

# **Under- and over-diagnosis of COPD: a global perspective**

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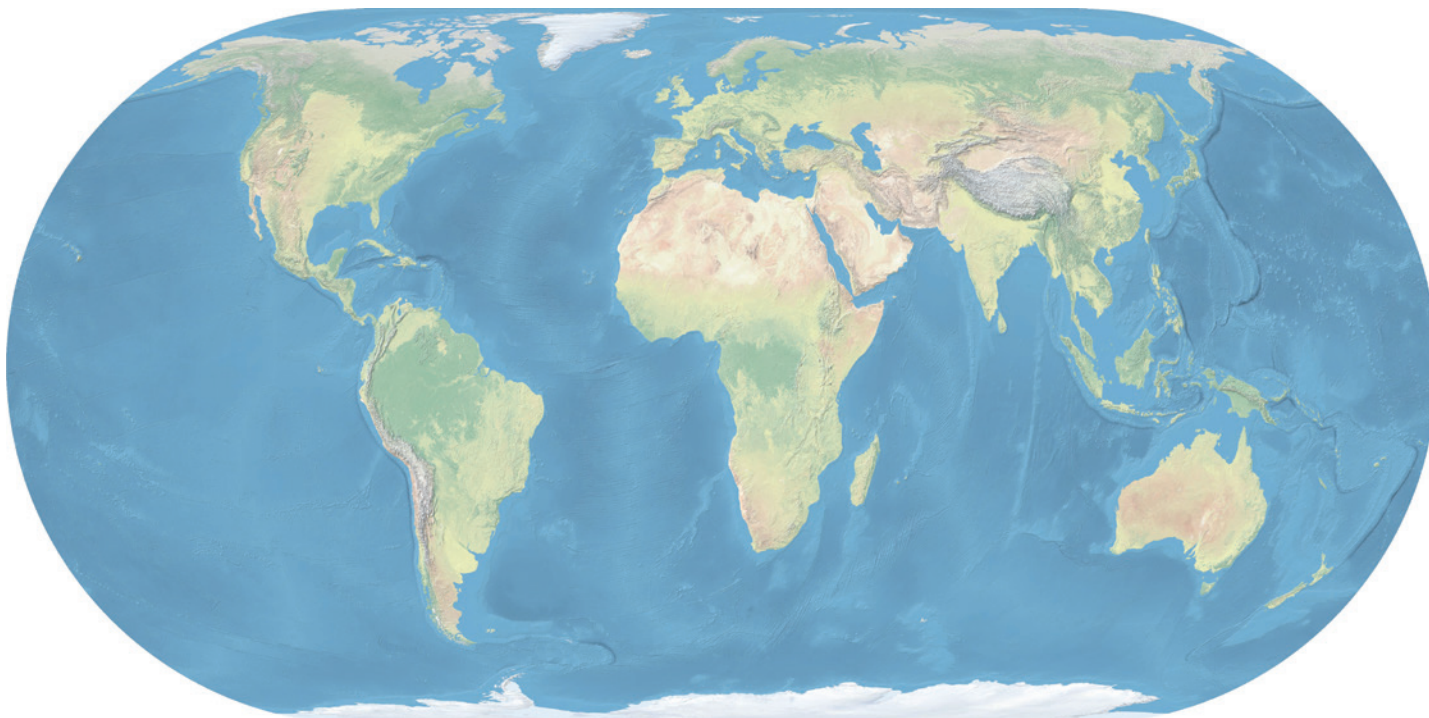
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## Key points

- Globally, there is large variation in the prevalence of COPD, with 10–95% under-diagnosis and 5–60% over-diagnosis (table 1) due to differences in the definition of diagnosis used, and the unavailability of spirometry in rural areas of low- and middle-income countries where the prevalence of COPD is likely to be high.
- In order to be diagnosed with COPD, patients must have a combination of symptoms with irreversible airflow obstruction defined by a post-bronchodilator  $FEV_1/FVC$  ratio of  $<0.7$  or below the fifth centile of the lower limit of normal (LLN), and with a history of significant exposure to a risk factor. Repeat spirometry is recommended if the ratio is between 0.6 and 0.8.
- Not performing spirometry is the strongest predictor for an incorrect diagnosis of COPD; however, additional factors, such as age, gender, ethnicity, self-perception of symptoms, co-existent asthma, and educational awareness of risk factor by patients and their physician, are also important.
- COPD can be associated with inhalation of noxious particles other than smoking tobacco.

## Educational aims

- To summarise the global prevalence of over- and under-diagnosis of COPD.
- To highlight the risk factors associated with the under- and over-diagnosis of COPD.
- To update readers on the key changes in the recent progress made regarding the correct diagnosis of COPD.



