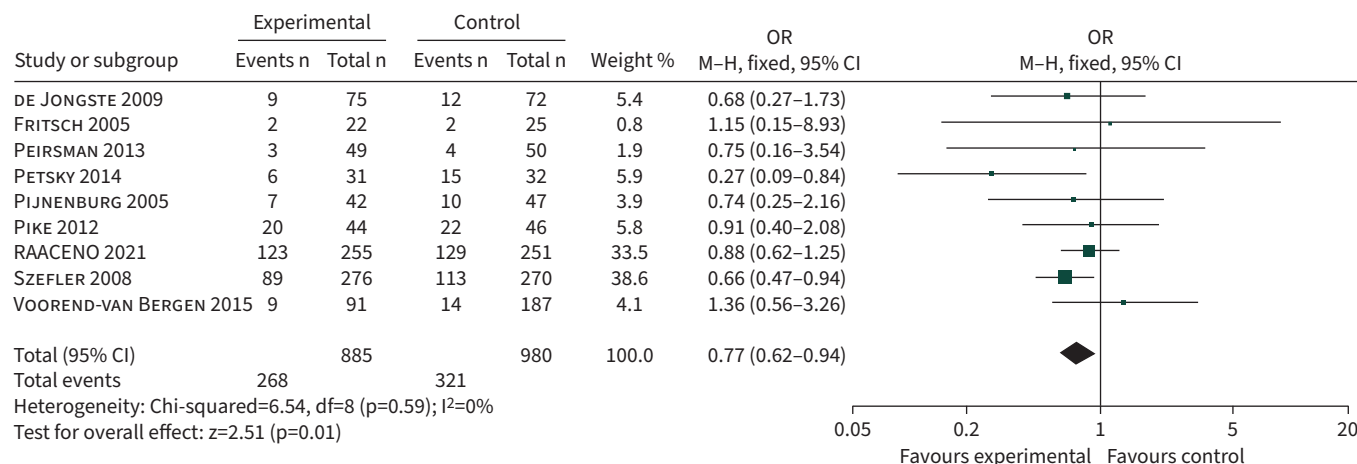


FIGURE 2 Forest plot comparing the number of participants in randomised clinical trials who had an asthma attack requiring treatment with oral steroids. Participants were randomised to asthma treatment guided by fractional exhaled nitric oxide plus standard care (symptoms+forced expiratory volume in 1 s) or standard care only. RAACENO: Reducing Asthma Attacks in Children Using Exhaled Nitric Oxide; M-H: Maentel-Haenszel; df: degrees of freedom.

FIELDING *et al.* [56] combined original data from six of the eight clinical trials cited in the Cochrane review [53] and explored whether F_{ENO} -guided treatment was more effective in certain subgroups of children. The individual patient data (IPD) analysis included information from 1112 children and found that F_{ENO} -guided treatment was associated with reduced exacerbations among those not on LTRA treatment (OR 0.68, 95% CI 0.49–0.94) [56]. Among children who were initially controlled, the odds ratio for losing control during follow-up when treatment was guided by F_{ENO} compared to standard treatment were reduced for those who were not treated with LTRA (OR 0.70, 95% CI 0.49–1.00) and who were not obese (OR 0.69, 95% CI 0.48–0.99) [56]. These findings suggest that treatment with LTRA may mask the relationship between F_{ENO} and ICS treatment. There was no evidence that F_{ENO} -guided treatment was more or less effective in improving asthma outcomes in other subgroups stratified by obesity, high/low ICS dose, atopy or ethnicity [56].

How should change in F_{ENO} values be expressed?

The distribution of F_{ENO} values is not normally distributed; a population median F_{ENO} value is considerably lower than the mean value. The implication of this is that expressing change in F_{ENO} on a linear scale is less meaningful, especially at higher concentrations; for example, a 10-ppb rise may be more relevant if the original concentration was 10 ppb, compared to 50 ppb. The consensus is that change in F_{ENO} should be expressed as absolute terms where values are <50 ppb and as a percentage change at higher values [13]. The IPD analysis mentioned previously found that a percentage change, but not absolute change, in F_{ENO} was associated with odds for losing control in future [52].

What is a significant change in F_{ENO} ?

