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## Key points

- Asthma presents with common respiratory symptoms and physical examination is often normal; in addition, the most widely available tests (peak flow and spirometry) can be normal unless the patient is exacerbating.
- Treating asthma prior to carrying out objective tests decreases their sensitivity and can make confirmation of the diagnosis difficult.
- There is no single gold standard test to diagnose asthma, and there are significant differences between the suggested algorithms in commonly used guidelines.
- Both under- and over-diagnosis are widespread and lead to significant risks to patients.

## Review

# Over- and under-diagnosis in asthma

Asthma is extremely common with a prevalence of approximately 10% in Europe. It presents with symptoms which have a broad differential diagnosis and examination can be entirely normal. There is no agreed gold standard to diagnose asthma, and the objective tests that can aid diagnosis are often poorly available to primary care physicians. There is evidence that asthma is widely misdiagnosed. Overdiagnosis leads to unnecessary treatment and a delay in making an alternative diagnosis. Underdiagnosis risks daily symptoms, (potentially serious) exacerbations and long-term airway remodelling. An agreed standardised approach to diagnosis, with inclusion of objective measurements prior to treatment, is required to reduce misdiagnosis of asthma.

**Cite as:** Kavanagh J, Jackson DJ, Kent BD. Over- and under-diagnosis in asthma. *Breathe* 2019; 15: e20–e27.

## Introduction

Asthma is a common disease, characterised by variable airflow obstruction and airway inflammation, leading to symptoms of breathlessness, wheeze, chest tightness and cough. It is estimated to affect 30–50 million people in Europe [1], approximately 10% of all Europeans. The direct costs of asthma care in Europe is estimated at EUR 17.7 billion per year. Although the disease is often mild, asthma sadly still kills: there were an estimated 1320 asthma deaths in England and Wales in 2017 alone [2].

Over diagnosis is increasingly recognised as a problem in a range of diseases, including asthma [3]. Asthma has traditionally been diagnosed on the basis of history and response to a trial of treatment; however, asthma presents with respiratory symptoms that are common to a wide range of disease processes and are not specific

to asthma (box 1). In addition, the physical examination is usually normal, unless a patient is exacerbating at the time of the examination. As asthma is so common, the majority of diagnoses are made in primary care, where access to objective testing in asthma is limited. Even if objective tests are available, there is no gold standard test for asthma and many of the tests that are available (*e.g.* spirometry, fractionated exhaled nitric oxide (*F<sub>e</sub>NO*) and bronchial provocation tests) do not necessarily exclude asthma even if they are normal, particularly if the patient has started treatment prior to testing. This complexity makes both under- and over-diagnosis an obstacle that clinicians need to work to avoid in asthma. Both possibilities carry costs to both the patient's health and to healthcare systems.

This review will examine how asthma is currently diagnosed and how this may change in the near future, it will then review the evidence and

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**Asthma is frequently misdiagnosed. Both over- and under-diagnosis are associated with inappropriate treatment and potential patient harm. Although no gold standard diagnostic test is available, objective testing can improve diagnostic accuracy.** <http://ow.ly/Ej3830ohfxj>



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**Box 1** *Differential diagnosis of asthma*

- Chronic obstructive pulmonary disease (COPD)
- Allergic or non-allergic rhinitis
- Gastro-oesophageal reflux disease
- Post-viral cough/upper airway cough syndrome
- Eosinophilic bronchitis
- Dysfunctional breathing pattern/hyperventilation/intermittent laryngeal obstruction
- Obesity/deconditioning
- Excessive dynamic airways collapse
- Interstitial lung disease
- Obstructive sleep apnoea/sleep disordered breathing
- Anxiety disorder/panic attacks
- Cardiac disease: congenital, heart failure, ischaemic heart disease
- Central airway obstruction
- Bronchiectasis
- Sarcoidosis
- Pulmonary hypertension
- Angiotensin-converting enzyme inhibitor related cough
- Pulmonary embolism

consequences of overdiagnosis of asthma, before turning to consider underdiagnosis in asthma.

## Diagnosing asthma

### Current guidelines

In recent years there has been a move to include objective testing in asthma diagnosis algorithms. The most widely used asthma guidelines worldwide are those issued by the Global Initiative for Asthma (GINA) [4]. The current iteration suggests only treating asthma prior to testing of spirometry/peak flow with reversibility if there is clinical urgency, and always documenting the basis on which an asthma diagnosis has been made. If the objective testing does not support a diagnosis of asthma it suggests repeating the tests at a later date or considering alternative tests. The British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) also regularly publish an asthma guideline, which is widely used in the UK and other countries. The most recent version [5] still suggests treating first for those with a typical history, although lists a range of other tests for those in whom the diagnosis is unclear. However, also in the UK, the National Institute of Clinical Excellence (NICE) have recently published a guideline outlining a diagnostic protocol for asthma that includes not only spirometry with reversibility [6].