## Review

# Under- and over-diagnosis of COPD: a global perspective

Globally, chronic obstructive pulmonary disease (COPD) is the fourth major cause of mortality and morbidity and projected to rise to third within a decade as our efforts to prevent, identify, diagnose and treat patients at a global population level have been insufficient. The European Respiratory Society and American Thoracic Society, along with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document, have highlighted key pathological risk factors and suggested clinical treatment strategies in order to reduce the mortality and morbidity associated with COPD. This review focuses solely on issues related to the under- and over-diagnosis of COPD across the main geographical regions of the world and highlights some of the associated risk factors. Prevalence of COPD obtained mainly from epidemiological studies varies greatly depending on the clinical and spirometric criteria used to diagnose COPD, *i.e.* forced expiratory volume in 1 s to forced vital capacity ratio <0.7 or 5% below the lower limit of normal, and this subsequently affects the rates of under- and over-diagnosis. Although under-utilisation of spirometry is the major reason, additional factors such as exposure to airborne pollutants, educational level, age of patients and language barriers have been widely identified as other potential risk factors. Co-existent diseases, such as asthma, bronchiectasis, heart failure and previously treated tuberculosis, are reported to be the other determinants of under- and over-diagnosis of COPD.

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a major chronic disease, highly prevalent in the ageing population exposed to tobacco smoke and airborne pollutants [1], and is currently the fourth leading cause of morbidity and deaths worldwide [2], accounting for around 3 million deaths globally. The current 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document defines COPD as “a common, preventable and treatable disease that is characterized by persistent

respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.” Exposure to noxious particles and gases has been recognised as another risk factor, other than smoking, that may contribute to obstructive airway disease. In a global context, other risk factors, such as exposure to airborne pollutants from household fuel burning, occupation and ambient sources, need to be considered [3, 4].

Our current strategy to diagnose individuals states that patients must have symptoms and



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**COPD is a major cause of morbidity and mortality, but misdiagnosis of COPD is a huge problem worldwide. Its main causes are under-utilisation of spirometry and lack of uniformity in diagnosis criteria, particularly in resource poor settings.** <http://ow.ly/KfP330nonkh>



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obstructive airflow limitation with a prior history of exposure to a known risk factor. In the absence of symptoms and/or physiological confirmation, the definition is not met. This potentially leaves many patients misdiagnosed, which may lead to negative impacts both at the individual and population levels.

The presence of symptoms can be assessed easily, but care must be taken of those patients who may under- or over-perceive their symptoms and those with the presence of comorbidities that could present with similar symptoms. The former can potentially leave patients under-diagnosed, whilst the latter may cause over-diagnosis leading to potentially excessive treatment, given that the treatment algorithm in the GOLD strategy is to offer inhaler therapy based on the modified Medical Research Council breathlessness scale, COPD assessment test score and exacerbation frequency using the ABCD tool.

The correct performance and interpretation of spirometry remains an issue of contention, more often in resource-poor settings of low- and middle-income countries (LMICs). Regular calibration of the spirometer is recommended, as failing to do so may lead to either under- or over-diagnosis of COPD. Traditionally, the presence of a post-bronchodilator forced expiratory volume in 1 s (FEV<sub>1</sub>) to forced vital capacity (FVC) ratio of <0.7 has been used to diagnose COPD; however, current European Respiratory Society (ERS)/American Thoracic Society guidelines recommend the use of a post-bronchodilator FEV<sub>1</sub>/FVC less than the fifth centile of the lower limit of normal (LLN), although this is mainly used in epidemiological research rather than daily clinical practice [5]. Many studies using the fixed ratio cut-off have reported over-diagnosis of COPD in the elderly and under-diagnosis in younger individuals (<40–45 years), particularly amongst those who are asymptomatic [6, 7]. The 2019 GOLD strategy preferred the use of the ratio, but recommended repeat spirometry testing if the value is between 0.6 and 0.8, due to the variability and the increase in positive predictive value of COPD if the value is less than 0.6 [8]. Given the challenges of performing single post-bronchodilator spirometry in LMICs in a primary care setting, the recommendation of repeating spirometry in borderline cases globally is a major challenge.

The proportion of under-diagnosis of COPD is likely to be high in LMICs for a number of reasons: limited access to healthcare, asymptomatic younger individuals, under-reporting of symptoms, and lack of knowledge about risk factors and hence under-reporting to a physician. Furthermore, under-diagnosis could also occur due to manifestations of respiratory symptoms (*e.g.* breathlessness) in individuals with other existing comorbidities, such as congestive heart failure. In contrast, patients with the presence of other comorbidities, such as asthma, bronchiectasis and post-tuberculosis, may present with respiratory symptoms and may be diagnosed with COPD based on a history of

exposure to noxious particles, hence leading to over-diagnosis.

The objective of this current literature review focuses on the global prevalence and risk factors for the diagnosis of COPD and the potential reasons for under- and over-diagnosis separated into geographical regions of interest: North America/Europe/Oceania; Africa; Central and South America; South-East Asia; and the Middle East and South Asia (table 1). Under-diagnosis was defined as those individuals with or without symptoms and chronic airflow obstruction (AFO) who were not yet diagnosed with COPD or those with presence of other comorbidities but symptoms common to COPD wrongly labelled for another disease. Over-diagnosis was defined as those who were labelled as COPD but without the associated symptoms of COPD or evidence of AFO or symptoms of other diseases labelled as COPD. Here, the term over-diagnosis is only meant to refer to correct diagnosis of COPD and may not be associated with increase in morbidity or mortality during their life-time.