The ATS guideline [13] recommends that a clinically relevant change is 10 ppb where concentrations are <50 ppb and 20% at higher concentrations. These changes are similar to the magnitude of difference between measurements when one person uses two different F_{ENO} devices [15], and this emphasises the importance of using the same device when comparing change in F_{ENO} values. One study of 178 children, including 47 with asthma, measured F_{ENO} at 2-month intervals over a year and found that F_{ENO} concentrations could rise by 100% over 2–4 months, independent of asthma and regardless of the initial concentration [57]. In a second study, a subgroup of 665 children in the previously mentioned IPD were identified as having controlled asthma and unchanged ICS treatment over a 3-month period [58]. In this subgroup with “stable asthma”, the interquartile range (IQR) for a change in F_{ENO} for those with an initial F_{ENO} <50 ppb was –7 to +9 ppb, meaning that in only ~50% of individuals F_{ENO} remained within 10 ppb of initial concentration. For children with “stable asthma” and an initial F_{ENO} of ≥50 ppb, the IQR for percentage change was between –33% and +51% [58]. These results cautiously support the ATS statement for F_{ENO} values <50 ppb, but suggest that the cut-off for values ≥50 ppb might be considerably more than 20%.

There have been nine clinical trials which have intervened by adding F_{ENO} to usual care, and table 2 describes the F_{ENO} cut-off values used in these trials. The cut-off values of F_{ENO} which triggered a change

TABLE 2 Methodological details of randomised clinical trials which have intervened with fractional exhaled nitric oxide (F_{ENO}) to guide asthma treatment

First author, year [reference]	Primary outcome(s)	Age years	Participants	Atopy as inclusion criterion?	FEV ₁ <80% also used in treatment algorithm?	F_{ENO} cut-off(s) (ppb) used to step-up/-down treatment	How often was F_{ENO} measured after initial assessment?	What did the trial find? (F_{ENO} treatment compared to standard care)
DE JONGSTE, 2009 [59]	Symptom-free days	F_{ENO} group 11.6±2.6 Control group 11.8±4.3	151	Yes	No	20 for 6–10-year-olds 25 for older children	Daily measurements over 3 months	No difference in outcomes
FRITSCH, 2006 [60]	FEV ₁	11.5±3.1	47	Yes	Yes	20	6, 12, 18 and 24 weeks	Higher mid-expiratory flow, higher dose of ICS
PEIRSMAN, 2014 [61]	Symptom-free days	10.7±2.1	99	Yes	Yes	20	3, 6, 9 and 12 months	Reduced exacerbations, increased LTRA and ICS dose No difference in primary outcome
PETSKY, 2015 [62]	Exacerbations	10.0±3.2	63	No	No	10 for nonatopic 12 with 1 PSPT 20 for >1 PSPT	1, 2, 3, 4, 6, 8, 10 and 12 months	Reduced exacerbation, increased ICS dose
PIJNENBURG, 2005 [63]	Cumulative ICS dose	12.3±2.8	85	No	No	30	3, 6, 9 and 12 months	Reduced F_{ENO} and bronchial hyperresponsiveness No increase in ICS dose
PIKE, 2013 [64]	ICS dose and exacerbation frequency	10.9±2.6	90	No	No	≤15 and ≥25	2, 4, 6, 8, 10 and 12 months	No differences in outcomes
SZEFLER, 2008 [65]	Days with asthma symptoms	14.4±2.1	546	Yes	Yes	20, 30 and 40	6, 14, 22, 30, 38 and 46 weeks	Reduced exacerbations, increased ICS dose No difference in primary outcome
TURNER, 2022 [54]	Exacerbation	10.1±2.6	509	No	No	>50% change	3, 6, 9 and 12 months	No differences in outcomes
VERINI, 2010 [66]	Exacerbation, symptoms and therapy score	F_{ENO} group 10.7±2.4 Control group 11.3±2.1	64	Yes	No	12	6 and 12 months	The F_{ENO} group were less likely to have an exacerbation at 6 and 12 months
VOOREND-VAN BERGEN, 2015 [67]	Proportion of symptom-free days	10.2±3.0	181 [#]	Yes	No	20 and 50	4, 8 and 12 months	Increased asthma control, but not the primary outcome

