ALL ROADS LEAD TO COPD … OR NOT?

Alvar Agusti[1-4] and Rosa Faner[1,3-5]

1. Cathedra Salut Respiratoria, University of Barcelona, Spain
2. Pulmonary Service, Respiratory Institute, Clinic Barcelona, Spain
3. Fundació Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (FCRB-IDIBAPS), Barcelona, Spain.
4. Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBER), Spain.
5. Immunology Unit, Department of Biomedicine, University of Barcelona, Spain.

Corresponding author: Prof. Alvar Agusti. Pulmonary Service, Respiratory Institute, Clinic Barcelona, C/Villarroel 170, 08036, Barcelona, Spain. Tel: +34 93 227 1701; e-mail: aagusti@clinic.cat

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Our understanding of the pathogenesis of Chronic Obstructive Pulmonary Disease (COPD) has changed very significantly over the past few years [1-4]. Since the seminal description by Fletcher and Peto back in 1976, COPD was traditionally understood as a self-inflicted disease by tobacco smoking occurring in old, "susceptible" males and characterized by an accelerated decline of lung function with age [5, 6]. By contrast, according to the 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations, COPD is now understood as a "*heterogeneous condition that results from gene (G) - environment (E) interactions occurring over the lifetime (T) of the individual (GETomics) that can damage the lungs and/or alter their normal development/ageing process*" [7]. As a result of this new understanding, GOLD 2023 recognizes the existence of a *pre-COPD* condition that identifies "… *individuals of any age with respiratory symptoms and/or other detectable structural (e.g., emphysema) and/or functional abnormalities (e.g., hyperinflation, reduced lung diffusing capacity, rapid FEV1 decline), in the absence of airflow obstruction on postbronchodilator spirometry. These patients may (or may not) develop persistent airflow obstruction (i.e., COPD) over time*" [7]. GOLD 2023 also recognizes the category of *PRISm* (Preserved Ratio (hence no airflow obstruction) with Impaired Spirometry) [8] which may (or not) develop chronic airflow limitation (CAL) over time [7]. Understanding better what pre-COPD patients eventually develop COPD or PRISm may allow better and earlier preventive and management strategies [9-12].

In this issue of the *European Respiratory Journal*, Divo and coworkers report the development and performance of a Simple, Low cost, and ease of IMplementation (SLIM) calculator of the risk of developing incident CAL in middle-aged, ever-smokers with normal spirometry [13]. To this end, they explored what combination of a number

of risk factors readily available in clinical practice (dichotomized at specific threshold values based on clinical criteria) can best predict the occurrence of incident CAL, defined by a postbronchodilator FEV_1/FVC ratio <0.7 [13]. They used a Least Absolute Shrinkage and Selection Operator (LASSO) to train the predictive model in 677 ever-smoker participants in the Lovelace Smokers' Cohort (LSC) with a mean age of 54 years and normal spirometry at baseline, who were followed for a median of 6 years with multiple spirometries (median 5, IQR 4-6) [13]; of note, SLIM was validated in an independent cohort (COPDGene) [13]. Main results in the LSC cohort showed that: *(1)* about half of participants (54%) were symptomatic at baseline (i.e., defined by having either chronic sputum production, cough, or a modified Medical Research Council score >2 points) and were categorized as pre-COPD. By design (all participants had normal spirometry), none had PRISm at baseline; *(2)* during follow-up most individuals (n=489; 72%) maintained normal spirometries, whereas a few (n=110; 16%) developed incident CAL, an "unstable" spirometric pattern (n=63; 9%) or PRISm (n=15; 2%); finally, *(3)* the combination of a cumulative smoking exposure ≥30 pack-years, presence of chronic bronchitis, a body mass index (BMI) value <25 $kg.m^2$, and an FEV1/FVC ratio between 0.75-0.70 predicted the development of CAL (AUC=0.84, 95% CI 0.81-0.89) [13]. Although age did not enter the model, it is of note that those patients who developed CAL during follow-up were significantly older at baseline (58±9 vs. 53±9, p<0.0001) [13]. Importantly, although these observations in the LSC have been derived from a population of individuals with very specific characteristics (82% females, no African American subjects), the validation of the findings in the COPDgene cohort with a great majority of men, and which included a significant proportion of African Americans, support their validity. Collectively, these observations are important because they contribute to better understand what combination of risk factors better

explain the transition (or lack of) from pre-COPD to COPD. However, we believe that several issues need careful consideration to frame them properly.

On the one hand, there may be some issues regarding the generalizability of results. By study design, authors only included in this analysis ever-smokers individuals with normal spirometry at the age of 54 years [13]. This strongly suggests that their lung function in early adulthood (25 years of age or so) must have been normal too. If so, we have to consider that the population studied here did not include individuals with abnormal lung development during infancy and adolescence, one of the two main mechanisms of COPD [7], so we have to interpret these results as risk factors for enhanced lung function decline in adulthood. In fact, this is documented in the study since participants who developed incident CAO had a higher mean rate of FEV_1 decline than that of those who remained in the normal spirometry category (31±48 *vs.*10 ± 37 ml/year, respectively; $p<0.0001$). Also, as acknowledged by the authors [13], one concern limiting the generalizability of these results is that Pre-COPD was defined at baseline based exclusively on symptoms (which were present in 54% of participants) in the context of a normal spirometry, but other potentially defining variables of pre-COPD, such as the diffusing capacity of carbon monoxide and/or chest computed tomography findings, were not available and thus not tested in this study.

