

Underdiagnosis and Overdiagnosis of Asthma

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Abstract

Asthma is diagnosed on the basis of respiratory symptoms of wheeze, cough, chest tightness, and/or dyspnea together with physiologic evidence of variable expiratory airflow limitation. The prevalence of asthma varies widely around the world, ranging from 0.2% to 21.0% in adults and from 2.8% to 37.6% in 6- to 7-year-old children. Population-based studies in children, adults, and the elderly suggest that from 20% to 70% of people with asthma in the community remain undiagnosed and hence untreated. Underdiagnosis of asthma has been found to be associated with underreporting of respiratory symptoms by patients to physicians as well as poor socioeconomic status. On the opposite side of the spectrum, studies of patients with

physician-diagnosed asthma suggest that 30–35% of adults and children diagnosed with asthma do not have current asthma, suggesting that asthma is also overdiagnosed in the community. Overdiagnosis of current asthma can occur because of physicians' failure to confirm variable airflow limitation at the time of diagnosis or when sustained clinical remission of disease goes unrecognized. In this review, we define under- and overdiagnosis and explore the prevalence and burden of under- and overdiagnosis of asthma both in patients and within healthcare systems. We further describe potential solutions to prevent under- and overdiagnosis of asthma.

Keywords: asthma; underdiagnosis; overdiagnosis; lung health; epidemiology

The prevalence of asthma varies widely around the world, ranging from 0.2% to 21.0% in adults and from 2.8% to 37.6% in 6- to 7-year-old children (1). In the United States, asthma prevalence is now at its historically highest level: 7.6% of U.S. adults and 8.4% of U.S. children report having current physician-diagnosed asthma (2, 3). An estimated 12.7% of adult Americans have been diagnosed with asthma during their lifetime (2, 3). Reliable prevalence estimates obviously depend on accurate diagnosis.

Asthma is defined according to the Global Initiative for Asthma (GINA) 2018 as a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by a history of respiratory

symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation (4). Past definitions of asthma were complex, including symptoms, airflow limitation, airway hyperresponsiveness, and airway inflammation, but with growing evidence of the heterogeneity of asthma, the new GINA definition in 2014 reflected the view that the essential features are a history of variable symptoms and variable airflow limitation (5).

In the past, a diagnosis of asthma was often established solely on the basis of symptoms; however, a necessary condition of the GINA definition is that the diagnosis of asthma should not be based on symptoms alone (4, 6). Spirometry allows for

assessment of both airflow limitation and response to bronchodilators. Similarly, bronchial provocation tests allow for noninvasive assessment of airway hyperresponsiveness. Analysis of blood and induced sputum for eosinophilia and measurement of fractional exhaled nitric oxide ($F_{E_{NO}}$) can also help to noninvasively suggest the presence of airway inflammation characteristic of some asthma phenotypes (7). However, despite the availability of such tests, there are still many potential pitfalls that can interfere with the correct diagnosis of asthma. Problems associated with diagnosis of current asthma can be divided broadly into those associated with underdiagnosis and those associated with overdiagnosis.

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Defining Under- and Overdiagnosis

Underdiagnosis occurs when a patient living with asthma has not been identified as having the condition. Underdiagnosis can occur either because the patient has not communicated his/her symptoms to a physician, because the physician has not assigned a diagnosis to explain the patient's symptoms, or because the physician has attributed the patient's respiratory symptoms to a condition other than asthma. Conversely, overdiagnosis occurs when a patient is identified as having current asthma when in fact he/she does not have the condition. Overdiagnosis can occur if a patient's respiratory symptoms are mistakenly attributed to asthma when in fact another disease or condition is responsible for the patient's symptoms. Overdiagnosis of current asthma can also occur if a patient has experienced a sustained clinical remission of asthma, but this has not been recognized. Table 1 illustrates a classification scheme outlining underdiagnosis and overdiagnosis of asthma.

Both under- and overdiagnosis of asthma may be associated with inappropriate treatment: Underdiagnosis leads to failure to prescribe appropriate pharmaceutical and nonpharmaceutical therapies for asthma, and overdiagnosis may lead to prescription of nonindicated

therapies, exposing the patient to adverse effects and costs of medications without the potential for benefit. The objective of this narrative review is to describe the prevalence of underdiagnosis and overdiagnosis of asthma globally in adults, adolescents, and school-age children, as well as the burden on patients and healthcare systems. The causes of under- and overdiagnosis of asthma are explored, together with potential strategies to reduce their incidence. Potentially relevant articles for this review were retrieved from the MEDLINE and PubMed databases (1998–2018) using the following search terms: asthma underdiagnosis, asthma overdiagnosis, or asthma diagnosis. Relevant articles that provided information on prevalence, risk factors, and burden of under- and overdiagnosis of asthma were included within the narrative review.

