



## Opinion

# A Clinician's View on Pre-chronic Obstructive Pulmonary Disease/Pre-non-obstructive Chronic Bronchitis: A Quest for More Research on Early Diagnosis and Treatment



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Current criteria for the diagnosis of chronic obstructive pulmonary disease (COPD) result in its relatively late detection, typically when the disease is well established. Cough, excessive sputum production and shortness of breath are not signs of an impending disease, but rather symptoms of a well-established disease. This review hypothesizes that earlier detection of a pre-stage of COPD (hereinafter referred to as Pre-COPD) enables earlier treatment and the elimination of identifiable provoking factors resulting in improved outcomes by starting treatment before the disease is established. Several criteria are proposed for the diagnosis of Pre-COPD or NOCB (pre-non-obstructive chronic bronchitis). These criteria include frequent and/or unusually prolonged respiratory tract infections, especially with bacterial superinfection, and notable findings during chest auscultation. To be useful at the forefront of patient care, the diagnosis of Pre-COPD should be straightforward and independent of a cost-intensive laboratory or technical support. Using the criteria outlined here, the diagnosis can be made globally, as it requires only the patient's history and an experienced healthcare worker. If future studies show an acceptable positive and negative predictive value of the proposed criteria, and that proposed actions such as enhanced physical activity and infection prevention are effective, the diagnosis and management of Pre-COPD could be introduced into guidelines as an entirely prophylactic measure.

A common desire of all clinicians is to diagnose a disease as early as possible to achieve a better outcome for the patient. The introduction of the troponin test and its highly sensitive assays is a good example of diagnosing myocardial ischemia long before severe myocardial injury occurs, significantly improving the outcomes for patients with ischemic heart disease. Another example is the identification of earlier stages of stroke by introducing the term transient ischemic attack. However, early identification of some diseases does not inevitably result in a more favorable long-term outcome, as seen in the case of diabetes mellitus. There have been

previous attempts to define a “pre-disease” status of COPD, which led to the introduction of the concept of GOLD 0 (Global Initiative For Chronic Obstructive Lung Disease). This referred to patients with lung function not diagnostic of COPD but with cough,<sup>1</sup> excessive sputum production and shortness of breath. This category was later abandoned because not all these individuals progressed to COPD.<sup>2</sup> More recently, it has been recognized that this dismissal may have been premature,<sup>3</sup> although it is clear that cough, expectoration and shortness of breath are likely associated with established disease. Furthermore, cigarette smokers represent the majority of individuals at risk of COPD,<sup>2</sup> and every physician with cigarette smokers as patients is aware that few of these patients interpret symptoms such as cough and excessive sputum production as signs of impending illness, especially if they fear being coerced into giving up smoking. Ideally, therefore, the criteria for a “Pre-COPD” diagnosis should be identifiable before significant airway remodeling has occurred, using simple indicators that any healthcare professional can recognize without technical assistance and independently of any initiative by the patient. Such encounters will most commonly occur in the surgeries of family physicians. In summary, the important requirements for such criteria are:

1. Simple, widely applicable, and preferably not complex or expensive;
2. Independent of the initiative of patients at risk;
3. Straightforward to conduct anywhere;
4. Accessible to any healthcare professional in any environment.

In the course of routine clinical practice in primary care, having seen many patients with COPD, it became apparent that repeated pulmonary infections (history, examination, possibly C-reactive protein and/or superinfections) are frequently the first signs of pre-disposition to the development of COPD.<sup>4</sup> This observation has contributed to the formulation of the hypothesis presented below regarding the definition of Pre-COPD. The hope is that taking appropriate action (avoidance of clear environmental triggers and in time, initiation of prophylactic therapy) at an early stage will help postpone or even prevent the development of COPD.

The question arises, as in any screening initiative, whether the criteria proposed here have (1) acceptable positive and negative predictive values, which might otherwise result in missed diagnoses or unnecessary treatment, and (2) whether earlier recognition of susceptibility to disease and an early diagnosis improves outcomes. To address this concern while awaiting long-term data on

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patient outcomes, we propose first-line therapy to include physical activity, regular vaccination and reduction of exposure to harmful environmental agents such as smoking and fumes generated in the kitchen, which are well-known factors in COPD management. These measures, which are known to be helpful and very unlikely to have unwanted effects on the vast majority of patients, will ensure that no harm comes to patients with a false diagnosis of Pre-COPD and will likely maximize the likelihood that the advantages of early intervention outweigh the risks. Furthermore, the proposed criteria are easy to recognize and available worldwide, as they do not require expensive laboratory and technical workups. Thus, in contrast to the GOLD criteria, our Pre-COPD criteria could be introduced globally, even in rural areas of developing countries, which are experiencing the most rapid increase in COPD due to dramatic environmental changes. The only screening requirement is a trained physician or other healthcare professional, not necessarily a pulmonologist, due to the high number of potential COPD patients compared to the limited number of pulmonologists in Europe and developing countries.