## North America, Europe, Australia and New Zealand

### Epidemiology of COPD

Published studies from high-income countries have reported a large variation in prevalence and incidence of COPD, both within a country and also among different countries [9]. These variations are likely due to inherent population differences between geographic regions, but also could be related to a host of factors, including the sampling method, the specific populations studied, and the multitude of criteria used to define COPD.

Data from the USA is primarily derived from the National Health and Nutrition Examination Survey (NHANES). Prevalence estimates in the USA range from 10.2–20.9% [10–12], with TILERT *et al.* [12] demonstrating that the observed variability in their study could be explained by the spirometric criteria applied. The Burden of Obstructive Lung Diseases (BOLD) study reported a prevalence of 19.6% at its US site, similar to the NHANES, using the GOLD definition of COPD [13]. Prevalence of self-reported but physician-diagnosed COPD in Canada and Australia ranged from 8.5% to 18% [11, 14], similar to the US estimates, but with the BOLD and COLD studies reporting rates of 19.3% and 17.4% for Canada, respectively, and 19.2% in Australia [13, 15].

In Europe, the prevalence of COPD ranged from 3% in the Netherlands [16] to 26.1% in Austria [17] when adhering to the GOLD criteria. Much like North America, a variety of spirometric criteria have been applied, with pre-bronchodilator spirometry associated with relatively higher estimates (compared to post-bronchodilator recommended by GOLD), and FEV<sub>1</sub>/FVC defined by the lower limit

**Table 1** Prevalence, under- and over-diagnosis of COPD

Continent	Country	Gender M:F	Age years	Prevalence (self-reported)	Prevalence (spirometry)	Under-diagnosis	Over-diagnosis	Year of data collection
<b>North America</b>	USA	55:45 [12] 57:43 [14] 48:52 [24] 96:4 [42]	40-79 [12] 55-75 [14] ≥45 [24]	18% [14]	10-21% [12]	12% [24]	48% [42]	1988-1994 [24] 2001 [14] 2003-2007 [42] 2007-2010 [12]
	Canada	45:55 [15]	≥40	8.9%	17%	14%	5.1%	2007-2011
	Austria	55:45 [22]	≥40		26%	95% [17]		2004-2006
	Finland	51:49 [37]	21-70		5.4-9.4%		60%	1995-1996
<b>Europe</b>	Italy	47:53 [21] 49:51 [39]	≥14 [21] >25 [39]	2.8% [21]	11-18% [39]			1998-1991 [39] 2009 [21]
	Netherlands	48:52 [16]	≥40		3%			2000-2007
	Norway	50:50 [30] 38:62 [43]	47-78 [30] ≥40 [43]		9% [30]	66% [30]	26% [43]	1992-1993 [30] 2009-2010 [43]
	Spain	47:53 [35]	40-80		10.2%	73%		2006-2007
<b>Oceania</b>	Sweden	48:52 [22]	≥40	12%	10-16%	71%		2004-2006
	Austria	55:45 [22]	≥40		26%	95%		2004-2006
	Finland	51:49 [37]	21-70		5.4-9.4%			1995-1996
	Australia	53:47 [44]	>55 [44]		19% [13]		31% [44]	2008 [44]
<b>Africa</b>	Nigeria	39:61 [51]	≥40	0.3%	7.7%			
	Malawi	39:61 [53] 42.1:57.9 [52]	≥30 ≥18		13.6% 4.3%			
	Cameroon	0:100 [54]	≥40		1.6%			2012
	Uganda	49.5:50.5 [50]	≥30		16.2%			2012
<b>South America</b>	South Africa	48:52 [57] 37:63 [87]	≥55 ≥40	11.2%	23.8%			2012
	Mexico	39.8:60.2 [63]	40-84	6.03%	20.6%	86.2%	40%	2008
	Peru	49.3:50.7 [62] 49.2:50.8 [88]	≥35 ≥35	0.4% 0.1%	6% 4.8%			2010

(Continued)