Data are presented as mean±SD or n, unless otherwise stated. FEV₁: forced expiratory volume in 1 s; ICS: inhaled corticosteroid; LTRA: leukotriene receptor antagonist; PSPT: positive skin-prick test. [#]: although 272 children were included in the study, the 91 participants randomised to a web-based intervention did not have F_{ENO} measurements and are not included here

in treatment differ, some studies use a single value of between 12 and 30 ppb or a 50% change; one used different cut-offs for certain phenotypes while others had different cut-offs for stepping-up or -down treatment. Table 2 describes how the design of these studies differed in several aspects, including:

- variable (but usually small) sample size;
- many studies included only atopic children;
- one study measured F_{ENO} on a daily basis, while others measured F_{ENO} at intervals between 6 weeks and 4 months;
- the studies used different F_{ENO} cut-offs to trigger different treatment steps;
- some studies also used changes in FEV_1 when considering treatment change in both arms of the trial.

The many heterogeneities in the design of these studies may explain the inconsistent results for reduction in exacerbations. Importantly, studies that used the same F_{ENO} cut-off (20 ppb) [59–61] did not have the same outcomes. Additionally, the four studies that found that the addition of F_{ENO} to usual care was associated with reduced exacerbations [61, 62, 65, 66] used different F_{ENO} cut-offs. These observations suggest that there is no ideal F_{ENO} cut-off for use in monitoring childhood asthma.

Looking ahead

A key priority is for the industry to provide more accurate devices (ideally with much smaller inter-user variability). A universally accepted definition of asthma would be welcome.

For diagnosis, F_{ENO} cut-offs from clinically relevant populations (*i.e.* children with possible asthma) should be applied to diagnostic algorithms which include symptoms and other objective markers, *e.g.* FEV_1 . Diagnostic uncertainty for asthma in children aged <5 years is very common and a method to measure F_{ENO} in this age group for incorporation into a diagnostic algorithm would be welcome. When you see a child with asthma in the next few weeks, a “low” F_{ENO} value (<20 ppb [13] or <19 ppb [29]) in a steroid-naïve child with low or intermediate likelihood of asthma based on symptoms may be helpful in excluding a diagnosis of asthma, and/or support a plan of watchful waiting before considering a diagnosis at a later date. A “high” F_{ENO} value (>35 ppb [13] or >25 ppb [29]) in isolation is of uncertain relevance and needs to be interpreted in the context of symptoms and FEV_1 .

For monitoring asthma, we know that there is good evidence that adding F_{ENO} measurements every 2–3 months to usual care leads to a modest reduction in asthma attacks (figure 2), but there is no clear indication of exactly how to integrate F_{ENO} into usual care, *e.g.* what change in F_{ENO} is clinically meaningful and what treatment should be altered in light of changing F_{ENO} concentrations? We know that there is no consistently reported subgroup of children in whom F_{ENO} is particularly suitable (or unsuitable) for monitoring. One guideline suggests that F_{ENO} may be useful in specialist asthma clinics, but this is not based on evidence [31]. What is not known is what benefit may come from using a combination of both F_{ENO} and FEV_1 to guide asthma treatment: F_{ENO} -guided asthma treatment is associated with increased FEV_1 [55], so there may be synergy between F_{ENO} - and FEV_1 -guided asthma treatment. An important limitation to research aimed at using objective markers to guide asthma treatment is that there are few treatment options at present: once a child is on ICS, LTRA and long-acting β -agonists, the step-up options for participants in different arms of a clinical trials are the same, *i.e.* increase ICS dose. So in tomorrow’s asthma clinic, regardless of any F_{ENO} result, you are still highly likely to step-up treatment in a child with poorly controlled symptoms (assuming they are compliant) and you are likely to step-down treatment in the spring and summer months for a child who has not needed their reliever for 3 months. At the time of writing, there is insufficient evidence to suggest that treatment decisions can be informed by F_{ENO} concentrations in identical twins with intermediate symptom control who are on the same treatment and have F_{ENO} values of 20 and 30 ppb.