On the other, Divo *et al* showed that cumulative smoking exposure ≥30 pack-years was significantly associated with incident CAL in this population but, somewhat surprisingly, active smoking was not [13]. According to the traditional Fletcher and Peto paradigm [5, 6] and the more recent GETomics proposal [4], the development of COPD requires the interaction of environmental factors (e.g., smoking) with the appropriate

genetic background (now more than one hundred genetic polymorphisms that increase the risk of COPD or abnormal lung function have been identified [14]) over the entire life-time of the individual. The fact that the population studied here comprises ever-smoker with normal spirometry at 54 years suggests that it may include a substantial proportion of "genetically resistant smokers" who, despite having smoked for many years, still managed to maintain their spirometry within the normal range. This, however, opens the possibility of comparing the genetic/epigenetic background of individuals in the LSC who developed incident CAL *vs.* that of those who did not. Alternatively, as shown in Figure 1, the population studied here includes many individuals with supranormal FEV1 values (>100% ref) who, in theory, may have lost lung function since early adulthood and still show a pseudo-normal spirometry at age 54 years [3, 15-17].

Likewise, Divo *et al* also reported that a BMI <25 kg.m^2 was a significant risk factor for incident CAL in this population [13]. This is in keeping with several previous epidemiologic observations in the Baltimore Longitudinal Study of Aging [18], the Tucson Epidemiologic Study of Airways Obstructive Diseases [19], the LEAD study in Vienna (Austria) [20] and the BODE cohort in Spain and the COPDGene study in the US [21]. What is surprising here, and somewhat difficult to understand, is that the mean (±SD) BMI value of the group of participants who developed incident airflow limitation was 25.9 ± 4.3 Kg/m^2, which is fully within the normal healthy weight range (18.5 - 24.9 Kg/m^2). By contrast, BMI in participants who did not develop CAL was 28.6 ± 5.4 Kg/m^2 ($p<0.0001$), which is closer (or at) the obesity range (BMI>30 Kg/m^2). This raises the possibility that a higher BMI may actually be protective for incident CAL, as suggested by a recent meta-analysis on the "obesity paradox" in COPD that showed that

123 a “lower” BMI was a risk factor for accelerated lung function decline whereas a
124 “higher” BMI had a protective effect [22].

125

126 It is also of note that a proportion of participants in the study by Divo *et al*. (9%)
127 showed an “unstable” spirometric pattern without a clear lung function trajectory [13].
128 This is in keeping with the results of Aaron and coworkers who showed that “diagnostic
129 instability” (i.e., how often patients initially met criteria for a spirometric diagnosis of
130 COPD but then crossed the diagnostic threshold to normal or *vice versa*) occurred in
131 19.5% of patients with already mild-moderate airflow limitation included in the Lung
132 Health Study, and 6.4% of those studied in the Canadian Cohort of Obstructive Lung
133 Disease (CanCOLD) [23]. Of note, the risk of diagnostic instability was greatest in
134 subjects whose baseline FEV_1/FVC value was closest to the diagnostic threshold, as it
135 was the case in the study by Divo *et al* (Figure 1). Also of note, Divo *et al* also showed
136 that only 2% of the patients studied in this particular subpopulation of the LSC
137 developed PRISm [8], suggesting that this abnormal spirometric pattern in middle aged
138 individuals may not be associated with cumulative smoking exposure causing enhanced
139 lung function decline but to abnormal lung development which, as discussed above, was
140 probably absent in the patients studied here.

141

142 Finally, despite the attractiveness of SLIM, its implementation in clinical practice
143 remains to be determined. Although the type of patients studied here (middle age, ever-
144 smoker with normal spirometry) are not frequently seen in the clinic, they represent the
145 majority of subjects participating in lung cancer screening programs [24], a setting,
146 where the SLIM could prove of use to better select subjects likely to develop COPD.

Importantly, the majority (72%) of the middle-age, ever-smokers with normal spirometry did not develop incident CAL during the 6 to 10 years of follow-up [13], thus raising the question on how should these individuals be managed beyond reinforcing quitting smoking as early as possible [25] and probably monitoring them more closely with periodic spirometries [26]. Yet, we should not ignore that, despite their normal spirometry, many of these individuals (54%) already had symptoms, thus a health problem, so what treatment should/can we offer to them is currently uncertain [12], but certainly most needed [10, 11].

In any case, with these caveats in mind, the data by Divo *et al* should be welcomed to better understand some of the risk factors that influence the transition (or not) from pre-COPD to COPD, as well as for providing an easy-to-use tool to help to assess the risk of incident CAL.

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256 **FIGURE LEGEND**

257 **Figure 1.** This figure is a modification of the original Figure E3 in the paper by Divo *et*
258 *al* [13]. It presents a scatterplot of the baseline FEV_1 (% predicted) *vs.* FEV_1/FVC ratio
259 of the 677 subjects studied in the LSC study. By design, all of them had normal
260 spirometry at baseline (FEV_1/FVC>0.7 *and* FEV1>80% ref). Of note, many of them had
261 supranormal FEV_1 values (>100% ref; vertical dashed blue line). The red dots represent
262 the 110 participants who developed incident CAL by the end of the observation period
263 (6 years). For further explanation, see text. Reproduced with permission from reference
264 [13].