Table 1 Continued

Continent	Country	Gender M:F	Age years	Prevalence (self-reported)	Prevalence (spirometry)	Under-diagnosis	Over-diagnosis	Year of data collection
South America (cont.)	Brazil	60.3:39.7 [64]	≥40	19%	31.5%	71.4%	14.6%	2011
		82.6:17.4 [70]	15-63	5.1%	1.1%			
South-East Asia	China	49.7:50.3 [71]	≥35 [71]		5.9% [71]	70% without CB; 30% with CB [72]	Urban 81%; rural 62.2% [74]	2000-2001 [71]
		49.8:50.2 [72, 73]	≥40 [73]		(male 7.3%; female 6.4%) [74]	(overall 88.8%; male 86.2%; female 90.7%) [74]	(male 67.7%; female 73.7%) [74]	2003 [72]
		41.59 [74]			(overall 13.6%; male 19.0%; female 8.1%) [75]			2004-2008 [74]
		49.6:50.4 [75]						2014-2015 [75]
		NA [76]	≥30		3.5%			2000
	Singapore <sup>#</sup>	NA [76]	≥30		3.5%			2000
	Thailand <sup>#</sup>	NA [76]	≥30		5.0%			2000
	Vietnam <sup>#</sup>	NA [76]	≥30		6.7%			2000
	Malaysia <sup>#</sup>	NA [76]	≥30		4.7%			2000
	Indonesia <sup>#</sup>	NA [76]	≥30		5.6%			2000
The Middle East and South Asia	Philippines <sup>#</sup>	NA [76]	≥30		6.3%			2000
	Taiwan <sup>#</sup>	NA [76]	≥30		5.4%			2000
	South Korea <sup>#</sup>	NA [76]	≥30		5.9%	36.9% [77]		2000
	Japan <sup>#</sup>	NA [76]	≥30		6.1%			2000
	Abu Dhabi	55:45 [78]	40-80		3.7%			2000
	India	51.6:48.4 [80]	17-64 [79]	CB 12.5% [79]	4.1% [80]			2007 [81]
		50.2:49.8 [82]	>35 [80]		2.44% [81]			2014 [83]
			>30 [81]	1.1-10% [82]	5.7-17.3% [83]			2016 [84]
			≥40 [83]		4.2% (crude) to 5.5% age-standardised [84]			
	Bangladesh	45.7:54.3 [85]	≥40		13.5% (GOLD) and 10.3% (LLN)			2011-2012

<sup>#</sup>: prevalence estimated. M: males; F: females; NA: not available; CB: chronic bronchitis.



of normal (LLN) associated with underestimation, particularly in the younger population. Three different studies from Denmark demonstrate the variation in prevalence estimates; 17.4% using pre-bronchodilator spirometry [18], 12% using GOLD criteria [19], and 3.9% using FEV<sub>1</sub>/FVC <LLN and FEV<sub>1</sub> <80%; [20]. Similar variation has been reported using physician diagnoses with 2.8% in Italy [21], 12% in Sweden [22], and 6.2% in a combined survey of eight European cities [23].

## Under-diagnosis of COPD

Despite the ease of access to spirometry in high-income countries, problems arise because of insufficient utilisation of testing, particularly in general practice, or testing not strictly adhering to the guidelines; this forms the basis of under-diagnosis. When spirometry is measured in empirically diagnosed populations, the degree of underestimation varies with the criterion applied. This holds true in the USA, where NHANES and NHANES III reported under-diagnosis rates of 12–72% [24, 25]. Pre-bronchodilator spirometry and a fixed FEV<sub>1</sub>/FVC ratio revealed that approximately 70% of individuals with AFO do not have a concurrent physician diagnosis [25]. However, with the inclusion of post-bronchodilator testing (GOLD criteria), approximately 50% of individuals are under-diagnosed [26]. AFO based on the LLN criteria led to a reduced under-diagnosis rate of 12% [24]. Similar under-diagnoses rates have been reported from Canada, ranging from 14% to 70% in the COLD and CanCOLD studies (using GOLD criteria [15, 27]), to 82% (using pre-bronchodilator spirometry and a fixed FEV<sub>1</sub>/FVC ratio [28]). However, in the CanCOLD study, LLN-defined AFO did not necessarily lead to a lower estimation of under-diagnosis, as would be expected, with the study reporting a rate of 26% [29]. For individual European countries, the estimates of under-diagnosis using GOLD criteria from randomly sampled populations were generally greater, ranging from 66% in Norway [30] to 95% in Austria [17]. A meta-analysis including North American and European studies reported that under-diagnosis was present in greater than 90% of cases [9].

Within this multi-continental region, patient characteristics, including sex, age, self-perceived health status and FEV<sub>1</sub> impairment were associated with under-diagnosis. Interestingly, separate cohorts from different countries demonstrated that both younger patients [31–33] and older patients [6] were prone to under-diagnosis. Mixed results were also seen with respect to gender, where females were less likely to have a diagnosis in cohorts from Europe [16, 33, 34], but males were less likely in Canada [6]. Preserved quality-of-life scores and a mild to moderate degree of lung function impairment also predicted under-diagnosis in multiple countries [25, 30, 33, 35]. Other factors associated with under-diagnosis include: either

being asymptomatic or presence of mild respiratory symptoms [33]; belonging to a racial or ethnic minority [25]; co-diagnosis of asthma [6]; and presence of lower overall comorbidity [6, 25].

The criteria for diagnosis of AFO can also contribute to under-diagnosis in different age groups. As expected, concurrently applying AFO defined by the LLN *versus* fixed ratio criteria led to lower prevalence estimates in Switzerland (8% *versus* 15.2% [36]) Canada (12% *versus* 17% [28]) and the USA (10.2% *versus* 14.2% [12]). In Europe, many studies over the past decade using the British Thoracic Society and ERS criteria, result in an underestimation compared with GOLD criterion; studies from Sweden and Finland reported almost half the prevalence estimates [37, 38]. The prevalence of COPD in Italy was 11% using the ERS criterion but increased to 18.3% when the GOLD criterion was used [39].