Take-home message

Even the greatest advocates for F_{ENO} cannot be certain that F_{ENO} should be routinely be used for diagnosing and monitoring childhood asthma. Equally, F_{ENO} ’s greatest critics cannot deny that there is persuasive evidence for its use in some aspects of care (figure 2). We do know that there is currently insufficient evidence to recommend F_{ENO} for routine diagnosis and monitoring of asthma in children; clinical decisions should not be made solely on a F_{ENO} result. Although data from nine randomised clinical trials suggest that adding F_{ENO} to usual asthma is associated with a reduction in exacerbations, it is not unclear what cut-off(s) should be used to trigger a change in treatment. So at this point in time, it is neither myth nor maxim that F_{ENO} should be used for diagnosing and monitoring childhood asthma.

Self-evaluation questions

1. Which of the following statements is most correct?
 - a) Age, height and active smoking are factors unrelated to asthma that are known to affect F_{ENO} measurements.
 - b) Age, height, active smoking and dietary factors are exposures unrelated to asthma that are known to affect F_{ENO} measurements.
 - c) Age, height, active smoking, dietary factors and ethnicity are exposures unrelated to asthma that are known to affect F_{ENO} measurements.
 - d) Age, height, active smoking, dietary factors, ethnicity and asthma treatment are exposures unrelated to asthma that are known to affect F_{ENO} measurements.
2. Which of the following statements is correct?
 - a) Reliable F_{ENO} measurements can be made in all children.
 - b) Reliable F_{ENO} measurements can be made in the majority of children aged >5 years.
 - c) F_{ENO} measurements made on apparatus made by different manufacturers can be reliably compared.
 - d) By convention, change in F_{ENO} measurements is expressed as a percentage change.
3. Which of the following statements regarding diagnosing asthma is most correct?
 - a) A F_{ENO} concentration of >35 ppb is diagnostic of asthma.
 - b) A F_{ENO} concentration of >25 ppb is diagnostic of asthma.
 - c) All international guidelines recommend that F_{ENO} should be measured in children aged ≥ 5 years.
 - d) No international guideline recommends F_{ENO} as the initial test for diagnosing asthma.
4. For monitoring asthma in children, which of the following statements is correct?
 - a) There is evidence from nine randomised controlled trials that the addition of F_{ENO} to usual care improves the odds for having controlled asthma symptoms in children.
 - b) There is evidence from nine randomised controlled trials that the addition of F_{ENO} to usual care reduces the odds of having an asthma exacerbation.
 - c) A rise in F_{ENO} of 10 ppb over 3 months in a child with asthma treated with ICS and whose asthma symptoms have intermediate control suggests that a LABA should be introduced.
 - d) A rise in F_{ENO} of 10 ppb over 3 months in a child with asthma treated with inhaled corticosteroids suggests that they are not adherent with their treatment.

Conflict of interest: S. Turner received F_{ENO} measurement apparatus from Circassia for a clinical trial at no cost between 2016 and 2018. None of the other authors has a conflict of interest to declare.

References

- 1 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2023. https://ginasthma.org/wp-content/uploads/2023/07/GINA-2023-Full-report-23_07_06-WMS.pdf. Date last accessed: 14 October 2023.
- 2 Bush A, Hedlin G, Carlsen K, *et al*. Severe childhood asthma: a common international approach? *Lancet* 2008; 372: 1019–1021.
- 3 Asher MI, Keil U, Anderson HR, *et al*. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8: 483–491.
- 4 Centers for Disease Control and Prevention. Asthma Surveillance in the United States, 2001–2021. 2023. www.cdc.gov/asthma/Asthma-Prevalence-US-2023-508.pdf. Date last accessed: 14 October 2023.
- 5 Krusche J, Basse S, Schaub B. Role of early life immune regulation in asthma development. *Semin Immunopathol* 2020; 42: 29–42.
- 6 Payne DN, Adcock IM, Wilson NM, *et al*. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. *Am J Respir Crit Care Med* 2001; 164: 1376–1381.
- 7 Pontin J, Blaylock MG, Walsh GM, *et al*. Sputum eosinophil apoptotic rate is positively correlated to exhaled nitric oxide in children. *Pediatr Pulmonol* 2008; 43: 1130–1134.
- 8 Warke TJ, Fitch PS, Brown V, *et al*. Exhaled nitric oxide correlates with airway eosinophils in childhood asthma. *Thorax* 2002; 57: 383–387.
- 9 Piacentini GL, Bodini A, Costella S, *et al*. Exhaled nitric oxide and sputum eosinophil markers of inflammation in asthmatic children. *Eur Respir J* 1999; 13: 1386–1390.
- 10 Karrasch S, Linde K, Rucker G, *et al*. Accuracy of F_{ENO} for diagnosing asthma: a systematic review. *Thorax* 2017; 72: 109–116.
- 11 Ricciardolo FLM. Multiple roles of nitric oxide in the airways. *Thorax* 2003; 58: 175–182.
- 12 Borland C, Cox Y, Higenbottam T. Measurement of exhaled nitric oxide in man. *Thorax* 1993; 48: 1160–1162.
- 13 Dweik RA, Boggs PB, Erzurum SC, *et al*. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (F_{ENO}) for clinical applications. *Am J Respir Crit Care Med* 2011; 184: 602–615.

