Chronic Respiratory Symptoms with Normal Spirometry: A Reliable Clinical Entity?

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CHRONIC RESPIRATORY SYMPTOMS WITH NORMAL SPIROMETRY: A RELIABLE CLINICAL ENTITY?

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ABSTRACT (249 words)

The 2001 *Global Initiative for Chronic Obstructive Lung Disease* (GOLD) Report defined five stages of spirometric severity (post-bronchodilator FEV₁/FVC ≥ 0.7): 0, and 1 (mild) to 4 (very severe). GOLD Stage 0 was defined by chronic cough and sputum production or chronic mucus hypersecretion (CMH) alone with preserved FEV₁/FVC. Subsequently, GOLD 0 was discarded as further evidence of COPD development in subjects with GOLD 0 was not more likely to develop. When expanding symptomatic burden in GOLD 0 to include other chronic respiratory symptoms, such as dyspnea, wheeze, poor quality of life, limited physical activity, and 'COPD exacerbations-like' events needing health resources, symptomatic smokers with normal FEV₁ resulted in larger risk of death. We review the evidence supporting a relationship between an increased symptom burden, long-term FEV₁ decline and development of COPD. We also address the evidence for the presence of respiratory symptoms with normal FEV₁ in smokers as a potential clinical entity. This subset of symptomatic patients encompasses a compelling category of smokers with normal spirometry but increased risk for poor outcomes. What exactly these symptomatic patients with intact FEV₁ represent remains unclear. Whether they exemplify smoking-induced just a broadening of respiratory abnormalities or a distinct clinical entity that precedes the development of COPD or both remains unknown. Other aims, such as providing information on pathogenesis and future areas of research, are just as vital. What ultimately prevails however is the importance of the public health message to the frightening presence of chronic respiratory symptoms in the whole population.

... "Would you tell me, please, which way I ought to go from here?" "That depends a good deal on where you want to get to." "I don't much care where –" "Then it doesn't matter which way you go."...

'Alice in Wonderland', Lewis Carroll (1832-1898)

The comparison of outcomes between symptomatic individuals with and without chronic obstructive pulmonary disease (COPD) is one of the many research questions posed in a recent *American Thoracic Society (ATS)/European Respiratory Society (ERS) Statement*¹ and represents the main thrust of this pulmonary perspective. We review the association between chronic respiratory symptoms, excess decline of FEV₁ and development of COPD and the evidence for a potential new clinical entity in individuals with chronic respiratory symptoms and normal spirometry (post-bronchodilator FEV₁/FVC ≥ 0.7). This subset of patients, roughly similar to the group previously labeled 'Stage 0' by the *Global Initiative for Chronic Obstructive Lung Disease (GOLD)*², suggests a category of symptomatic smokers with normal spirometry but increased risk of poor outcomes. Notwithstanding, it is of note that other functional measures of earlier and more subtle changes in small peripheral airways have been investigated previously. In the 1960s, a large number of studies were devoted to identify susceptible smokers likely to progress to chronic airflow limitation³. In the 1970s, it was observed in young cigarette smokers that inflammation was evident in the small airways in the absence of pulmonary emphysema⁴. A better understanding of the biological mechanisms underlying symptoms in smokers with intact FEV₁/FVC should improve our ability to treat respiratory symptoms that occur before the development of COPD.

GOLD 0: SPLENDOR AND DECLINE

Traditionally, the typical chronic respiratory symptoms of COPD are cough and sputum production, usually referred to as chronic bronchitis or chronic mucus hypersecretion (CMH) (phlegm on most days at least 3 months per year for 2 yrs). In the past, these were considered common in smokers and strongly related to chronic airflow limitation. In the 1980s, a follow-up study in men concluded that the risk of death from COPD was associated to the initial degree of airflow limitation but not to CMH, supporting that airflow limitation and CMH were largely independent disease processes⁵. These findings were, however, at variance with data from the *Copenhagen City Heart Study* (CCHS) cohort showing an association between CMH and mortality⁶ and analyses of data, at two surveys 5 years apart, that concluded that CMH was significantly associated with an excess of FEV₁ decline⁷.