Prevalence of Underdiagnosis of Asthma

Van Schayck and colleagues studied a random sample of 1,155 adult subjects from the Netherlands and found that 86 (7.4%) had airflow limitation demonstrated by spirometry as well as symptoms consistent with asthma. Of the 86 subjects with asthma, 63 (73%) had never been diagnosed with asthma (8). A similar study was performed in a random sample of 2,523 South

Australian adults. Current asthma was defined as a history of physician-diagnosed asthma and/or a greater than or equal to 12% and greater than or equal to 200-ml improvement in FEV₁ post-bronchodilator. Of the 2,523 sampled subjects, 292 (11.6%) had asthma, and of these, 56 (19.2%) were undiagnosed (9).

Backer and colleagues selected a random population sample of 10,877 subjects aged 14–44 years living in Copenhagen. Those who reported respiratory symptoms suggestive of asthma underwent pre- and post-bronchodilator spirometry and subsequent methacholine challenge to diagnose asthma. Of 1,149 subjects who reported respiratory symptoms 493 were found to have definite asthma, and of these, 249 (51%) were undiagnosed (10). Similarly, de Marco and colleagues studied a random, population-based sample of Italians aged 20–44 years and used spirometry, methacholine challenges, and specialist assessments to diagnose current asthma. Of 811 subjects, 105 (13%) were diagnosed with current asthma, and of these, 34 (32%) were undiagnosed (11).

Studies in school-age children have shown a prevalence of underdiagnosed asthma comparable to that seen in adults. A study of 495 Danish schoolchildren aged 12–15 years assessed symptoms, spirometry, and bronchial provocation tests. Asthma was defined as coexistence of asthma-like symptoms and one or more obstructive airway abnormalities (airflow limitation, bronchial hyperresponsiveness, or increased peak flow variability). The study found asthma in 71 children (14.3%), of whom 26 (37%) were undiagnosed (12).

Van Gent sampled 1,614 children aged 7–10 years old from 41 primary schools in Holland. Undiagnosed asthma was defined by the presence of asthma symptoms combined with either airway reversibility or hyperresponsiveness without a previous physician diagnosis of asthma. Among the sample of 1,614 children, 130 (8%) had undiagnosed asthma and 81 (5%) had diagnosed asthma, suggesting that in Dutch schoolchildren, 62% of subjects with current asthma were undiagnosed (13).

Underdiagnosis of asthma has been shown to be prevalent at both ends of the age spectrum, including elderly patients. Enright and colleagues studied 2,527 elderly subjects older than 65 years old sampled from the community who had no smoking history and no history of congestive heart

Table 1. Classification of Underdiagnosis and Overdiagnosis of Asthma

	Patient's True Disease or Condition	Patient's Assigned Diagnosis
Correct diagnosis	Current asthma	Current asthma
Underdiagnosis of current asthma	Current asthma	No diagnosis has been assigned to the patient, or a disease or condition other than asthma that causes respiratory symptoms has been assigned to the patient
Overdiagnosis of current asthma	1. A disease or condition other than asthma that causes respiratory symptoms (e.g., allergic rhinitis, GERD, or vocal cord dysfunction) or 2. Patient's previous asthma is in sustained clinical remission (in the absence of controller treatment or after controller treatment has been stopped)	Current asthma

Definition of abbreviation: GERD = gastroesophageal reflux disease.

failure. Overall, 4% had a diagnosis of asthma, but another 4% had had one or more attacks of wheezing in the previous 12 months, suggesting a 50% underdiagnosis of asthma (14). Parameswaran and colleagues studied 369 subjects older than 65 years of age from U.K. general practices with FEV₁/FVC less than 70%, of whom 95 patients had typical symptoms and bronchodilator reversibility, but only 7 (7.4%) reported a diagnosis of asthma (15).

In summary, recent studies of adults and children suggest that the prevalence of undiagnosed asthma is highly variable, depending on the population studied. Generally, population-based studies suggest that 7–10% of the adult and pediatric populations have current asthma, and in those with current asthma, between 20% and 73% remain undiagnosed.

Factors Associated with Underdiagnosis of Asthma

Patient Underreporting of Symptoms

The DIMCA (Detection, Intervention and Monitoring of COPD and Asthma) project explored whether underdiagnosis of asthma could be explained by underreporting of patients' symptoms to the family physician, or alternatively whether patients were reporting their symptoms but family physicians were underdiagnosing cases of asthma. In a random sample of 1,155 Dutch adults, 86 (7%) were found to have asthma. Of these 86 subjects, only 29 (34%) had consulted their general practitioners (GPs) previously for asthma symptoms, indicating that 66% of subjects with asthma had not reported their respiratory symptoms to their physician. Of 29 subjects with objective airflow limitation who presented to their GPs with respiratory symptoms, 23 (79%) were recorded in the medical files as having asthma, indicating underdiagnosis by the GP in 21% of cases. The investigators concluded that underreporting of respiratory symptoms to GPs by patients with asthma contributes significantly to the problem of underdiagnosis of asthma and conversely that underdiagnosis by the GP seems to play a smaller role (8, 16).