- 14 Paraskakis E, Brindicci C, Fleming L, *et al.* Measurement of bronchial and alveolar nitric oxide production in normal children and children with asthma. *Am J Respir Crit Care Med* 2006; 174: 260–267.
- 15 National Institute for Health and Care Excellence (NICE). Measuring Fractional Exhaled Nitric Oxide Concentration in Asthma: NIOX MINO, NIOX VERO and NObreath. 2014. www.nice.org.uk/guidance/dg12. Date last accessed: 7 January 2015. Date last updated: 2 April 2014.
- 16 Franklin PJ, Turner SW, Mutch RC, *et al.* Comparison of single-breath and tidal breathing exhaled nitric oxide levels in infants. *Eur Respir J* 2004; 23: 369–372.
- 17 Napier E, Turner SW. Methodological issues related to exhaled nitric oxide measurement in children aged four to six years. *Pediatr Pulmonol* 2005; 40: 97–104.
- 18 Yang Y, Lo DK, Beardsmore C, *et al.* Implementing spirometry and fractional exhaled nitric oxide testing in childhood asthma management in UK primary care: an observational study to examine training and implementation cost and impact on patient's health use and outcome. *Arch Dis Child* 2022; 107: 21–25.
- 19 Onisor MO, Turner S. Routine FEV₁ measurement is essential in diagnosis and monitoring of childhood asthma: myth or maxim? *Breathe* 2023; 19: 230048.
- 20 Nelson BV, Sears S, Woods J, *et al.* Expired nitric oxide as a marker for childhood asthma. *J Pediatr* 1997; 130: 423–427.
- 21 Silvestri M, Sabatini F, Spallarossa D, *et al.* Exhaled nitric oxide levels in non-allergic and allergic mono- or polysensitized children with asthma. *Thorax* 2001; 56: 857–862.
- 22 Franklin PJ, Turner SW, Le Souëf PN, *et al.* Exhaled nitric oxide and asthma: complex interactions between atopy, airway responsiveness, and symptoms in a community population of children. *Thorax* 2003; 58: 1048–1052.
- 23 Turner S. Exhaled nitric oxide and the management of childhood asthma – yet another promising biomarker “has been” or a misunderstood gem. *Paediatr Respir Rev* 2015; 16: 88–96.
- 24 Abuzayan I, Turner SW. Changes in exhaled nitric oxide after ingestion of L-arginine in children: a pilot study. *Pediatr Pulmonol* 2010; 45: 236–240.
- 25 Abuzayan I, Paraskavi U, Turner SW. Changes to exhaled nitric oxide in asthmatic children after drinking a caffeine-containing cola drink. *Pediatr Pulmonol* 2010; 45: 1228–1232.
- 26 Saito J, Gibeon D, Macedo P, *et al.* Domiciliary diurnal variation of exhaled nitric oxide fraction for asthma control. *Eur Respir J* 2014; 43: 474–484.
- 27 Blake TL, Chang AB, Chatfield MD, *et al.* Does ethnicity influence fractional exhaled nitric oxide in healthy individuals? A systematic review. *Chest* 2017; 152: 40–50.
- 28 Barreto M, Villa MP, Montesano M, *et al.* Reduced exhaled nitric oxide in children after testing of maximal expiratory pressures. *Pediatr Pulmonol* 2006; 41: 141–145.
- 29 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.
- 30 Buchvald F, Hermansen MN, Nielsen KG, *et al.* Exhaled nitric oxide predicts exercise-induced bronchoconstriction in asthmatic school children. *Chest* 2005; 128: 1964–1967.
- 31 Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society (BTS). SIGN 158: British Guideline on the Management of Asthma. Edinburgh, Scottish Intercollegiate Guidelines Network, 2019.
- 32 National Institute for Health and Care Excellence (NICE). Asthma: Diagnosis, Monitoring and Chronic Asthma Management. 2017. <https://www.nice.org.uk/guidance/ng80>. Date last updated: 22 March 2021.
- 33 Cloutier MM, Baptist AP, Blake KV, *et al.* 2020 focused updates to the asthma management guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee expert panel working group. *J Allergy Clin Immunol* 2020; 146: 1217–1270.
- 34 Khatri SB, Iaccarino JM, Barochia A, *et al.* Use of fractional exhaled nitric oxide to guide the treatment of asthma: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2021; 204: e97–e109.
- 35 Wang R, Fowler SJ, Turner SW, *et al.* Defining the normal range of fractional exhaled nitric oxide in children: one size does not fit all. *ERJ Open Res* 2022; 8: 00319–2022.
- 36 Quanjer PH, Stanojevic S, Cole TJ, *et al.* Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40: 1324–1343.
- 37 Högman M, Bowerman C, Chavez L, *et al.* ERS technical standard: Global Lung Function Initiative reference values for exhaled nitric oxide (F_{ENO}). *Eur Respir J* 2023; in press [<https://doi.org/10.1183/13993003.00370-2023>].
- 38 de Jong CCM, Pedersen ESL, Mozun R, *et al.* Diagnosis of asthma in children: findings from the Swiss Paediatric Airway Cohort. *Eur Respir J* 2020; 56: 2000132.
- 39 Murray C, Foden P, Lowe L, *et al.* Diagnosis of asthma in symptomatic children based on measures of lung function: an analysis of data from a population-based birth cohort study. *Lancet Child Adolesc Health* 2017; 1: 114–123.
- 40 Zacharasiewicz A, Wilson N, Lex C, *et al.* Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med* 2005; 171: 1077–1082.