The first 2001 GOLD Report² stated that a clinical diagnosis of COPD had to be confirmed by spirometry, all values referred to post-bronchodilator FEV₁/FVC. The GOLD document originally defined five spirometric stages (or grades⁸): 0 and 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe), a classification also endorsed by the *ATS/ERS Task Force for COPD*⁹. GOLD 'Stage 0: At Risk', namely the sole presence of chronic cough and phlegm with normal spirometry, offered a unique opportunity to identify individuals at risk for COPD akin to increase awareness among health care providers.

Traditionally, the natural history of COPD has been viewed as synonymous with decline in FEV₁ from early adulthood and throughout life following the seminal work by Fletcher and Peto¹⁰. However, it was acknowledged that most smokers whose FEV₁ is

already below the normal range for non-smokers by early adulthood are at risk of death due to airflow limitation. Alternatively, the majority of smokers whose FEV₁ is still above average at this age are unlikely to develop severe airflow limitation. However, recent data from three large cohorts have confirmed that approximately half of the individuals with airflow limitation followed the hypothesis that implied a rapid FEV₁ decline within normal limits in early adulthood, whereas the other half had a rather normal FEV₁ decline at this age but started from a low initial value of FEV₁¹¹, thus supporting the effect of early life events on the likelihood of having airflow limitation in adulthood.

CHRONIC RESPIRATORY SYMPTOMS, LONG-TERM FEV₁ DECLINE AND COPD DEVELOPMENT

In the 2006 GOLD Revision¹², GOLD 0 was no longer included, as there was incomplete evidence that the individuals who meet GOLD 0 necessarily progress on to GOLD 1+. Nonetheless, the importance of the public health message, to highlight that the presence of cough and sputum in the population is not normal, remained unchanged. GOLD 0 was discarded based on data from the CCHS cohort¹³ in which 7.1% of men and 4.8% of women (mean age, over 52 years each) had GOLD 0 at baseline with a prevalence of 6.1%. After 5 and 15 years, COPD developed in 13.2% and 20.5% of smokers with GOLD 0 at enrollment, respectively, although symptoms of cough and sputum in unobstructed smokers were associated with an excess lung function decline of 19 ml/yr, in addition to the FEV₁ reduction observed in unobstructed smokers without these symptoms. Despite these findings, the data from this study suggested that most of cases of new airflow limitation were observed among subjects without

symptoms of cough and sputum and, consequently, it was felt that GOLD Stage 0 was of little help in identifying subjects at risk for COPD.

Subsequently, the *European Community Respiratory Health Survey Study* (ECRHS) ¹⁴ determined that the prevalence of GOLD 0 was 11.8% in a randomly selected population. Moderate to heavy smoking and second-hand tobacco exposure were significantly associated with GOLD 0 and GOLD 1+. Individuals with GOLD 0 presented the same risks factors, including environmental tobacco exposure and childhood respiratory infections, as those with COPD with similar high percentages of healthcare resources referred to as 'breathing problems'. In a cohort of middle-aged and elderly subjects with GOLD 0 (non-smokers, 21%), the 10-year incidence of COPD was 13.5% ¹⁵. Increasing age, smoking and sputum production but not sex, were risk factors for COPD so GOLD 0 appeared to identify individuals at risk for COPD. The study from the large *Atherosclerosis Risk in Communities* (ARIC) cohort ¹⁶ of smokers and non-smokers brought the novelty that patients with GOLD 0, defined by the association of any chronic respiratory symptom including breathlessness with normal FEV₁, had an increased risk of mortality. A parallel study of healthy, middle-aged men, found an association between symptoms and risk of death when widening GOLD 0 definition to subjects with any respiratory symptom (*i.e.*, dyspnea) than those of CMH alone ¹⁷. A re-assessment of the ECRHS cohort alluded to above determined the presence of CMH and shortness of breath and future occurrence of COPD ¹⁸. It was concluded that the presence of CMH but not dyspnea identified individuals with a high risk of developing chronic airflow limitation and was considered to be an early marker of COPD regardless of smoking habits. The prevalence of GOLD 0 was 6.2% in the *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (PLATINO) study ¹⁹. In

