In their new paper, Stern and colleagues try to define phenotypes of asthma with special features early in life, favouring ongoing airway disease later in life on the one hand and characterisation of patients with asthma who developed the disease after puberty on the other. Most cases with current asthma in early adult life already had episodes of wheezing during the first 3 years of life. In 27% of the individuals with asthma at 22 years, asthma was newly diagnosed and most of them were female (71%). Predictive factors for chronic asthma in adulthood were late onset of wheezing (6 years and older), persistent wheeze in early life (before 3 years, and at 6 years and later), sensitisation to the fungus *Alternaria alternata*, and low airway-function and bronchial hyperresponsiveness to cold dry air at 6 years. These findings identify a population at risk of chronic obstructive airway disease in early adulthood, and they already showed a predisposition during preschool years. Whether therapeutic approaches at early preschool age can affect progression of the disease is yet to be established.

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I declare that I have no conflict of interest.

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Exhaled nitric oxide in guideline-based asthma management

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The importance of good asthma control has been amply documented and new guidelines focus on achievement and maintenance of good asthma control.[1] However, although validated scoring systems have been developed to facilitate asthma control, several studies have found that assessment of asthma control varies markedly between health-care professionals as well as patients.[2] The result is high risk of too little or too much treatment, or both. Therefore the medical community has been hoping for a single, easy-to-measure, and reliable biomarker (such as haemoglobin A_{1c} in diabetes) that could facilitate the assessment of asthma control and help physicians to appropriately increase or decrease treatment. In this respect, exhaled nitric oxide (FE_{NO})—an indirect marker of airway inflammation—has generated much enthusiasm. FE_{NO} is easy to measure, correlates with eosinophilic airway inflammation, and is increased during periods of uncontrolled asthma and reduced during treatment with anti-inflammatory agents.[3-5] However, before a new biomarker is implemented in daily practice, it should be assessed in light of the words of Albert Einstein: "What counts cannot always be measured and what can be measured does not always count."

The measurement of FE_{NO} is relatively easy and has shown promising results, but is not cheap. Therefore the important question is: does addition of FE_{NO} to guideline-recommended clinical assessments and treatment algorithms reduce over-treatment or under-treatment (or both), and does it improve daily asthma control? In today's *Lancet*, Stanley Szefler and colleagues report the findings of a large well-conducted study designed to address these questions.[6] The investigators conclude that adding measurements of FE_{NO} to guideline-recommended asthma management did not provide any important clinical benefit. No differences were found in clinical scores for asthma control or other asthma

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outcomes, and the occurrence of under-treatment was not improved. These findings agree with the results from smaller trials.[7–10] So, it seems unlikely that adding FE_{NO} measurement to guideline-recommended asthma management is going to improve asthma control or reduce under-treatment. This finding is highly relevant to daily practice.

Even if daily asthma control was not improved by the use of FE_{NO}, the measurement might still have improved individualised dosing, such that the same level of asthma control could be achieved with less treatment. However, Szefler and colleagues did not see that result. By contrast, the use of FE_{NO} resulted in higher doses of inhaled corticosteroids and more frequent use of long-acting β_2 agonists. At first glance, this finding could lead to the conclusion that, in the population studied, use of FE_{NO} to help manage asthma could lead to over-treatment because of the use of a "measure that did not count". This finding could also be due to the design of the study. Although the study followed the recommendations of guidelines to regularly assess asthma-control status and tailor and adjust treatment in regular cycles, the approach did not use FE_{NO} concentrations to reduce the amount of treatment. FE_{NO} measurement was mainly used to increase the amount of treatment in patients with increased concentrations, even if clinical variables were stable. The conclusions in earlier trials about the potentially treatment-saving effects of adding FE_{NO} to clinical assessment have varied from no change in the daily dose of inhaled corticosteroid,[9,10] to an increase,[8] and to a reduction in daily dose of inhaled corticosteroid.[7]

Although Szefler and colleagues' study was not designed to assess the value of the guideline recommendations, the substantial clinical benefits achieved during the run-in period, when guideline-recommended treatment was introduced, agree with findings from other studies.[11,12] This finding emphasises, once again, the importance of even low doses of effective anti-inflammatory drugs in asthma management.