## Over-diagnosis of COPD

Most studies examining the prevalence of over-diagnosis used electronic medical registry data in primary care cohorts applying GOLD criteria. Within North America, rates ranged from 16.4% in Canada [40] to 42.5% in the USA [41]. Random sampling of a Canadian population revealed that over-diagnosis occurred in 5.1% of cases [15]. Another large North American study of US veterans demonstrated that overestimation occurred in 48% [42]. European countries also exhibited a significant degree of over-diagnosis and variability, with the lowest estimate from Norway at 25.8% [43], and the highest from Finland at 60% [37]. Similar overestimates (31–42%) were reported by Australian studies [44, 45].

The diagnosis of COPD without spirometry testing is common and unquestionably contributes to the majority of over-diagnosis [46]. This occurs often in the setting of advancing age [17, 47], nonsmokers [6], male sex, higher education levels, and symptoms of chronic bronchitis and other comorbidities [47]. Over-diagnosis is also more common in the setting of elevated body mass index [44, 48] and having an older primary care provider [6]. In addition, the specific spirometry protocol ordered can also influence the results, particularly if regular calibration of equipment is not done. Exclusion of post-bronchodilator spirometry provides an estimate for obstructive lung disease in general, and thus overestimates the prevalence of COPD [25], particularly where prevalence of other obstructive diseases such as asthma is significantly high. Applying a fixed FEV<sub>1</sub>/FVC <0.7 rather than the LLN to older populations also leads to an increase in prevalence, as reported by Swiss (15.2% *versus* 8% [36]) and Swedish (16.2% *versus* 10% [22]) studies.

Furthermore, a clinician's reliance on a single spirometry outcome can also lead to overestimation, given the instability demonstrated in serial tests. In fact, in two large cohorts from the USA and Canada, a spirometric diagnosis of COPD was overturned

in 12–27% of individuals. The only predisposing factor for diagnostic reversal was smoking cessation during the 5-year follow-up period [8].

## Africa

### Epidemiology of COPD

COPD has been poorly studied in Africa, particularly in sub-Saharan countries. An autopsy study performed in Uganda in 1974 reported emphysema was found in 23.5% of lungs [49]. A study in 2012 from rural Ugandan communities reported that the prevalence of spirometry-defined COPD using the GOLD criterion in people older than 30 years of age was 16.2% [50]. The main risk factors were previous smoking history, non-Bantu ethnicity and exposure to biomass fuel for cooking or heating purposes.

However, the prevalence of chronic AFO has differed widely, not only among different countries, but also between different communities within a country. The prevalence of chronic AFO was 7.7% in Ile-Ife in a Nigerian population aged 40 years and over [51] although only 0.3% of people reported a diagnosis of chronic bronchitis, emphysema or COPD. A population-based study in Malawi reported that 4.3% of men and 4.1% of women had post bronchodilator obstruction when spirometry was performed [52].

In many African countries, use of solid fuel (biomass and coal) and paraffin for cooking and heating is quite common and the majority of small-scale cross-sectional studies have reported that it is an independent risk factor for COPD. Self-reported biomass exposure is more common in an African neighbourhood than smoking, particularly among the rural communities, and has an incidence of up to 85.2% [52]. Wood smoke has previously been shown to contribute to reduced lung function in rural Africa, particularly in nonsmoking women [53, 54].

The low prevalence of COPD is thought to be due to a younger population and lower smoking rates than developed countries [55]. Sub-Saharan smoking rates have ranged between 9.2% and 29% for men and 0.7% and 4.0% for women [52, 55].

### Under- or over-diagnosis

There is very limited information on the prevalence of under- and over-diagnosis of COPD in Africa. A report by CHAN-YEUNG *et al.* [55] in 2004 reported that epidemiological data regarding the prevalence of COPD in a large part of Africa is patchy or localised with reports in local languages only. They reported that prevalence studies require the administration of questionnaires in several languages within the same country with high illiteracy rates, at a higher cost and with the limited availability of spirometry devices. Furthermore, the misdiagnosis of COPD in African communities could also be due to high unfamiliarity with the term “COPD”. A qualitative

study in rural Ugandan communities found that among the general public, there was poor knowledge on the risk of tobacco and biomass smoke on respiratory health, and the term COPD was almost unknown [56].

Nkosi *et al.* [57] performed a cross sectional study with face to face interviews to assess the relationship between mine dumps and chronic respiratory disease in a community in South Africa. The prevalence of self-reported chronic bronchitis was 13.4% and that of emphysema was 5.6%.

Sub-Saharan Africa has the greatest proportion of the world's population living with HIV, while having a low proportion of smokers, thus it was hypothesised that HIV may contribute to COPD in this population, and thus be an under-recognised risk factor. However, a case-control study in Cameroon between 2012 and 2013 showed the prevalence of COPD was 5.2% (24/461) in HIV-positive participants and 5% (23/461) in HIV-negative participants, with no statistical correlation between HIV status and increased prevalence of COPD [58].