A study in schoolchildren aged 12–15 years showed that only 31% of adolescents with undiagnosed asthma had reported any asthma-like symptom to a doctor, suggesting that underreporting of respiratory symptoms to physicians

contributes to underdiagnosis in adolescents as well as in adults (12). A study in children aged 7–10 years old suggested that children with undiagnosed asthma may have poor perception of airflow limitation and may have few respiratory symptoms and therefore go undiagnosed. Van Gent and colleagues found undiagnosed asthma in 70 of 1,758 children (4%). Children with undiagnosed asthma had poorer perception of worsening airflow limitation during a methacholine-induced bronchoconstriction than children with diagnosed asthma, and their parents were less likely to report respiratory symptoms to a physician (13, 17).

Poor Diagnostic Sensitivity of Spirometry

Schneider and colleagues performed a cross-sectional study to determine the sensitivity, specificity, and predictive values of using pre- and post-bronchodilator spirometry to diagnose or exclude asthma at the time of initial presentation (18). The patients underwent spirometry by their primary physicians, who were all trained in the use and interpretation of spirometry. After spirometry, bronchial provocation tests and measurements of air trapping were undertaken. Ultimately, the investigators concluded that the diagnosis of asthma based only on office spirometry had a sensitivity of 29%, with a positive predictive value of 77% and negative predictive value of 53% (18). A similar study in specialized settings reported that pre- and post-bronchodilator spirometry had a sensitivity of 49%, positive predictive value of 85%, and negative predictive value of 29% for detecting current asthma (19).

Diagnosis of asthma via spirometry can be confounded by varying definitions of airflow limitation (20). For example, GINA states that the FEV₁/FVC ratio is “normally >0.75–0.80 in adults and >0.90 in children,” and the NHLBI, in its Expert Panel Report 3, provides values for normal FEV₁/FVC of 85% for ages 8–19 years, 80% for ages 20–39 years, 75% for ages 40–59 years, and 70% for ages 60–80 years (21), whereas the Global Initiative for Chronic Obstructive Lung Disease uses a fixed FEV₁/FVC ratio of less than 0.70 for the definition of airflow limitation (22). With spirometers now computerized, age- and sex-specific reference values for FEV₁/FVC can be used by most clinicians.

Low Socioeconomic Status

Several studies have investigated patient-related factors associated with underdiagnosis of asthma in adults. Gonzalez-Garcia and colleagues found that in Colombian adults, undiagnosed asthma was associated with low education level; female sex; and occupational exposure to fumes, dust, or gases (23). Adams and colleagues found that among Australian adults, those undiagnosed were more likely to be elderly, receiving government benefits, and to have a household income less than \$40,000 (9).

Burden of Underdiagnosis of Asthma

Adams and colleagues showed that quality of life in adult individuals with undiagnosed asthma was more impaired than in those without asthma. Subjects with undiagnosed asthma had poorer SF-12 (12-item Short Form Health Survey) scores on general health and physical functioning, as well as poorer vitality and mental health scores, than the nonasthma population. They also had a significantly higher mean number of visits to GPs over the previous year than those without asthma (9).

Van Gent and colleagues examined quality of life and school absenteeism in children aged 7–10 years with undiagnosed asthma. Children with undiagnosed asthma had lower quality-of-life scores than healthy control individuals ($P < 0.05$) in all domains of the Pediatric Asthma Quality of Life Questionnaire. Children with undiagnosed asthma experienced, on average, more than 1 week's greater absence from school in the previous 12 months because of respiratory symptoms than healthy control individuals (13).

Accordini and colleagues found that adults in Italy with a history of “asthma attacks and/or use of antiasthmatic drugs in the past 12 months without a physician diagnosis of asthma” reported a prevalence of work productivity losses and hospitalizations for respiratory illness similar to or greater than that of those with diagnosed asthma (24). Backer and colleagues examined quality of life in patients aged 14 to 44 years with both diagnosed and undiagnosed asthma. At study entry, disease-specific quality of life was poorer in patients with asthma who knew they had a respiratory disease than in

patients with undiagnosed asthma. Three years later, after those with undiagnosed asthma had been diagnosed and treated, quality-of-life scores improved by more than 0.5 points (the minimal important difference) in 45% of the undiagnosed patients compared with 26% of the patients with known asthma ($P < 0.05$). However, scores at 3 years in the undiagnosed patients were not improved compared with baseline (10).

