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Chronic obstructive pulmonary disease: missed diagnosis versus misdiagnosis

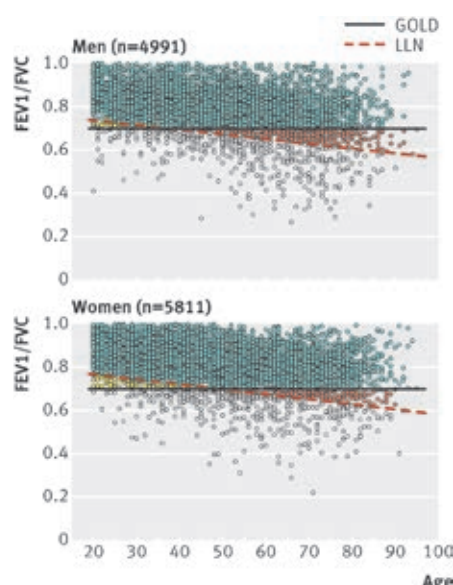
This article is part of a series of overdiagnosis looking at the risks and harms to patients of expanding definitions of disease and increasing use of new diagnostic technologies

By 2004 chronic obstructive pulmonary disease (COPD) was claimed to be the fourth most important cause of death worldwide,¹ and its global prevalence and mortality are on the increase.² Smoking accounts for about 75% of cases,³ but environmental exposures to tobacco smoke and other pollutants such as biomass fuels and occupational exposures may account for the remaining cases.⁴⁻⁶ COPD is a progressive disease, and in the later stages patients have frequent admissions to hospital, with over a third being readmitted in 30 days, contributing to an annual cost of £800m (€1bn; \$1.24bn) in the UK.⁷ In the UK concern has been expressed that COPD is severely underdiagnosed,⁸ particularly among people with early stages of the disease who could benefit from preventive strategies.⁹⁻¹⁰ However, we argue that current diagnostic criteria are leading to overdiagnosis in some groups.

Criteria for diagnosis

COPD should be considered in any patient who has symptoms of cough or sputum production, dyspnoea, or a history of exposure to risk factors. The diagnosis requires confirmatory spirometric evidence of airflow limitation that is not fully reversible.¹¹ This is defined from the ratio of forced expiratory volume in 1 second (FEV_1) divided by the forced vital capacity (FVC). Internationally agreed standards for defining the lower limits of normal (LLN) for FEV_1/FVC have been established for many years following accepted best practice for statistical analysis of data approximating to a normal distribution.¹²⁻¹⁴ These criteria take account of height, age, sex, and ethnicity and use 90% confidence limits of the normal distribution obtained from the data of many thousands of healthy people.¹⁵

In the 1990s the Global Initiative for Obstructive Lung Disease (GOLD) was set up "to raise awareness of COPD and to improve prevention and treatment of this lung disease for patients around the world," with its first report released in 2001.¹⁶ However, GOLD defined airways obstruction as a post-bronchodilator FEV_1/FVC



FEV_1/FVC data for men and women from the 2001 Health Survey for England against age. The blue circles above both lines are normal by both the GOLD and lower limit of normal (LLN) criteria (true negatives) and white circles below both lines are abnormal by both criteria (true positives). Yellow circles in the left triangle are false negatives by the GOLD criterion and red circles in the right triangle are false positives

of <0.7 with no account taken of age, sex, or other factors. This definition has subsequently been adopted by the UK National Institute for Health and Care Excellence (NICE)¹⁷ and is also widely used in the United States, Europe, and Australasia.¹⁸⁻²⁰

Rationale for the change

GOLD argued that using a fixed ratio of $FEV_1/FVC < 0.7$ was a pragmatic step that was simple to follow and so could easily be applied anywhere in the world. It argued that nurses and general practitioners would not be able to understand LLN, and yet LLN is used for numerous blood tests; furthermore electronic spirometer software includes LLN values. Although the 2006 version of GOLD recommendations acknowledged that use