Previous pulmonary tuberculosis has also been associated with increased prevalence in chronic bronchitis and airflow limitation. A prior history of tuberculosis was associated with an irreversible AFO irrespective of smoking history, and could result in the over-diagnosis of COPD [59, 60].

## Central and South America

### Epidemiology of COPD

The prevalence of smoking in Central and South America is high, with a median prevalence of 30%, contributing significantly to the burden of respiratory diseases [61]. Studies have assessed the prevalence of COPD in a small number of cities across the region and COPD prevalence has ranged from 7.8% to 19.7%; however, more widespread studies, representative of the different communities in different countries (including isolated areas) have not been performed to date [61]. In Peru, a study of four separate resource-poor areas showed an overall prevalence of 6.0% for COPD, despite a low daily smoking rate of 3.3% [62].

### Under- or over-diagnosis

A case-finding study in Mexico in patients with risk factors for COPD reported 20% prevalence of COPD [63]. Of the patients who had a clinical diagnosis of COPD from their family physician, 40% had normal spirometry, while only 13.8% with chronic AFO had been diagnosed clinically with COPD. QUEIROZ *et al.* [64] studied 200 patients to understand the potential risk factors for COPD in primary care centres in South Brazil. Based on the results of spirometry (15% of patients), they reported that 71.4% of patients were under-diagnosed for COPD, and 14.6% were over-diagnosed.



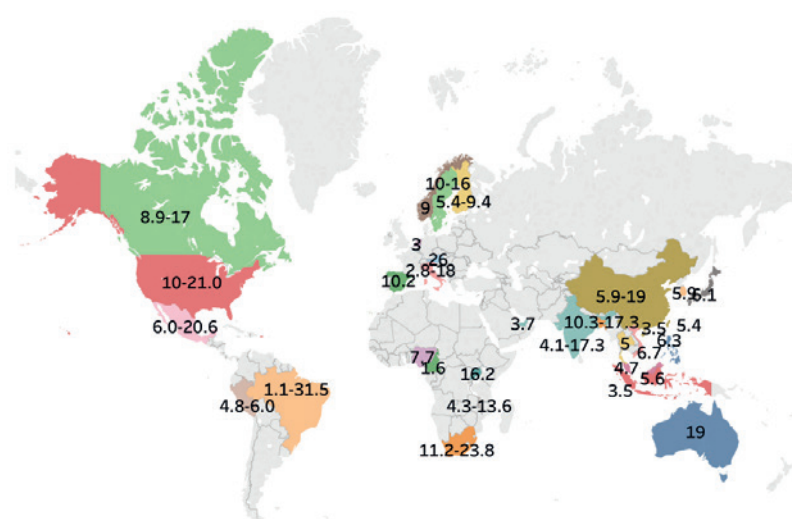
JAGANATH *et al.* [62] found that in four different areas of Peru, COPD was not fully explained by smoking, and also reported that biomass exposure and tuberculosis were attributable risk factors, particularly in women. A retrospective spirometry and clinical study of 170 patients in Brazil assessed the contribution of risk factors including wood smoke and tobacco exposure [65]. They reported that patients with tobacco smoke had more severe COPD; however, 19.4% of participants had been exposed to wood smoke over a long period, and 85.3% were women. These results are consistent with a study of Mexican Mayan women that showed biomass smoke exposure was associated with more air trapping but less emphysema than tobacco smoke exposure [66]. Women with biomass exposure presented with fewer symptoms than those with tobacco smoke exposure. Thus, exposure to biomass fuel, particularly in nonsmoking women in rural areas, may be underestimated as a risk factor for COPD and may lead to an under-diagnosis. Furthermore, a study from Colombia suggested that replacing biomass fuel with natural gas could reduce the prevalence of severe obstructive lung disease and could be an important public health intervention [67].

Occupational exposure is associated with around 15% of total COPD; however, this has been poorly studied in Central and South America [57, 68, 69]. A study of pig farmers in Brazil showed a prevalence of chronic bronchitis of 5.1% in workers aged more than 40 years [70]. In addition, there was a higher prevalence of chronic bronchitis associated with the use of disinfectants, and significant increase in dyspnoea due to the use of ammonia [68].

## South-East Asia

### Epidemiology of COPD

The prevalence of COPD in China in population-based surveys ranges from 3.9% to 13.7% in different regions of China. The crude prevalence of COPD was significantly higher in men than in women (7.2–12.4% *versus* 4.7–5.1%), and in rural areas than in urban areas (4.4–8.8% *versus* 6.7–7.8%) [71–73]. A population-based cohort of more than half a million participants from 10 different regions of China reported that the prevalence of COPD based on pre-bronchodilator lung function test (using LLN criteria) was 7.3% in men (range 2.5–18.2%) and 6.4% in women (1.5–18.5%) [74]. The prevalence of COPD was higher in rural areas compared to urban areas for both men (9.2% *versus* 4.8%;  $p < 0.001$ ) and women (7.7% *versus* 4.8%;  $p < 0.001$ ). A recent study of 66752 Chinese individuals older than 40 years of age reported an overall prevalence of COPD of 13.6%, with significant difference between men and women (19.0% *versus* 8.1%;  $p < 0.0001$ ), highest in southwest China (20.2%) and lowest in central China (10.2%) [75]. The difference in prevalence between genders was mainly attributed to smoking status between