- 41 Pijnenburg MW, Hoffhuis W, Hop WC, *et al.* Exhaled nitric oxide predicts asthma relapse in children with clinical asthma remission. *Thorax* 2005; 60: 215–218.
- 42 Cabral ALB, Vollmer WM, Barbirotto RM, *et al.* Exhaled nitric oxide as a predictor of exacerbation in children with moderate-to-severe asthma: a prospective, 5-month study. *Ann Allergy Asthma Immunol* 2009; 103: 206–211.
- 43 Baraldi E, Dario C, Ongaro R, *et al.* Exhaled nitric oxide concentrations during treatment of wheezing exacerbation in infants and young children. *Am J Respir Crit Care Med* 1999; 159: 1284–1288.
- 44 Comberiati P, Peroni D, Malka-Rais J, *et al.* Fractional exhaled nitric oxide response to oral corticosteroids in children with mild-to-moderate asthma: influence of race. *Ann Allergy Asthma Immunol* 2020; 125: 440–446.
- 45 Montuschi P, Mondino C, Koch P, *et al.* Effects of montelukast treatment and withdrawal on fractional exhaled nitric oxide and lung function in children with asthma. *Chest* 2007; 132: 1876–1881.
- 46 Szefer SJ, Casale TB, Haselkorn T, *et al.* Treatment benefit with omalizumab in children by indicators of asthma severity. *J Allergy Clin Immunol Pract* 2020; 8: 2673–2680.
- 47 Petsky HL, Cates CJ, Lasserson TJ, *et al.* A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). *Thorax* 2012; 67: 199–208.
- 48 Fleming L, Bush A. Use of sputum eosinophil counts to guide management in children with severe asthma. *Thorax* 2012; 67: 1015–1016.
- 49 Buchvald F, Eiberg H, Bisgaard H. Heterogeneity of F_{ENO} response to inhaled steroid in asthmatic children. *Clin Exp Allergy* 2003; 33: 1735–1740.
- 50 Paracha R, Lo DKH, Montgomery U, *et al.* Asthma medication adherence and exacerbations and lung function in children managed in Leicester primary care. *NPJ Prim Care Respir Med* 2023; 33: 12.
- 51 Jochmann A, Artusio L, Jamalzadeh A, *et al.* Electronic monitoring of adherence to inhaled corticosteroids: an essential tool in identifying severe asthma in children. *Eur Respir J* 2017; 50: 1700910.
- 52 Fielding S, Pijnenburg M, de Jongste JC, *et al.* Change in FEV_1 and F_{ENO} measurements as predictors of future asthma outcomes in children. *Chest* 2019; 155: 331–341.
- 53 Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. *Cochrane Database Syst Rev* 2016; 11: CD011439.
- 54 Turner S, Cotton S, Wood J, *et al.* Reducing asthma attacks in children using exhaled nitric oxide (RAACENO) as a biomarker to inform treatment strategy: a multicentre, parallel, randomised, controlled, phase 3 trial. *Lancet Respir Med* 2022; 10: 584–592.