Prevalence of Overdiagnosis of Asthma

General Population

Recent studies confirm that approximately 30–35% of adult patients within the community diagnosed with asthma do not have current asthma and may be overdiagnosed (25, 26). Aaron and colleagues studied 613 Canadian adults who had been diagnosed with asthma within the previous 5 years (26). The subjects were randomly recruited from the community via random-digit dialing. All participants were assessed with home peak flow and symptom monitoring, spirometry, and serial bronchial challenge tests, and participants using daily asthma medications had their medications gradually tapered off over four study visits. The primary outcome was the proportion of participants in whom a diagnosis of current asthma was ruled out, defined as participants who exhibited no evidence of acute worsening of asthma symptoms, reversible airflow obstruction, or airway hyperresponsiveness after all asthma medications were tapered off and after a study pulmonologist established an alternative diagnosis. Ultimately, current asthma was ruled out in 203 of 613 study participants (33%). After an additional 12 months of follow-up off all asthma medications, 181 participants (30%) continued to exhibit no clinical or laboratory evidence of asthma (26).

In an earlier study, the same group of investigators examined whether overdiagnosis of asthma is more prevalent in obese subjects compared with normal-weight subjects. Aaron and colleagues studied 496 adults with a physician diagnosis of asthma who were recruited randomly from the community via random-digit dialing; 242 were obese and 254 were of normal weight. A similar diagnostic algorithm was used to rule in or rule out

asthma. A diagnosis of current asthma was ultimately excluded in 32% of the obese group and in 29% of the nonobese group (25).

Although fewer studies exist in children, overdiagnosis of asthma in the pediatric population may be as common as in adults (27). Yang and colleagues recruited 203 Canadian children aged 9–12 years from a community-based sample, including 102 with parent-reported physician-diagnosed asthma. Eighty-six percent (88 of 102) of subjects with parent-reported asthma had a clinical diagnosis of asthma assigned by the study physician; however, only 53 of 88 had a study physician's clinical diagnosis of asthma plus objective evidence of reversible airway obstruction or bronchial hyperreactivity and therefore fulfilled the study's reference diagnosis of asthma (28). Results from this study suggest that asthma may be overdiagnosed in up to 48% of pediatric subjects.

Primary Care and Specialty Practices

Shaw and colleagues studied 262 patients from the United Kingdom labeled as having asthma in primary care practices and found that one-third had normal spirometry and normal bronchoprovocation results, suggesting that their respiratory symptoms may have been due to a condition other than asthma (29). A Canadian study of 263 patients referred to an asthma clinic used methacholine bronchoprovocation testing followed by full assessment by a respirologist as the gold standard for diagnosis of asthma. The study found that 160 of 263 patients (61%) did not have objective evidence of asthma (30).

A similar primary care study was done in 86 Swedish patients who had been diagnosed with asthma. These patients were evaluated by an allergist specializing in asthma, who performed spirometry testing and then a single methacholine challenge. Results of this study revealed that 29 participants (34%) had no evidence of asthma (31).

Looijmans-van den Akker and colleagues performed a retrospective analysis of children enrolled in primary healthcare practices in the Netherlands. Of 4,960 children aged 6–18 years, 652 children had received a diagnosis of asthma or were treated for asthma. A clinical review concluded that 349 children (54%) were most likely overdiagnosed (32).

Factors Associated with Overdiagnosis of Asthma

Failure to Use Objective Tests of Lung Function at Time of Diagnosis

Conditions such as vocal cord dysfunction and eosinophilic bronchitis can closely mimic asthma symptoms, so it is essential to obtain objective confirmation of variable airflow limitation. Aaron and colleagues demonstrated that 33% of 613 randomly chosen Canadian adults with recent physician-diagnosed asthma did not have current asthma (26). Those in whom current asthma was ruled out had significantly better lung function, were less likely to be using asthma medications, and were less likely to have had spirometry performed at the time of their initial diagnosis of asthma than subjects in whom current asthma was confirmed. Only 44% of those in whom asthma was ruled out had undergone assessment for variable airflow limitation in the community, compared with 56% of those in whom asthma was confirmed ($P = 0.02$) (26).

Studies in children have similarly confirmed that failure to arrange objective testing of lung function at the time of initial diagnosis is associated with overdiagnosis of asthma. A Dutch study of children aged 6–18 years found that of 652 children who had been diagnosed or treated for asthma in primary care practices, only 16.1% had an asthma diagnosis that had been confirmed by spirometry (32). A clinical review concluded that 54% were most likely overdiagnosed (32). A Canadian study of 102 children aged 9–12 years with a parent-reported diagnosis of asthma found overdiagnosis in 48% of the cohort and showed that only 18% had undergone previous pulmonary function testing (28). Researchers in a population-based study in Ontario, Canada, observed that only 43% of subjects diagnosed with asthma had received any kind of objective pulmonary function testing during the year before or 2.5 years after diagnosis (33).

Sustained Remission

In some patients, particularly adolescents and those with childhood-onset asthma, clinical remission of asthma can occur with no symptoms and normal lung function, although many may still have airway hyperresponsiveness and about one-third subsequently relapse (34–36). De Marco and colleagues reported that the rate of

symptomatic remission for patients with early-onset asthma was 68%, compared with 25% remission rates in patients with late-onset asthma (37). Aaron and colleagues found that 24 of 203 participants (12%) without evidence of current asthma had previously undergone pulmonary function tests in the community that had been diagnostic of asthma (26). These participants presumably experienced spontaneous remission of their asthma at some time between their initial community diagnosis and entry into the study.