**Figure 1** Prevalence (%) of COPD in different countries. The prevalence data is based on narrative review and not systematic review of all the literature.

men and women (current smokers 58.2% *versus* 4.0%, respectively). Prevalence data from many other South-East Asian countries are still sparse. COPD prevalence estimates vary widely in Asian countries, with 3.5% in Hong Kong and Singapore, 6.7% in Vietnam, 4.7% in Malaysia, 5% in Thailand, 5.6% in Indonesia, 6.3% in the Philippines, 5.4% in Taiwan, 5.9% in South Korea and 6.1% in Japan [76].

### Under- or over-diagnosis of COPD

The prevalence of under-diagnosis in China is greater than that in Western countries. A study from 10 different regions in China reported that the physician correctly diagnosed 11.2% of those with AFO; under-diagnosis was highest (96.7%) among the 30–39 years age group and lowest (81.1%) in those older than 70 years [74]. The prevalence of COPD was higher in rural areas compared to urban areas for both men (9.2% *versus* 4.8%;  $p < 0.001$ ) and women (7.7% *versus* 4.8%;  $p < 0.001$ ). Another population-based study from China sampled 20245 adults and reported an overall prevalence of 8.2% of persistent AFO. Among those who had post-bronchodilator AFO ( $FEV_1/FVC < 0.70$ ), only 35% had a previous physician diagnosis of COPD, suggesting that 65% of subjects with chronic AFO in China remain undiagnosed [73].

A study in China recruited 25627 subjects, of whom 20245 (79%) completed questionnaires and performed acceptable spirometry, reported that 1668 subjects (8.2%) had COPD. Among those who had COPD, only 589 (35.3%) reported a history of chronic bronchitis. Among those with AFO and without chronic bronchitis, about 92% were under-diagnosed, compared to 54% those who were symptomatic. Hence, COPD without symptoms of chronic bronchitis is often referred to as “silent”, due to their lack of symptoms and under-reporting to the

physician and thus are usually under-diagnosed [72]. A study from Korea showed that 36.9% of COPD patients did not show any respiratory symptoms [77].

It is likely that the use of clinical definitions of COPD based on current symptoms and exposure history and under use of spirometry, particularly in rural areas, have led to the majority of under- and over-diagnosis of COPD. Furthermore, lack of awareness about risk factors other than smoking among physicians had led to delayed diagnosis and interventions for patients with COPD [26].

## The Middle East and South Asia

### Epidemiology of COPD

A cross-sectional survey in a random sample of individuals 40–80 years old in Abu Dhabi, showed the prevalence of COPD to be 3.7%, with no difference, however, between gender [78].

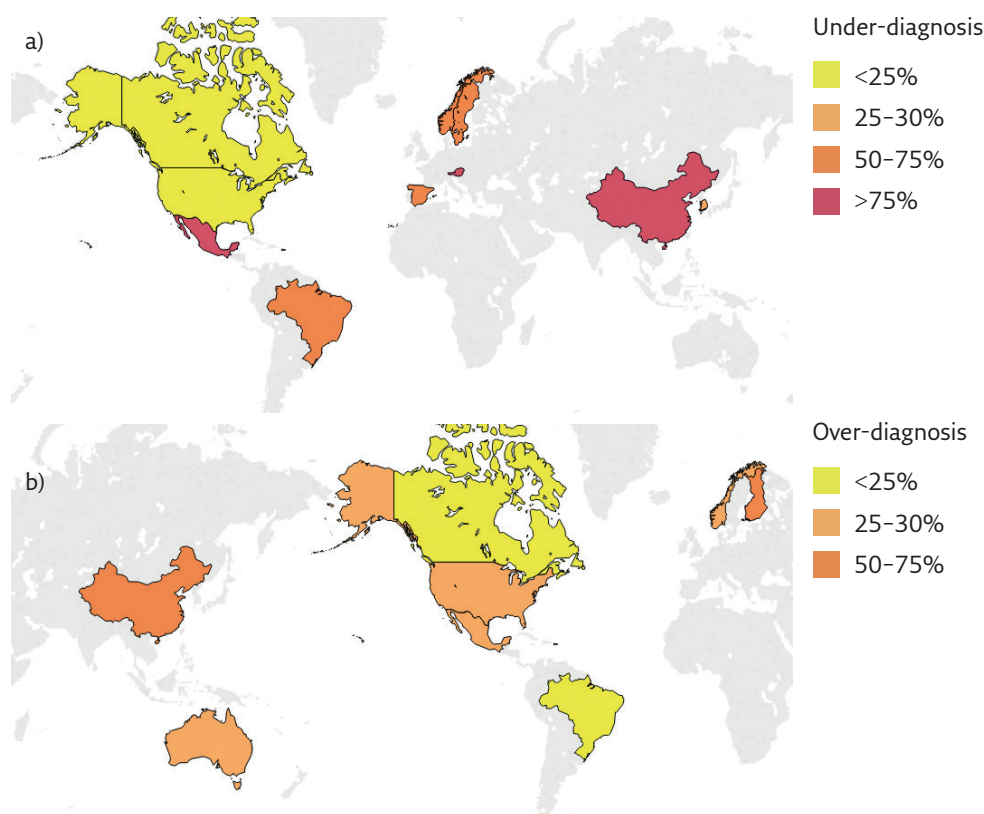
Around 40 years ago, the prevalence of chronic bronchitis in an industrial town in India was reported to be 12.5% and around five times higher in smokers compared to nonsmokers [79]. Thereafter, many studies have reported COPD prevalence as low as 2.0–4.1% [80, 81]. A study in 2011 conducted in different states of India estimated the self-reported prevalence of chronic bronchitis at 3.5% in India (ranging