All three of these guidelines suggest using bronchial provocation testing where asthma is suspected, but where prior investigations have been nondiagnostic. These tests can utilise direct bronchial provocation testing with histamine or methacholine, or indirect provocation with exercise, inhaled mannitol, nebulised hypertonic saline or eucapnic hyperventilation. Although often

considered to be “gold-standard” investigations in suspected asthma, challenge tests can be positive in non-asthmatic patients, have a low but meaningful false negative rate, and can be influenced by baseline lung function and inhaled corticosteroid (ICS) therapy. Therefore, they need to be appropriately interpreted on a case-by-case basis. GINA and BTS/SIGN endorse both direct and indirect challenge tests, whereas only direct provocation protocols are currently recommended by NICE.

Another important difference between current diagnostic guidelines regards the utility of  $F_{eNO}$  testing. This is quite strongly endorsed by NICE, but remains much less emphatically recommended in the other guidelines. This reflects a lack of consensus within the respiratory community regarding the utility of  $F_{eNO}$  testing: although a potentially valuable surrogate marker of lower airway inflammation, it is influenced by extrinsic factors such as diet and smoking, as well as comorbid pathology such as nasal polyposis. Moreover, the absence of clear normative values can make identifying a pathological  $F_{eNO}$  level challenging.

These different approaches reflect the lack of consensus within the respiratory community about how to diagnose asthma, and differing opinions regarding the usefulness of  $F_{eNO}$  and other measures of type 2 inflammation in making the diagnosis [7]. Table 1 outlines the tests commonly used to support a diagnosis of asthma, and the potential confounding factors in interpreting these tests.

## Overdiagnosis of asthma

### How common is it?

Estimates of the overdiagnosis of asthma vary, probably in part due to the different populations studied and the varying definitions and approaches to diagnosing asthma within the studies. The most comprehensive analysis, to date, is that published recently by AARON *et al.* [8], which re-examined 613 Canadian adults with a diagnosis of asthma. Those included underwent an assessment with pre- and post-bronchodilator spirometry, and had a bronchial provocation test if this did not confirm asthma. If this was negative, asthma medication was reduced and the provocation test repeated. If still negative, asthma medication was stopped and the provocation test repeated again. If all of these tests were negative, participants were reviewed by a chest physician to make a final diagnosis of asthma or an alternative cause for their symptoms. The patients were followed up for a year, including repeat provocation tests at 6 months and 1 year, and if they had symptoms at any point during follow-up were encouraged to be seen by the study physician and spirometry was repeated at that stage. Asthma was ruled out in 33% of participants at the end of this diagnostic