Based on the experience of myself and my colleagues, following more than 30 years of practice as family physicians with a focus on chronic respiratory diseases, we propose the following hypothesis:

The criteria for the diagnosis of Pre-COPD are:

1. Repeated viremic respiratory tract infections, with frequent bacterial superinfections (defined by more than 1 bacterial pulmonary tract infection per year);<sup>4</sup>
2. Respiratory tract infections with a protracted course (defined by duration of symptoms exceeding four weeks). This could alternatively be termed an exacerbation-like event;<sup>5</sup>
3. Wheezing or early signs of congestion with normal lung function support the suspicion of Pre-COPD, especially in the case of a pathological coughing test (when the patient is asked to cough during chest auscultation to check whether or not the airways are clear, which may reveal hidden wheezing).

The predisposition of patients with established COPD to respiratory tract infections and the danger of exacerbations are well described and known.<sup>6-8</sup> However, there is only one retrospective observational study, to the knowledge of the authors, addressing the difference in the number of these infections in demographically matched patients who do not suffer from chronic airway disease.<sup>4</sup> While patients with and without chronic airway diseases get viral infections at similar frequencies, patients with chronic airway diseases more frequently develop protracted courses and bacterial superinfections (in this study, five to six times more often).<sup>4</sup>

Cough, sputum production, and chronic productive cough were significantly associated with incident COPD in women, while dyspnea and wheezing were significantly associated with incident COPD in men.<sup>9</sup>

Using the suggested criteria will result in a large number of diagnoses of Pre-COPD, a proportion of which will be false positives. However, this offers the possibility of early intervention and prevention of established disease, which cannot be reversed. On the other hand, diagnosis by technical means such as detailed pulmonary function tests or computed tomography scanning is much more expensive and requires greater resources,<sup>3</sup> and arguably occurs too late, when the disease is established. This also applies to future investigation methods that are yet to be developed.<sup>10</sup>

All patients showing one or more of the symptoms mentioned above should be re-examined regularly (once a year or whenever they consult their doctor after a longer period) by a suitable health

professional. In addition to the information available from guidelines, each practitioner managing patients labeled as Pre-COPD should receive brief training to clarify and detect the diagnostic criteria in a standardized way, which needs to be defined after further research. This regular observation should include lung function testing, including a post-bronchodilator test to identify patients with low-normal FEV1 (first expiratory volume in 1 second) with a “rapid” loss of FEV1 greater than 40 mL/yr (normal rate of loss after the third decade of life is less than 25 mL/yr).<sup>11</sup>

The initiative and hypothesis for the recognition of Pre-COPD are based on the assumption that early intervention can prevent, at least in some patients, the change from Pre-COPD to COPD based on the GOLD criteria or NOCB. To prevent harm from unwanted effects in falsely positively diagnosed patients, we recommend only safe and well-established interventions, including exercise, vaccination against influenza and pneumococcus, and possibly vaccination against respiratory syncytial virus. Additionally, smoking cessation and minimizing other relevant environmental exposures (which may occur not only in the workplace but also in the home kitchen) are advised.

Any early diagnosis has value only if, by early initiation of treatment or other preventive measures, the development of COPD and its associated complications can be avoided or at least delayed. Consequently, prospective randomized trials are required in the future to:

1. Establish the specificity and sensitivity of the above-mentioned criteria;
2. Determine the rates of false positive and false negative diagnoses;
3. Determine the effectiveness of the early interventions described above;
4. Determine the characteristics of patients responding and not responding to the early treatment strategies (e.g., dependence on smoking, sex, ethnic background, living and working environment);
5. Determine whether the diagnostic criteria and therapy can be successfully applied in developing countries (which currently show a steep increase in COPD).

Ultimately, the recommendation to add Pre-COPD to current management guidelines can be made only when the diagnostic and therapeutic criteria have been confirmed to be clinically useful in prospective interventional trials. We trust that our observations will facilitate this process so that validated criteria for the diagnosis and management of Pre-COPD can be incorporated into international guidelines.

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#### Author contributions

Both authors contributed equally to this work. TH and CJC jointly

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