that study individuals with CMH had worse lung function and general health conditions with more respiratory symptoms, *i.e.* wheezing and dyspnea, limited physical activity, 'COPD exacerbations-like' events and use of respiratory medications. In the *Tucson Epidemiological Study of Airway Obstructive Disease* (TESAOD)²⁰, CMH at baseline significantly increased the risk for incident airflow limitation and all-cause mortality among individuals younger than 50 years-old, but not among those subjects older than 50 years. The conclusion was that CMH with preserved FEV₁ in the former group may represent an early marker of susceptibility to COPD and all-cause mortality. In the *Medical Research Council National Survey of Health and Development* (MRC-NSHD), a prospective study of a representative cohort of women and men²¹, the prevalence of CMH alone among smokers at enrollment increased between ages 36 and 43 from 7.6±2.0% to 13.0±2.6%, respectively. At these ages, the prevalence of CMH was associated with a higher risk of subsequent airflow limitation with a dynamic, fluctuating pattern subject to decrease after smoking cessation to levels observed in never smokers. Moreover, the longer individuals had symptoms, the higher the FEV₁ decline (Figure 1). The contention was that CMH in middle-aged smokers may modulate the early phase of COPD development and reflect activity of the chronic airway disease, a hypothesis that was challenged given the background of different clinical and developmental phenotypes²².

CLINICAL AND RADIOGRAPHIC CHARACTERISTICS OF SYMPTOMATIC, UNOBSTRUCTED INDIVIDUALS

Recent data from five large cohorts have characterized the clinical and radiographic features of symptomatic individuals with normal FEV₁. From an urban population-based study²³, two subsets of current smokers with normal spirometry were randomly

selected and followed over 3-4 years. In the first group of 59 individuals with normal diffusing capacity (DL_{CO}), only 2 subjects (3%) developed significant reductions in FEV_1/FVC and DL_{CO} . In the second subset with 46 participants with low DL_{CO} at baseline, 10 (22%) developed COPD. There were no respiratory clinical and radiographic differences between the two groups.

In the *Canadian Cohort of Obstructive Lung Disease* (CanCOLD) study²⁴, the occurrence of 'exacerbation-like' events in individuals with and without COPD was highlighted. Furthermore, compared with subjects with COPD, those without COPD had half the frequency of exacerbations and were independently associated with several risk factors (*i.e.*, female sex, presence of wheezing, use of respiratory therapies and poor health status). In individuals without COPD, those with exacerbations were more likely to have poorer health-related quality of life and missing social activities than those without exacerbations.

In parallel, the *Genetic Epidemiology of COPD* (COPDGene)²⁵ determined similar acute events of respiratory disease, more common in current and former smokers. In a second study from this same COPDGene cohort, a large sample of unobstructed subjects was compared with patients with GOLD 1+ and also with a cohort of never smokers²⁶. One or more of seven pre-defined respiratory-related impairments (*i.e.*, chronic bronchitis, severe respiratory exacerbations, modified Medical Research Council score ≥ 2 , computed tomography (CT) percentage emphysema $>5\%$ and gas trapping $>20\%$, St George's Respiratory Questionnaire total score >25 , and a 6-minute walking distance (6MWD) <350 m) were observed in 54% of unobstructed individuals. Never smokers without airflow limitation had worse quality of life and lower physical

activity and had percentage emphysema or airway-wall thickening on high resolution (HR) CT scan. Current smoking was associated with more respiratory symptoms, although former smokers had more HRCT findings. Advancing age was associated with smoking cessation. Individuals with respiratory impairments were more likely to use common respiratory medication and exhibited worse manifestations. Of note that in the *Multi-Ethnic Study of Atherosclerosis* (MESA) cohort study²⁷, including participants (51% never smokers) without airflow limitation, emphysema-like lung changes on cardiac CT were associated with all cause mortality among subjects without airflow limitation, particularly among smokers.