Table 1 Diagnostic tests in asthma

	Risk of overdiagnosis	Risk of underdiagnosis	Notes
<b>Peak flow variability</b> <sup>‡,¶,†</sup>	Patient may have variable technique and/or have inaccurately charted PEFr.	Poorly sensitive (3–46% for identifying physician diagnosed asthma) [5]. Less sensitive if carried out when asymptomatic.	This test is dependent on patient effort and technique and it is unobserved. Patients need to do peak flows twice daily for 2 weeks and accurately chart them. Peak flow charts are easily available to healthcare professionals and low cost.
<b>Spirometry</b> <sup>‡,¶,†</sup>	Obstructed spirometry may be due to other conditions (e.g. COPD, bronchiolitis obliterans). In the elderly a ratio of <0.7 can be normal.	Usually a ratio of <0.7 (FEV <sub>1</sub> /FVC) is interpreted as obstructive; however, in the young a normal FEV <sub>1</sub> /FVC ratio is significantly higher than this, leading to possible false negatives. Normal spirometry at a single time point does not rule out asthma.	Need to have reproducible results for this to be a reliable measurement and this is dependent on the operator and patient effort, and potentially on patient coughing etc. Widely available (but not universally in primary care).
<b>Bronchodilator response</b> <sup>‡,¶,†</sup>	Patients may have reversibility in other diseases (e.g. COPD).	Patients may have used a bronchodilator on the day of the test, or a long-acting one even 1–2 days before. If patients are well at the time of the test and have normal spirometry no response may be seen. In chronic asthma patients may develop fixed airflow obstruction.	Need to have reproducible results for this to be a reliable measurement and this is dependent on the operator plus patient effort, and potentially limited by patient coughing etc. Widely available (but not universally in primary care).
<b>Measures of airway hyperresponsiveness</b> Direct provocation (methacholine, histamine) <sup>‡,¶,†</sup> Indirect provocation (mannitol, hypertonic saline, exercise, eucapnic hyperventilation) <sup>‡,¶,†</sup>	A proportion of the normal, asymptomatic population will have a positive test. False positives more likely in COPD, cystic fibrosis, allergic rhinitis.	If patients are on asthma treatment the sensitivity of the test drops and a negative test does not rule out asthma.	Generally not available in primary care. Of less value if patient has established airflow obstruction.
<b>FeNO</b> <sup>†</sup>	FeNO can be raised in other conditions (e.g. allergic rhinitis, eosinophilic bronchitis, COPD with an eosinophilic phenotype).	FeNO is suppressed in smokers. Some asthmatics will not have eosinophilic airway inflammation at the time of testing (e.g. neutrophilic/paucigranulocytic asthma). Asthma patients who are already on ICS treatment may have a normal FeNO.	Not consistently available in primary care.
<b>Blood eosinophils</b>	May be raised in numerous other conditions including COPD, allergic conditions, parasitic infections.	Treated asthmatics or those who are not currently exacerbating may have normal blood eosinophils. Does not help identify non-eosinophilic asthmatics.	Not a point of care test, so information not available to the treating clinician immediately.
<b>Sputum eosinophils</b>	May be raised in other conditions (e.g. COPD with an eosinophilic phenotype, eosinophilic bronchitis).	May be suppressed by treatment with ICS or OCS.	Only available in specialist centres, requires expertise and is expensive and time consuming.

PEFr: peak expiratory flow rate; FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC: forced vital capacity; OCS: oral corticosteroids. ‡: GINA guidelines; ¶: BTS/SIGN guidelines; †: NICE guidelines.

algorithm and after 12 months 30% remained off asthma medication. Although subjects were approached at random by an automated phone message, there is a possibility that patients who had doubts about their asthma diagnosis were more likely to agree to participate in the study, thus overestimating the extent of overdiagnosis. However, some of the inclusion criteria could also have resulted in an underestimate (*e.g.* excluding those with an asthma diagnosis made more than 5 years ago). The figure of 30% is not dissimilar to other published data: a study of patients in primary care in the UK by SHAW *et al.* [9] found that one third of patients labelled as having asthma had normal spirometry and provocation tests.

Obese patients are known to have more respiratory symptoms than the non-obese, and so one might expect them to have an even greater rate of overdiagnosis of asthma. VAN HUISSTEDÉ *et al.* [10] examined both over- and under-diagnoses in the morbidly obese by recruiting 86 patients who were undergoing pre-operative screening for bariatric surgery. 32 of the participants had a physician diagnosis of asthma, with the remainder free of an asthma diagnosis. They underwent pre- and post-bronchodilator spirometry,  $F_{eNO}$  measurement, impulse oscillometry and a methacholine provocation test. Asthma was diagnosed when symptoms were present in the presence of either significant reversibility in their FEV<sub>1</sub> with a short-acting  $\beta_2$ -agonist (SABA) or a positive provocation test. 40% of patients with a prior diagnosis of asthma did not meet these criteria, although it is possible that some of those patients did still have asthma, in particular as not all patients agreed to stop their inhaled therapy prior to testing. Interestingly, underdiagnosis was also present: 31% of patients with no diagnosis of asthma had asthma symptoms plus a positive test. The authors concluded that symptoms were “unreliable for an adequate diagnosis of asthma” in this population.

### What are the consequences of overdiagnosis?

One of the problems of misdiagnosis is that there may be an alternative diagnosis that is not made in a timely fashion. Some of the final diagnoses in the study by AARON *et al.* [8], such as ischaemic heart disease, subglottic stenosis and pulmonary hypertension, were serious and could lead to patient harm if unrecognised. In addition to this risk, patients are often on long-term inhaled therapy unnecessarily, leading both to potential side-effects and significant ongoing healthcare costs as these drugs are likely to be issued for many years after a diagnosis of asthma. In the past, many “mild” asthma patients were simply on an as required SABA inhaler, but increasingly this is discouraged with daily ICS therapy recommended for all but a few

[4, 5]. This represents a burden to the patient (taking an inhaler twice daily long term) and could conceivably cause side-effects such as an increased risk of adrenal suppression, diabetes, cataract formation and pneumonia [11, 12]. If the wrong diagnosis is made patients are also likely to remain symptomatic, and potentially have their asthma treatment “stepped up”, adding to both the cost and the potential for side-effects.