SUMMARY BOX

Clinical context—The prevalence and mortality of chronic obstructive pulmonary disease (COPD) is increasing globally

Diagnostic change—A new diagnostic threshold for airflow obstruction ($FEV_1/FVC < 0.7$) was introduced in 2001 (GOLD). This contrasts with internationally agreed criteria using statistically defined lower limits of normal (LLN) for different populations

Rationale for change—The new diagnostic criterion was simple so could be easily implemented in non-specialist settings

Leap of faith—Treatment of people identified by GOLD criteria would reduce morbidity and mortality

Increase in disease—The new definition estimates COPD prevalence at 22% in those aged over 40 years in England and Wales compared with 13% using LLN criteria

Evidence of misdiagnosis and missed diagnosis—Up to 13% of people thought to have COPD on GOLD criteria have been found to be misdiagnosed

Harms from misdiagnosis and missed diagnosis—Cardiovascular mortality is unexpectedly high among mildly breathless patients with GOLD diagnosed COPD

Limitations—Few studies have compared patient outcomes with GOLD and other criteria for diagnosing COPD

Conclusions—COPD management programmes and guidelines should adopt LLN criteria for defining airflow obstruction to avoid overdiagnosis in elderly people and missed diagnosis in younger patients

of LLN would reduce overdiagnosis in elderly people, they cited one study as evidence for continued use of the fixed ratio.²¹ This suggested that 0.7 was the LLN for men irrespective of age. However, the poor sampling of men in older age groups makes this finding unreliable, and the study also found that LLN declined with age in women, which has been shown to be true for both sexes in more than 50 other published datasets.²²

Furthermore, GOLD did not provide evidence of the effectiveness of its definition of airflow obstruction and severity grading (based on arbitrary levels of FEV₁ expressed as percentage of predicted) in managing COPD in clinical practice. In 2010, over 150 international experts and 12 international organisations asked GOLD to change its definition of airflow obstruction to the internationally accepted LLN criterion.²³ Proponents of GOLD have stated that they think further discussion about LLN versus fixed ratio is not important.²⁴ However, patients who are unnecessarily treated for COPD or whose cardiac disease is misdiagnosed as COPD might view this differently.

Changes in disease prevalence

The population prevalence of airflow obstruction in 40 to 95 year olds in England and Wales was recently found to be 22.2% (95% confidence interval 21.2% to 23.2%) by the GOLD criterion but only 13.1% (12.2% to 13.9%) by LLN.²⁵ The GOLD definition of airflow obstruction has an important influence on disease prevalence based on the age and sex of the population being considered. The figure shows the FEV₁/FVC data from the 2001 Health Survey for England plotted for each sex against age (mean age 49). The health survey has been undertaken annually since 1991,²⁶ and its data are used to help design appropriate healthcare programmes for the UK.²⁷ The triangular area in the right of both plots represents people with airflow obstruction diagnosed by GOLD criteria but not by LLN (false positives). This triangle is larger in men than women. In this survey population GOLD suggests 11.8% of participants have airflow obstruction, a third of whom (4% of the total) have false positive results. This finding is supported by many other studies.^{25 28-30}

The GOLD criterion also misses one in eight cases of airflow obstruction identified by the LLN in the health survey (1% of total population). Those missed by GOLD tend to be younger (under 50) and are predominantly female, as found elsewhere.^{31 32} The GOLD criterion has a sensitivity of 88% and positive predictive value of only 66% when using the lower 90% confidence limit as the LLN. The positive predictive value drops to 51% if the 95% confidence limit is used as appropriate for sampling an unselected population.

Evidence of misdiagnosis and missed diagnosis

GOLD classifies patients with COPD into four groups on the basis of symptoms, spirometric classification, breathlessness, and history of exacerbations.¹⁶ Groups A and B have less airflow obstruction and lower risk of exacerbations compared with groups C and D. A recent paper studied a cohort of 1465 people with COPD in China (mean age 68 years) to determine how different methods for registering dyspnoea affected the prevalence of COPD in each of the four GOLD groups.³³ When the researchers used the COPD assessment test,³⁴ the distribution of COPD was 12% in group A, 20% in group B, 12% in group C, and 56% in group D. They also found that 14.2% (208) of the 1465 participants had FEV₁/FVC values within the normal range (defined by LLN) and most of these (146) were in the low risk groups A and B.