from 1.1% in Mumbai to 10% in Trivandrum) [82]. The BOLD study in 2014 used standardised spirometry and reported overall COPD prevalence estimates of 5.7%, 6.0% and 17.3% in Pune, Mumbai and Srinagar for males and 6.8%, 7.6% and 14.8% for females, respectively [83]. A recent global burden of diseases study in India reported a 29.2% increase in crude prevalence of COPD from 3.2% in 1990 to 4.2% in 2016; however, the age-standardised prevalence decreased by 5% during the same period (5.8% to 5.5%) [84]. The percentage of total deaths attributed to COPD in India was 8.7% (males 8.7% and females 8.6%) in 2016 and disability adjusted life-years 4.8% (males 5.2% and females 4.4%).

In Bangladesh, the prevalence of COPD was 13.5% by GOLD definition criteria and 10.3% by LLN criteria. The prevalence of COPD was higher among rural than urban residents and in males than females. More than half of the COPD cases were stage II COPD by both criteria. Mild cases (stages I and II) were overestimated by the GOLD fixed criteria, but more severe cases (stages III and IV) were similarly classified [85].

### Under- and over-diagnosis

There is a lack of data from the Middle East and South Asia on under- and over-diagnosis of COPD, similar to that from the Africa region. However, under-diagnosis of COPD in the region are likely to



**Figure 2** a) Under- and b) over-diagnosis of COPD.

be due to the lack of the availability of spirometry, lack of awareness of hazards of various risk factors of COPD, such as exposure to biomass fuel, a low level of education and lack of awareness of the healthcare provider, particularly those in rural areas, who are often semi-skilled [86].

## Conclusions

This review on the global assessment of misdiagnosis of COPD has identified large variations in the prevalence of COPD across different geographical regions, ranging between 3% and 21% (figure 1). Estimation of the true burden of COPD will remain a challenge unless a more uniform approach to diagnosis of COPD is adopted by all regions where the associated risk factors are common. One of the major reasons for the huge variation in COPD prevalence is the different criteria used to define COPD. The vast majority of data on under- and over-diagnosis of COPD has been generated from the developed world, whilst very limited or poor quality data is available from LMICs (figure 2). Access to healthcare and under-utilisation of spirometry remains a large global challenge. Although spirometry is recommended for confirmatory diagnosis of COPD, its uniformity of use for test procedures, regular maintenance and calibration remain global challenges. Furthermore, the use of different reference values for lung function, *i.e.* country-specific or Global Lung Function Initiative (GLI) values, remains a hotly debated area but one that is beyond the scope of this review. Additional risk factors for misdiagnosis include age, gender, ethnicity, self-perception of symptoms, co-existent

## Self-evaluation questions

1. A 45-year-old female smoker with a 20 pack-year smoking history presents to your clinic with persistent respiratory symptoms over the previous 6 months. You perform spirometry which demonstrates a post-bronchodilator FEV<sub>1</sub>/FVC ratio of 0.75 and an FEV<sub>1</sub> of 88% predicted. How would you investigate this patient further to diagnose COPD?
  - a) No further testing.
  - b) Full pulmonary function test
  - c) Repeat spirometry in 3 months
  - d) Check if the FEV<sub>1</sub>/FVC ratio is below the LLN
2. Which of the following is not a known associated risk factor for under- or over-diagnosis of COPD?
  - a) Tuberculosis
  - b) Age of patient
  - c) Use of spirometry
  - d) High protein diet
3. Which of the following is not an independent risk factor for COPD?
  - a) Exposure to biomass smoke
  - b) Tobacco smoke
  - c) Alcohol drinking
  - d) Diesel fume exposure
4. Compared to the use of FEV<sub>1</sub>/FVC ratio of <0.7, the use of 5% below the LLN results in a lower over-diagnosis of COPD in the elderly?
  - a) True
  - b) False

disease, and educational awareness of risk factors, both for the patients and their physicians, are also important.

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## Conflict of interest

None declared.

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## Suggested answers

1. c.
2. d.
3. c.
4. a.

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