Ever or former smokers and never smokers with normal FEV₁ from the very recent observational *Subpopulations and Intermediate Outcome Measures in COPD Study* (SPIROMICS) cohort²⁸ were investigated. Chronic respiratory symptoms, based on a COPD assessment test (CAT) cut-off score ≥ 10 , were observed in 50% of smokers with a prevalence of CMH of the order of 33% alone in symptomatic smokers. Importantly, the use of CAT, a questionnaire designed for COPD²⁹, provides a broader assessment of symptomatic burden than just respiratory symptoms. Compared with asymptomatic current or former smokers and never smokers, symptomatic smokers were younger and more likely to be current smokers, and reported symptoms of CMH and a history of wheezing and asthma than those with lesser symptoms (CAT score < 10). Moreover they had significantly less physical activity, slightly lower lung function, more respiratory exacerbations, and HRCT findings consistent with greater airway wall thickening and low percentage emphysema. These differences persisted despite adjustment for reported co-morbidities. There were no differences in the spectrum of symptoms between symptomatic smokers with normal FEV₁ and GOLD 1-2 patients.

Interestingly, the *Exacerbations of Chronic Pulmonary Disease Tool* (EXACT) *Patient Reported Outcome* (EXACT-PRO)³⁰ approach developed to identify and characterize exacerbations provides a broader conceptual basis than just respiratory symptoms. Finally, the very recent development of the *COPD Assessment in Primary Care To Identify Undiagnosed Respiratory Disease and Exacerbation Risk* (CAPTURE) tool (Martinez FJ et al., unpublished data) has suggested that a broader concept of symptoms than simple focused respiratory symptoms is useful in identifying undiagnosed COPD. These concepts, including the prominent role of fatigue, may provide some insights into systemic effects of smoking and explain the greater clinical impact identified by recent work on symptomatic, unobstructed smokers than the original GOLD 0 label.

In summary, these data suggest that many individuals with respiratory symptoms but without airflow limitation have CT findings consistent with large airway abnormalities and these individuals experience significant morbidity and increased health care utilization lending credence to the concept that the presence of chronic respiratory symptoms in unobstructed smokers represents a clinically significant entity. The weight of the evidence would suggest that a greater symptom burden, particularly those respiratory in nature, is a risk factor for rapid lung function decline and therefore likely represents one form of early COPD, although this likely only represents one pathway for COPD development as other individuals without symptoms also go on to develop COPD. A study in smokers with GOLD 0-4 from the COPDGene cohort observed a significant association between functional small airways disease, assessed by CT-Parametric Response Mapping (PRM), that identifies areas of non-emphysematous gas trapping, and FEV₁ decline over 5 years³¹. Small airways (<2 mm in diameter) are known to be the major site of narrowing in patients with COPD³² and disease in the

small airways is thought to precede the onset of developing emphysematous lesions³³. While the signal was attenuated in unobstructed individuals as opposed to those with established airflow limitation, CT-assessed small airways disease was still associated with more rapid lung function decline in this group. Notably, however, those unobstructed individuals with excess small airway abnormality were not more symptomatic based on the presence of chronic bronchitis, again reinforcing the multiple trajectories towards the development of airflow limitation. This is further emphasized by data from the *Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints* (ECLIPSE) cohort study, in which there was no association between CMH and long-term FEV₁ decline whereas the presence of pulmonary emphysema was associated^{34;35}.

CLINICAL SIGNIFICANCE AND REMAINING QUESTIONS

The new data on this clinical condition derived from these cohort studies^{24;26;28} provide valuable insights into this condition as a distinct clinical entity, irrespective of whether it progresses to COPD. This subset of smokers is predominantly observed in middle-aged subjects without sex differences. Breathlessness associated with limited physical activity and frequent 'COPD exacerbations-like' events that require respiratory therapies constitute key clinical features. Moreover, it is associated with HRCT percentage airway wall thickness changes. Data from long-term longitudinal clinical studies described above^{24;26;28} suggest that symptoms in unobstructed smokers are associated with higher risk for the future development of airflow limitation, even in the data that ultimately led to the withdrawal of GOLD 0 stage¹³. However, passage through a GOLD 0 stage is not the only pathway to airflow limitation, and many patients with GOLD 0 do not necessarily progress to chronic airflow limitation.