Obesity

It was previously believed that overdiagnosis of asthma may be more prevalent in obese adults. Scott and colleagues noted that more than one-third of obese patients with previous physician-diagnosed asthma did not demonstrate bronchial hyperresponsiveness (38). Van Huisstede and colleagues found that 41% of morbidly obese individuals with a previous diagnosis of asthma did not qualify as having current asthma (39). However, a study by Aaron and colleagues suggested that overdiagnosis of asthma is not significantly more prevalent in obese subjects than in normal-weight subjects. Of 496 adults with a physician diagnosis of asthma, 242 were obese and 254 were of normal weight. A diagnosis of current asthma was ultimately excluded in a similar proportion from both groups: in 32% of the obese group and 29% of the nonobese group ($P = 0.46$) (25).

Burden of Overdiagnosis of Asthma

One of the most important consequences of asthma overdiagnosis may be the lost opportunity to investigate and treat the actual cause of the patient's respiratory symptoms. In a prospective study, Aaron and colleagues showed that 12 of 203 subjects (6%) with overdiagnosed asthma had unrecognized serious cardiorespiratory conditions responsible for their respiratory symptoms, such as critical coronary artery disease or subglottic stenosis (26). Misdiagnosis of serious cardiorespiratory diseases as asthma can result in patient suffering and unnecessary delays in initiating appropriate treatment.

In some countries, overdiagnosis of asthma may also lead to elevated insurance rates. Bachler and colleagues conducted a

comparative analysis study demonstrating that insurance rates for patients with chronic respiratory disease were well above those for people without chronic conditions (40).

Prolonged use of asthma medications can result in side effects without opportunity for benefit if the patient being treated does not actually have the disease (41–44). In some cases, this harm can be mitigated if patients with intermittent asthma are prescribed treatment only as needed (45). Although adverse effects of asthma controller medications are infrequent, the relatively high population prevalence of asthma overdiagnosis, as well as the frequent use of bronchodilator and inhaled

corticosteroid medication in those with physician-diagnosed asthma, makes the absolute occurrence of medication side effects and complications significant from a public health perspective (46).

Finally, the cost of overdiagnosis can be directly measured in the cost of unnecessary asthma medications in those who have been overdiagnosed. Aaron and colleagues found that 79% of overdiagnosed patients were using asthma medications and 35% were using asthma-controlling medications on a daily basis. These medications were tapered and then stopped for 12 months with few ill effects (26). Pakhale and colleagues showed that in Canada, the discounted