It takes more than one good study to completely rule out potential benefits of a new biomarker. Although Szefler and colleagues' findings convincingly show that addition of FE_{NO} measurement to guideline-recommended asthma management will not improve daily asthma control or under-treatment in the population studied, more studies are needed to explore the usefulness of FE_{NO} in subgroups of patients with asthma and its treatment-saving potential. Until such data are available, a recommendation to use FE_{NO} measurements routinely in patients treated according to guidelines is not ready to be made yet.

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Inflammometry to assess airway diseases

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The diagnostic labels used to characterise common airway diseases have always been a problem. The term asthma implies the presence of variable airflow obstruction; however, objective demonstration can be difficult. Commonly used tests, such as spirometry or serial peak-flow measurements, are neither sensitive nor specific,[1] especially in patients with mild disease and normal or near-normal lung function, or in those with fixed airflow obstruction. Conversely, the term chronic obstructive pulmonary disease (COPD) implies largely irreversible airflow obstruction, yet clinicians may attempt to confirm the presence of reversibility, and having done so, label the disease as having an "asthmatic" component. Furthermore, the use of specific diagnostic labels implies a probable natural history, and influences expectations about treatment outcomes.

Although causative factors in the various airway diseases are different, the natural history and treatment responsiveness are less distinct. For example, accelerated decline in lung function and fixed airflow obstruction are features of COPD, but not exclusively so; they also occur in some patients with asthma, and the mechanisms might be similar.[2] In view of this picture, diagnostic labelling on the basis of physiological data can be confusing and misleading.

Treatment with corticosteroids, usually by inhalation, is arguably the most important therapeutic intervention in patients with airway disease. Judicious use of these agents improves symptoms and reduces exacerbations. However, the response to inhaled corticosteroids is heterogeneous. The identification of clinical or physiological features that predict corticosteroid responsiveness in patients with symptoms that suggest airway disease is difficult, irrespective of the final diagnosis. A common approach is to base long-term use of corticosteroid on the response to a short-term trial of treatment. This approach is potentially flawed for several reasons.

First, symptoms that suggest asthma are non-specific, and are mimicked by acute conditions such as postviral bronchial hyper-responsiveness, anxiety hyperventilation syndrome, vocal cord dysfunction, and gastro-oesophageal reflux, and by chronic conditions such as COPD or bronchiectasis. Most of these conditions do not respond to corticosteroids, but spontaneous improvement over time leads to the mistaken belief that such treatment has been beneficial. The correct diagnosis is thus delayed, or inappropriate treatment might be increased when symptoms worsen. Second, it is not valid to draw inferences about the longer-term benefits of treatment (ie, reduction in exacerbation frequency) from the outcome of a short-term trial. Third, expectation, observer or ascertainment biases, and incomplete adherence to the prescribed treatment can also influence results. Most of these problems, together with the natural tendency of clinicians to be cautious in borderline cases, increase the likelihood that patients may be started on inappropriate corticosteroid therapy, with associated cost and potential toxicity.

An alternative approach is to identify the need for corticosteroids in relation to the underlying inflammation. It is logical that both the indications and the outcomes for anti-inflammatory treatment should be related to the presence of airway inflammation. There is now consistent evidence that eosinophilic airway inflammation is the most reliable predictor of a response to corticosteroids in patients with airway disease,[3–7] irrespective of which diagnostic label applies. The long-term benefits of corticosteroids on exacerbation frequency also occur predominantly in patients with evidence of eosinophilic airway inflammation.[8–10] Management strategies that seek to minimise eosinophilic airway inflammation substantially reduce the frequency of severe exacerbations, both in asthma[8,9] and COPD,[10] and hence result in more efficient use of corticosteroids.