Whatever the relevance and the robustness of the reported data the list of shortcomings or unmet needs (Table 1) is large and overcome in part the established findings. Of note, however, that in several of these studies^{26;28} cough and phlegm production are not present in all smokers, suggesting that systemic symptoms (*i.e.*, dyspnea, limited physical activity, fatigue) may be more representative of the broad effects of smoking *per se*. One conclusion is that the full breadth of symptoms associated with early lung disease in smokers has been underestimated and even unrecognized³⁶. However, it could also be that *e.g.* muscles and the cardiovascular system were affected in these smokers. Accordingly, we may probably need to reconsider the strategy of early diagnosis and preventative measures by paying more attention to symptoms. It has been observed that excess mortality in smokers is largely due to associations with diseases, such as renal failure, hypertensive heart disease, and respiratory diseases, not properly caused by smoking³⁷.

Alternatively, these unmet needs bring opportunities for future research studies to enhance the understanding of the natural history of COPD while further supporting preventative and therapeutic approaches. According to a retrospective analysis from primary and secondary care cohorts, opportunities to diagnose COPD at an earlier stage are being missed, particularly during the 5 years immediately before diagnosis³⁸. These needs extend from the selection of appropriate cohorts of participants between population-based and disease-specific cohorts, including people with risk factors other than tobacco smoking, such as environmental and occupational exposures³⁹. A skillful exploitation of tools, such as clinical symptoms (respiratory and non-respiratory) and serum biomarkers⁴⁰ to assess disease activity⁴¹, including sensitive small airways disease and exercise tests, may be complementary. Likewise, 'COPD exacerbations-

like' events and coexisting co-morbidities need to be better characterized to provide new insights^{42,43}. Furthermore, the different HRCT patterns, combined with novel CT volumetric scans and other imaging novelties, have to be better investigated. The association between endothelial dysfunction, FEV₁ and CT percentage of emphysema in former smokers with normal FEV₁ suggests that pulmonary vascular disturbances can be considerably involved in the development of emphysema⁴⁴, which supports the potential role of pulmonary vessels into the pathogenesis of COPD⁴⁵⁻⁴⁷. Finally, as in most smokers respiratory and non-respiratory symptoms may come before airflow limitation, we need to reconsider the strategy of early diagnosis and management to give first particular attention to symptoms. Last but not least, pharmacologic and non-pharmacologic therapies to pave the potential of personalized medicine⁴⁸ need also to be re-assessed.

CONCLUSIONS

It is now time to move beyond GOLD 0⁴⁹ to decipher the fundamental question regarding the short- and long-term clinical significance of the presence of chronic respiratory symptoms and preserved lung function. Indeed, the dilemma remains as to whether we are simply confronted with an "early phase" of what will become COPD in the traditional sense or a separate smoking-related condition which is chronic and remains symptomatic without progression to COPD. Indeed it is possible that both patterns occur. Research studies targeting this likely distinct condition in the context of the systemic effects of smoking by itself should shed light for sure on current understanding of the natural history of COPD^{36,37}.

LEGEND TO FIGURE 1

The estimated FEV₁ decline (*Y axis*) is influenced by the duration of chronic mucus hypersecretion (CMH) between ages 43 and 60–64 years (*Y axis*) calculated for man (A) and woman (B) smokers of average height and weight at age 43. The presence of CMH on all three occasions was associated with an additional 10.8 ml/yr FEV₁ decline between ages 43 and 60–64 years compared with those without CMH on any occasion (Reproduced by permission from ref²¹).

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Table 1. Unmet Needs for Research Studies

- Appropriate population-based cohorts
- Symptoms (respiratory and non-respiratory); serum biomarkers
- Health-related quality of life tools: *COPD Assessment Test* [CAT]; *Exacerbations of Chronic Pulmonary Disease Tool* (EXACT) Patient Reported Outcome (EXACT-PRO); Saint George's Respiratory Questionnaire [SGRQ]
- Sensitive small airways function and exercise (6 min walking distance; incremental cycle) tests
- COPD 'exacerbation-like' events: triggers; clinical characteristics; differential diagnosis
- Co-morbidities: cardiovascular; depression; gastroesophageal reflux disease; metabolic; skeletal and muscle
- Computed tomographic (CT) and novel CT volumetric scans and other imaging novelties
- Preventative (smoking cessation; environmental exposures control) and therapeutic (pharmacologic and non-pharmacologic) strategies

Figure 1