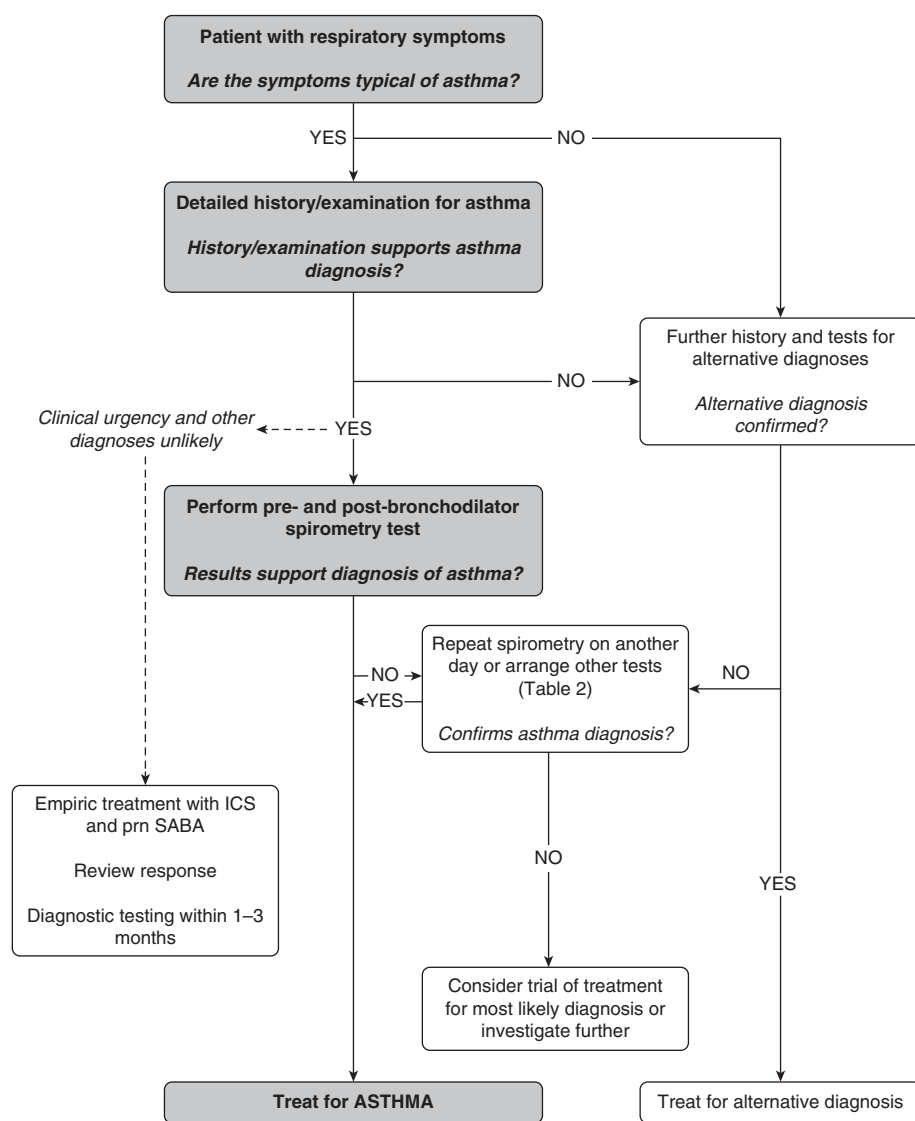


Figure 1. Diagnostic algorithm for confirming or ruling out asthma in a patient with respiratory symptoms. ICS = inhaled corticosteroids; SABA = short-acting β_2 -agonist. Reprinted by permission from Reference 4.

accumulated cost of asthma medication was approximately \$2,000 per patient per decade in 2009 Canadian dollars and that removing a diagnosis of asthma from a patient who had been overdiagnosed resulted in cost savings arising from lifetime costs of medication use averted (47).

Potential Solutions to Reduce the Incidence of Underdiagnosis of Asthma

Increased Patient Reporting of Respiratory Symptoms and Case Finding of Undiagnosed Patients

Increased public education about asthma aimed at encouraging patients to report

respiratory symptoms to their physicians could help to decrease underdiagnosis. In addition, a case-finding approach could identify individuals with symptoms of asthma who remain undiagnosed. However, unlike the case for chronic obstructive pulmonary disease, few large population-based case-finding studies have been performed for asthma, and there are few validated tools available to screen for asthma symptoms in the community (48).

Increased Use of Lung Function Testing to Confirm a Diagnosis of Asthma

Underdiagnosis frequently occurs if objective testing at the initial diagnostic assessment of respiratory symptoms is not

performed. A study conducted by Emerman and colleagues revealed that physicians underestimated the degree of airflow obstruction via FEV₁ values by 8.1% when no objective tests were performed at the initial assessment for asthma (49). Pre- and post-bronchodilator spirometry can identify and confirm variable airflow limitation. When spirometry is performed, use of available age- and sex-specific reference values for FEV₁/FVC improves diagnostic sensitivity (20, 50). Test results may be more likely to be positive if tests are performed during symptomatic periods or after exercise. Bronchial challenge testing can help to confirm the diagnosis in patients in whom asthma is suspected but results of spirometry are negative. The

Table 2. Objective Tests of Airflow Limitation Recommended by Global Initiative for Asthma 2018 to Confirm a Diagnosis of Asthma in a Patient with Typical Symptoms

Diagnostic Feature	Criteria for Confirming the Diagnosis of Asthma
Documented excessive variability in lung function* (one or more of the tests below) AND documented airflow limitation*	The greater the variations, or the more occasions when excess variation is seen, the more confident the diagnosis At least once during diagnostic process (e.g., when FEV ₁ is low), confirm that FEV ₁ /FVC is reduced
Positive BD reversibility test* (more likely to be positive if BD medication is withheld before test: SABA, ≥4 h; LABA, ≥15 h)	<i>Adults:</i> Increase in FEV ₁ of >12% and >200 ml from baseline, 10–15 min after 200–400 µg of albuterol or equivalent [†] (greater confidence if increase in >15% and >400 ml) <i>Children:</i> Increase in FEV ₁ of >12% predicted
Excessive variability in twice-daily PEF over 2 wk*	<i>Adults:</i> Average daily diurnal PEF variability >10% [‡] <i>Children:</i> Average daily diurnal PEF variability >13% [‡]
Significant increase in lung function after 4 wk of antiinflammatory treatment	<i>Adults:</i> Increase in FEV ₁ by >12% and >200 ml (or PEF [§] by >20%) from baseline after 4 wk of treatment, outside respiratory infections
Positive exercise challenge test*	<i>Adults:</i> Fall in FEV ₁ of >10% and >200 ml from baseline <i>Children:</i> Fall in FEV ₁ of >12% predicted or PEF >15%
Positive bronchial challenge test (usually performed only in adults)	Fall in FEV ₁ from baseline of ≥20% with standard doses of methacholine or histamine or ≥15% with standardized hyperventilation, hypertonic saline, or mannitol challenge
Excessive variation in lung function between visits* (less reliable)	<i>Adults:</i> Variation of FEV ₁ of >12% and >200 ml between visits, outside respiratory infections <i>Children:</i> Variation in FEV ₁ or >12% in FEV ₁ or >15% in PEF [§] between visits (may include respiratory infections)

Definition of abbreviations: BD = bronchodilator (SABA or rapid-acting LABA); LABA = long-acting β₂-agonist; PEF = peak expiratory flow (highest of three readings); SABA = short-acting β₂-agonist.