The most significant direct harm from overdiagnosis is likely to be in patients whose symptoms have led to them being inappropriately commenced on OCS. Although extremely useful in the short-term management of significant asthma exacerbations, and previously in the care of the relatively small group of asthma patients with genuine severe asthma that is refractory to inhaled medication, medium- to long-term OCS use is associated with significant treatment-related morbidity. A recent systematic review of the published literature found significantly increased likelihood of bone and muscle, psychiatric, cardiovascular, ocular and metabolic disease in asthma patients receiving long-term OCS therapy [13].

At a societal level, overdiagnosis of asthma may lead to significant opportunity cost, as resources required elsewhere are inappropriately spent on overdiagnosed asthma. This is of particular relevance as high-cost therapies such as targeted biologic drugs and bronchial thermoplasty come into more widespread use. The direct costs related to asthma in Europe have been estimated at EUR 17.7 billion per annum [1], mostly related to outpatient care and drug costs. One Canadian study has completed a cost analysis of direct costs (doctor visits and asthma-related drugs) to estimate the cost-benefit of screening patients with a physician diagnosis of asthma with objective testing [14]. They calculated a saving of CAD >35000 (approximately EUR 23700 or GBP 21150) per 100 patients screened. In the UK, NICE recently published a guideline on the diagnosis of asthma, attempting to make a protocolised objective testing standard care for all patients with suspected asthma, and has assessed the cost of its diagnostic protocol as GBP 92 per patient (EUR 103). It anticipates an associated saving of GBP 12 million per year in England alone (EUR 13.5 million), assuming that 33% of patients diagnosed with asthma do not have the condition (this assumption was based on the study of AARON *et al.* [8]). The implementation of this guidance is likely to be slow, however, as at present  $F_{eNO}$  testing is not readily available in primary care in the UK.

## Underdiagnosis of asthma

### How common is it?

The estimates of underdiagnosis of asthma vary widely from as little as 19% to as much as 73%. The

largest study, to date, was carried out in Copenhagen in 2000, and involved questionnaires being sent to over 10000 randomly selected subjects aged 14–44 years of age [15]. Those who reported symptoms suggestive of asthma were further assessed according to the GINA recommendations at the time, which included tests of reversible airflow obstruction. 493 were diagnosed with “definite asthma”, and of these 50% had not been diagnosed previously. DE MARCO *et al.* [16] reported similar rates in Italy, when patients who reported respiratory symptoms on questionnaires were reviewed by a physician and had methacholine challenge testing, skin prick tests and serum IgE measurement. ~32% of patients with asthma identified in this fashion had not been previously diagnosed. In the USA, a study among young adults entering military service demonstrated that of those diagnosed with asthma at enrolment (this included spirometry in all and challenge testing in 67%), in 30% a diagnosis of asthma had never been considered [17].

It should be noted that all of these studies had upper age limits in their inclusion criteria and participants were universally <44 years of age. The rate of underdiagnosis in the elderly may well be different, although there are fewer available data. A US based study conducted in the early 1990s used Medicare eligibility lists to recruit a cohort of patients who underwent a physical examination, spirometry, and questionnaires [18]. 2527 patients who were ≥65 years of age, with <10 pack-years smoking history and no history of congestive heart failure were included. It was estimated that 15% of the elderly who did not have physician-diagnosed asthma had symptoms that would be consistent with asthma. PARAMESWARAN *et al.* [19] recruited 390 patients who were >65 years-old and reported respiratory symptoms on a questionnaire for further evaluation in their homes. 95 patients were diagnosed with asthma on the basis of obstructive spirometry (FEV<sub>1</sub>/FVC ratio <0.7) with bronchodilator reversibility and symptoms consistent with asthma. The majority of these patients (75 out of 95) were lifelong never-smokers and only seven reported a previous asthma diagnosis. Even if all the ex-smokers are assumed to have COPD rather than asthma, this suggests >70% of asthma patients in this cohort were undiagnosed.

### Why does it occur?

Underdiagnosis may be due to medical professionals failing to recognise the disease, and perhaps attributing symptoms to obesity, deconditioning, cardiac disease or other causes. The patient may appear well with no abnormality on examination and if objective tests for asthma are carried out, particularly as a one off or when the patient is already on treatment, they may be falsely reassuring or misunderstood by the treating physician as excluding asthma. One might speculate that

because asthma is so prevalent, patients are less likely to be referred to specialists for confirmation of the diagnosis when it is unclear, whereas patients with suspected diseases that are less familiar may be more likely to be referred.