- 55 Wang X, Tan X, Li Q. Effectiveness of fractional exhaled nitric oxide for asthma management in children: a systematic review and meta-analysis. *Pediatr Pulmonol* 2020; 55: 1936–1945.
- 56 Fielding S, Pijnenburg MW, de Jongste JC, *et al.* Does treatment guided by exhaled nitric oxide fraction improve outcomes in subgroups of children with asthma? *Eur Respir J* 2020; 55: 1901879.
- 57 Cutts R, Turner S. Longitudinal measurements of exhaled nitric oxide in children – what is a significant change in FE_{NO} ? *Pediatr Allergy Immunol* 2013; 24: 540–548.
- 58 Fielding S, Pijnenburg M, de Jongste J, *et al.* What is a clinically meaningful change in exhaled nitric oxide for children with asthma? *Pediatr Pulmonol* 2020; 55: 599–606.
- 59 de Jongste JC, Carraro S, Hop WC, *et al.* Daily telemonitoring of exhaled nitric oxide and symptoms in the treatment of childhood asthma. *Am J Respir Crit Care Med* 2009; 179: 93–97.
- 60 Fritsch M, Uxa S, Horak FJ, *et al.* Exhaled nitric oxide in the management of childhood asthma: a prospective 6-months study. *Pediatr Pulmonol* 2006; 41: 855–862.
- 61 Peirsman EJ, Carvelli TJ, Hage PY, *et al.* Exhaled nitric oxide in childhood allergic asthma management: a randomised controlled trial. *Pediatr Pulmonol* 2014; 49: 624–631.
- 62 Petsky HL, Li AM, Au CT, *et al.* Management based on exhaled nitric oxide levels adjusted for atopy reduces asthma exacerbations in children: a dual centre randomized controlled trial. *Pediatr Pulmonol* 2015; 50: 535–543.
- 63 Pijnenburg MW, Bakker EM, Hop WC, *et al.* Titrating steroids on exhaled nitric oxide in children with asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2005; 172: 831–836.
- 64 Pike K, Selby A, Price S, *et al.* Exhaled nitric oxide monitoring does not reduce exacerbation frequency or inhaled corticosteroid dose in paediatric asthma: a randomised controlled trial. *Clin Respir J* 2013; 7: 204–213.
- 65 Szefer SJ, Mitchell H, Sorkness CA, *et al.* Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet* 2008; 372: 1065–1072.
- 66 Verini M, Consilvio NP, Di Pillo S, *et al.* F_{ENO} as a marker of airways inflammation: the possible implications in childhood asthma management. *J Allergy* 2010; 2010: 691425.
- 67 Voorend-van Bergen S, Vaessen-Verberne AA, Brackel HJ, *et al.* Monitoring strategies in children with asthma: a randomised controlled trial. *Thorax* 2015; 70: 543–550.

Suggested answers

1. c. Asthma treatment (stated in d) is an asthma-related exposure.
2. b. Differences in F_{ENO} measurements between devices are comparable to what is considered a clinically meaningful difference. Change in F_{ENO} can be expressed as both absolute change and percentage change.
3. d.
4. b.