If bronchodilator reversibility is not present at initial presentation, the next step depends on the availability of other tests and the urgency of the need for treatment. In a situation of clinical urgency, asthma treatment may be commenced and diagnostic testing arranged within the next few weeks, but other conditions that can mimic asthma should be considered, and the diagnosis of asthma should be confirmed as soon as possible.

*These tests can be repeated when symptoms are present or in the early morning.

[†]We note that in order to exclude significant reversibility, a dose of 400 µg of albuterol or equivalent may be needed. This change has been made with permission of the Global Initiative for Asthma.

[‡]Daily diurnal PEF variability is calculated from twice-daily PEF as [(day's highest minus day's lowest)/mean of day's highest and lowest] and averaged over 1 week.

[§]For PEF, use the same meter each time because PEF may vary by up to 20% between different meters. BD reversibility may be lost during severe exacerbations or viral infections.

sensitivity of direct bronchial challenge tests (methacholine) to detect asthma is 98% (51), and indirect bronchial challenge tests have high specificity; however, access to these tests is limited in most primary care settings.

Potential Solutions to Reduce the Incidence of Overdiagnosis of Asthma

Ensuring Testing before Starting Asthma Treatment

Current British Thoracic Society/Scottish Intercollegiate Guidelines Network guidelines recommend commencing inhaled corticosteroids for patients with suspected asthma (52). However, variability in lung function rapidly decreases with treatment, so the diagnosis should, whenever possible, be confirmed before starting treatment. Improved access to spirometry in primary care is needed to reduce asthma overdiagnosis.

GINA suggests an efficient series of tests to diagnose new asthma (Figure 1) (4), starting with pre- and post-bronchodilator spirometry, and if spirometry is inconclusive, further tests can be ordered. Table 2 (from GINA 2018) lists additional tests other than spirometry that can confirm a diagnosis of asthma, including bronchial challenge tests, exercise testing, monitoring of peak flow rates, assessments of intervisit variability in FEV₁, or a significant increase in lung function after 4 weeks of antiinflammatory treatment. Use of an algorithm ensures that multiple diagnostic methods can potentially be used to validate the accuracy of the diagnosis.

Confirming Asthma Diagnosis in Patients Already on Controller Treatment

If symptoms fail to respond to initial asthma treatment, GINA advises review of the diagnosis rather than automatically stepping up the dose, and GINA provides an algorithm for confirming the diagnosis of asthma in patients already receiving controller treatment (4). Aaron and colleagues used a series of four physician visits with gradual medication tapering to either confirm or exclude asthma in patients who had recently been diagnosed with asthma in the community (25) (Figure 2). Current asthma was ruled out in those patients who had no evidence

of worsening of symptoms or airflow obstruction or direct bronchial hyperresponsiveness after gradually being tapered off all asthma medications (25). Alternative algorithms for undiagnosing asthma and de-escalating treatment have also been proposed (53). However, once the diagnosis of asthma has been confirmed and treatment has been downtitrated to the minimal effective dose, further assessments are likely unnecessary.

Biomarkers as Additional Tests to Help Confirm Asthma

The National Institute for Health and Care Excellence recommends that F_{ENO}, which has a moderate correlation with sputum eosinophilia (7, 54), should be measured in all patients with suspicion of asthma (55). Wang and colleagues reported that the best cutoff value for F_{ENO} tests for identifying bronchodilator reversibility was 41 ppb, resulting in a specificity of 75% and sensitivity of 72% for the test (56).

