EDITORIAL

Avoiding confusion in COPD: from risk factors to phenotypes to measures of disease characterisation

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Because chronic obstructive pulmonary disease (COPD) is a complex disorder with different pulmonary and extrapulmonary manifestations [1], there is great interest in better understanding the complexity of COPD in order to facilitate a more accurate risk stratification of patients and a better understanding of disease pathobiology, and eventually develop more targeted therapy and improved management of patients with the disease. One end-product of the great number of studies addressing the complexity of COPD has been the emergence of several concepts and terms that are often used (and misused) in scientific discussions and publications (table 1). The purpose of this article is to contribute to the clarification of these concepts by summarising the meaning of the terms, so the scientific community can communicate and discuss advances in the field of COPD, being confident that there is no uncertainty or misunderstanding in their use. We accept this to be only a first proposal and that some investigators may disagree with its content. We invite them to correspond with us in the *European Respiratory Journal* such that, eventually, a consensus may emerge.

RISK FACTOR

A risk factor is “an aspect of personal behaviour or lifestyle, environmental exposure, or inborn or inherited characteristic, which, on the basis of epidemiological evidence, is known to be associated with a health-related condition” [2]. Examples of well-established risk factors in COPD include age [9], smoking [10], sex [11], lower socioeconomic and educational level [12], and α_1 -antitrypsin deficiency [13]. Some of the risk factors are modifiable and, therefore, are to be “prevented”, while others influence the expression of the disease but are not modifiable, such as age or sex. From this definition, it is evident that a risk factor, therefore, is not a phenotype.

PHENOTYPE

Generally speaking, a phenotype is any “observable structural and functional characteristics of an organism determined by its genotype and modulated by its environment” [3]. Having brown or blue eyes, for example, is a phenotype. Yet, a recent consensus definition [4] highlighted that, in order to be clinically useful, a “clinical” phenotype must be related to

clinically meaningful outcomes, such as symptoms, response to therapy, rate of disease progression or death [14]. So far, brown and blue eyes are not known to be related to any of those. By contrast, having upper lobe emphysema and poor exercise capacity is known to be associated with a significantly better outcome after lung volume reduction surgery compared with standard medical therapy [15]. Thus, this combination of disease attributes that requires a specific form of therapy to change an important outcome (mortality) fulfils perfectly the definition of a clinical phenotype [4]. The frequent exacerbator is another recently described clinical phenotype [16]. Other phenotypes that are associated with poor outcomes in COPD are patients with low body mass index (BMI) [17], increased functional dyspnoea [18] and poor exercise capacity [19]. These phenotypes may respond to therapies such as pulmonary rehabilitation and appropriate nutrition, and are therefore important to identify. The clinical relevance of other proposed phenotypes requires prospective validation [20]. Finally, some risk factors (e.g. α_1 -antitrypsin deficiency) may also be considered, in some cases, as phenotypes, since they may require specific therapeutic measures.

A different concept that is often used, and we predict will be increasingly used in the future, is that of “intermediate phenotypes” or “endotypes” [5, 6], which correspond to the genome or proteome responses that form the basis of the human biological armamentarium to respond to injury (thrombosis, inflammation, immune response, fibrosis and apoptosis/necrosis) [6]. Eventually, it is the intensity and combination of these intermediate phenotypes that lead to the clinical and pathological manifestations of diseases [6].

DISEASE CHARACTERISATION: SEVERITY, ACTIVITY AND TIMING

Finally, three disease-related concepts need discussion. The severity of any disease (including COPD) relates to the “extent of functional impairment of the target organ(s)” [7]. In the case of COPD, severity has traditionally been determined by the degree of airflow limitation (assessed by measuring forced expiratory volume in 1 s (FEV₁)) [21], although in recent years, several composite measures, such as the BODE (BMI, airflow obstruction, dyspnoea and exercise capacity) [22] and ADO (age, dyspnoea and obstruction) [9] indices, among others, have been shown to prognosticate survival more accurately in these patients. Importantly, FEV₁, BODE and ADO are not risk factors and are not phenotypes, although they may include components of both; they are measurements of disease severity

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TABLE 1 Terms and definitions

Term	Definition	[Ref.]
Risk factor	An aspect of personal behaviour or lifestyle, environmental exposure, or inborn or inherited characteristic, which, on the basis of epidemiological evidence, is known to be associated with a health-related condition	[2]
Phenotype	Observable structural or functional characteristics of an organism determined by its genotype and modulated by its environment	[3]
Clinical phenotype	A single disease attribute or combination of disease attributes that describes differences between individuals with COPD as they relate to clinically meaningful outcomes	[4]
Intermediate patho-phenotype or endo-phenotype	Types of human biological responses to injury (thrombosis, inflammation, immune response, fibrosis and apoptosis/necrosis)	[5, 6]
Disease severity	Extent of functional loss of the target organ(s)	[7]
Disease activity	Level of activation of the biological processes that drive disease progression	[7, 8]
Early/late disease	Time-point in the natural history of a disease at which it is diagnosed or studied	

For further explanation, see the main text. COPD. Chronic obstructive pulmonary disease.

that are useful to establish prognosis (prognostic factors) and guide therapy.

However, the activity of a disease is a concept that relates to the “level of activation of the biological processes that drive disease progression” [7, 8]. This is a well-established concept in other diseases (*e.g.* rheumatoid arthritis and tuberculosis) but, to date, is not well defined in COPD [7]. Clearly, this is a gap that requires novel research [8]. It is probable that identification and therapy that addresses disease activity will differ from maintenance therapy for stable and inactive disease, independent of its severity.

Finally, the concept of the temporal presentation of disease (early *versus* late disease) refers to the time-point during the natural history of a disease at which it is diagnosed or studied. These terms are often misused synonymously with severity of disease (mild and severe, respectively). A 75-yr-old COPD patient with an FEV₁ of 70% predicted has mild disease but, most likely, not early disease. Conversely, a 45-yr-old COPD patient with an FEV₁ of 50% predicted certainly has severe disease and, temporally, it is likely to represent early disease [23]. So, severity refers to the loss of function whereas early refers to a timescale, and both may coincide or not. This consideration is important since several recent *post hoc* analyses of large, randomised clinical trials suggest that patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II COPD can have a faster rate of FEV₁ decline than those with GOLD stage III–IV disease [24, 25]. These otherwise very interesting and challenging observations are often misinterpreted as relating to early disease when, strictly speaking, they relate to disease severity.

We hope that this proposal will help stimulate critical thinking on these issues and, in particular, help reach an agreement on concepts and terminology, with the long-term goal of facilitating a better understanding of the complexity of COPD [7] and, eventually, a better treatment of these patients.

STATEMENT OF INTEREST

None declared.

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