Misdiagnosing COPD may thwart research into the disease. Smaller, more focused, and thus cheaper trials using the LLN for COPD may also be more likely to give reliable answers about COPD and its treatment.

Harms from misdiagnosis and missed diagnosis

Misdiagnosing patients may lead to poorer outcomes because of adverse effects of inappropriate medication or incorrect treatment. For example, people meeting only the GOLD criterion for COPD have a higher prevalence of heart disease than people who meet both LLN and GOLD criteria (27% versus 15%).³⁷ A study found patients in GOLD group B, who have only mild airflow obstruction but are breathless, had an unexpectedly high three year mortality from cardiac disease of 10.6%³⁸; this compared with 3.8% for patients in group C, who had less breathlessness but more severe airflow obstruction.³⁸ Others found that 27% of patients in group B had no airflow obstruction by LLN criteria,³³ and if heart disease caused the symptoms in these patients this might account for the unexpectedly high cardiovascular mortality.

This raises the possibility that GOLD group B may include people who have cardiac disease but have had COPD misdiagnosed. Death from COPD usually occurs after a long period of slow decline and so high early mortality in group B is anomalous. People with heart disease often die suddenly and so timely treatment is important. COPD and ischaemic heart disease are often comorbid conditions, since smoking is the common causative agent, but coexistence should be more prevalent in those with higher smoking exposure and consequently more airflow obstruction.

The clinical harm from misdiagnosis is potentially compounded because inhaled treatment for COPD with anticholinergic compounds has been associated with increased cardiac mortality.^{39 40}

In a meta-analysis of 12 studies involving a total of over 12 000 patients, inhaled anticholinergics were associated with a significant increased risk of cardiovascular death (relative risk 1.80, 95% confidence interval 1.17 to 2.27).³⁹ The unexpected mortality arising from use of these drugs may be due to the fact they are being given to patients with heart disease who have COPD misdiagnosed with the GOLD criteria. Furthermore, current use of inhaled corticosteroids in COPD increases the likelihood of developing severe pneumonia, with a relative risk of 1.69 (1.63 to 1.75).⁴¹ Patients with misdiagnosed COPD are exposed to these risks for no benefit.

Resources are also wasted by prescribing inhalers for people with a FEV₁/FVC above the LLN. Recent data estimate that about 40% of patients newly diagnosed by GOLD criteria have a normal FEV₁/FVC,²⁵ and so using LLN criteria might make considerable savings on the budget for inhalers and associated drugs.

The GOLD criteria also miss the diagnosis in younger people, predominantly women (figure). This means that patients with the most potential gain from prevention strategies are denied such interventions and will potentially go on to develop more serious disease before COPD is diagnosed.

Conclusions

The current NICE guidelines and the GOLD strategy documents for COPD should be modified because they overdiagnose COPD in older men while missing the possibility of diagnosing heart disease; they also underdiagnose COPD in young women. Continued use will lead to suboptimal outcomes and use of resources. We argue that clinicians should use the LLN instead when assessing patients for COPD. Adoption of this criterion, which is programmed into most spirometry software, will help to improve patient care through more accurate diagnosis of obstructive airflow diseases as well as leading to other investigations for alternative diagnoses when appropriate. Use of LLN will also improve the accuracy of epidemiological data and save money by reducing admissions resulting from misdiagnosis and inappropriate therapy. Clinics focusing on breathless patients should consider including echocardiography and other cardiovascular investigations as well as spirometry to ensure correct diagnosis. Furthermore, editors of respiratory journals and their reviewers should increasingly challenge authors to examine the effect of different methods of diagnosis on their results.

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