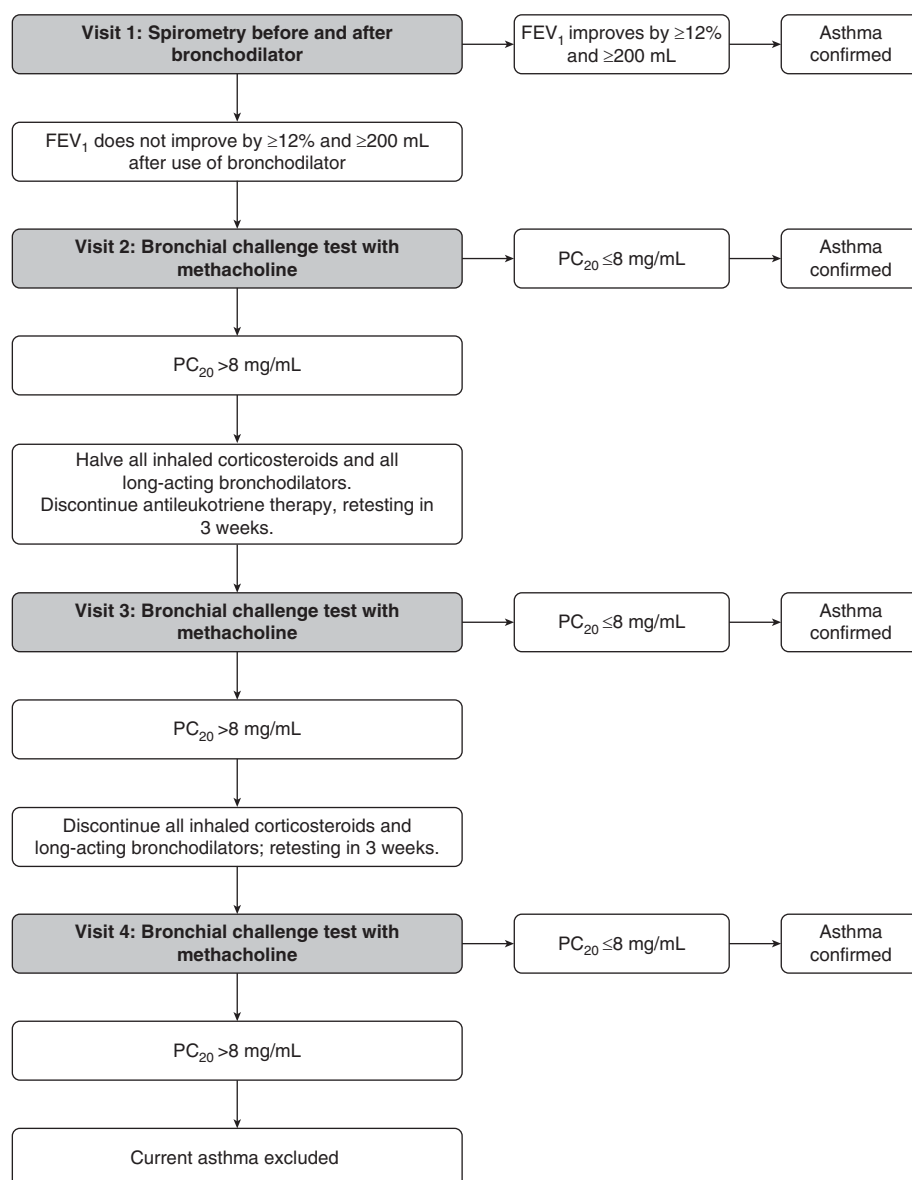


Figure 2. Diagnostic serial testing algorithm to confirm or exclude asthma in patients who have previously been diagnosed with asthma and who are receiving asthma medications. Current asthma is ruled out in those patients who have no evidence of worsening of symptoms or airflow obstruction or bronchial hyperresponsiveness after being gradually tapered off all asthma medications. Reprinted by permission from Reference 26.

However, asthma is heterogeneous, and noneosinophilic asthma is well recognized. There are multiple confounders for FE_{NO} , including age, sex, height, bronchoconstriction, atopy, and allergen exposure, and the association with sputum eosinophilia is lost with smoking and in obesity (57). FE_{NO} is also elevated in nonasthma conditions, including eosinophilic bronchitis and allergic rhinitis.

In patients with nonspecific respiratory symptoms, a higher FE_{NO} is associated with greater short-term response to inhaled corticosteroids, as seen in a randomized, placebo-controlled trial by Price and colleagues (58). However, this does not help in distinguishing between eosinophilic bronchitis (for which short-term treatment is sufficient) and asthma (for which long-term risk reduction is important), and

to date there are no long-term studies suggesting that it is safe to withhold inhaled corticosteroids in patients with a low FE_{NO} .

Assessing the degree of sputum eosinophilia can help to predict the response to treatment with inhaled steroids as well as biologic agents. However, a study by Lemi re and colleagues demonstrated that sputum eosinophil tests exhibited a weak correlation with airway responsiveness, and the test taken in isolation has relatively poor sensitivity and specificity for diagnosing asthma (59).

Conclusions

A relatively high prevalence of underdiagnosis and overdiagnosis of

asthma has been reported in the literature, producing significant consequences to patients and to healthcare systems. People with undiagnosed asthma have poorer health-related quality of life and more absenteeism from work and school. People with overdiagnosed asthma experience potential side effects related to unnecessary use of medications, the burden of increased drug costs, and the lost opportunity to diagnose the true cause of their respiratory symptoms. Incorporation of standardized diagnostic algorithms into clinical settings, together with development of new predictive biomarkers, might possibly help lower the prevalence of under- and overdiagnosis of asthma. ■

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