While this may account for some underdiagnosis, it appears that a substantial proportion of patients simply don't ever report their symptoms to a doctor. In the DIMCA (early detection, intervention and monitoring of asthma and COPD) project 66% of the patients with asthma symptoms and objective airflow obstruction, but no previous diagnosis of asthma, had never presented their symptoms to their general practitioner (GP) [20]. VAN SCHAYCK *et al.* [20] hypothesised that this may be due to the patients' ability to perceive airflow obstruction. A subgroup of subjects underwent histamine challenge alongside a Borg score and were then divided into “good perceivers”, who had an increase in their Borg score when their FEV<sub>1</sub> dropped by 20%, and “poor perceivers” who did not report symptoms with a 20% drop in FEV<sub>1</sub>. Poor perceivers were less likely to have presented to the GP with their respiratory symptoms.

### What are the consequences?

Asthma that is undiagnosed is also untreated, and this is likely to result in patients with ongoing symptoms. Patients may avoid exercise, may miss work and be less productive, and their quality of sleep and overall quality of life are likely to be adversely affected. These patients are likely to have unsuppressed airway inflammation and eosinophilic airway inflammation is associated with more asthma exacerbations [21], which may lead to the requirement for OCS and potentially hospitalisation.

It is possible that patients may also die of asthma prior to diagnosis, or on their first presentation of asthma. The UK national review of asthma deaths examined 195 deaths attributed to asthma between 2012 and 2013 [22]. Importantly, 38% of these patients had four or fewer inhalers with a steroid component issued in the previous year, indicating that undertreatment was a probable important factor in their deaths. Almost half of the patients that died of asthma were being managed as “mild” or “moderate” asthma. While this does not directly deal with underdiagnosis, it is an important reminder that even in the developed world undertreatment of asthma remains a problem.

As well as the impact on quality of life and risk of exacerbations, patients whose asthma is untreated may also be at risk of airways remodelling. Before ICS were routinely prescribed in asthma, the natural course of the disease was for a decline in FEV<sub>1</sub> over time [23] and the patient's degree of obstruction was related to the duration and severity of their asthma [24]. In 1994, HAAHTELA *et al.* [25] first demonstrated the importance of early ICS treatment. This was a follow-on study from a previous trial in which asthma patients were either

treated with as required terbutaline or with inhaled budesonide for 2 years. At the end of that study, the patients who had only had terbutaline were given ICS and the authors demonstrated that they had a significant improvement in lung function measurements (PEFR, FEV1 and provocative concentration causing a 15% fall in FEV1); however, this improvement was to a lesser degree than that observed in the group who were treated with ICS from within a year of diagnosis. By not diagnosing asthma in a timely manner, the opportunity may be missed to stop this decline in lung function [26].

## Summary

Asthma misdiagnosis appears to be widespread. This is in part due to the wide differential diagnosis for common respiratory symptoms and the lack of a standardised approach to diagnosis or gold standard test for asthma. It remains a clinical diagnosis, requiring the synthesis of history, examination,

physiological tests and possibly trials of treatment. The risks of overtreatment, missing an alternative diagnosis and the financial cost of long-term unnecessary medicines make overdiagnosis a considerable problem. Overdiagnosis is likely to be reduced by the routine use of objective tests of airflow obstruction or bronchial hyperreactivity before any treatment is commenced. This is likely to be further improved by including a measure of airway type 2 inflammation, such as FeNO. Priority should be given to prospectively testing diagnostic algorithms that include combinations of these measures, and increasing access to these tests from primary care. Underdiagnosis is more difficult to address, and is equally concerning given the potential risks to the patient of delayed treatment. Public health campaigns to encourage patients to present to primary care if they have symptoms of asthma may be required, or screening of patients for respiratory symptoms when, for example, joining a primary care practice could identify patients who need to have further assessment.

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## Conflict of interest

J. Kavanagh has nothing to disclose. D.J. Jackson reports personal fees from Astra-Zeneca, Napp Pharmaceuticals, Chiesi Pharmaceuticals, and GSK, and non-financial support from Boehringer-Ingelheim and Teva Pharmaceuticals, outside the submitted work. B.D. Kent reports personal fees from Astra-Zeneca, Napp Pharmaceuticals, and Chiesi Pharmaceuticals, and non-financial support from Boehringer-Ingelheim and Teva Pharmaceuticals, outside the submitted work.

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