The Challenges of Defining Early Chronic Obstructive Pulmonary Disease in the General Population

Chronic obstructive pulmonary disease (COPD) remains a huge global health burden that is projected to become the third-leading cause of mortality by 2030 (1). Established COPD is highly heterogeneous with a lack of disease-modifying treatments (2). A clearer understanding of the condition is often impeded by the high rate of comorbidities that patients typically exhibit at the point of diagnosis. It is now apparent that there are a range of subpopulations at risk for accelerated disease progression (3, 4). The mechanisms underpinning these varying trajectories that lead to the development of COPD are highly complex but are significantly influenced by early life exposures (5). Furthermore, it is now understood that at the point of diagnosis, individuals with COPD have been symptomatic for at least 5 years, underlining the critical need for detection of the disease and efficacious interventions at the early stage (6).

To date, the majority of COPD studies attempting to examine the concept of early COPD have included populations with mean ages older than 60 years (7). As Martinez and colleagues highlight in a recent review, these studies therefore inform on late "mild disease" as opposed to "early disease" (5). Although the initial events responsible for ultimate development of pathology currently cannot be described, this expert group proposed an operational definition for early COPD based on surrogate end points that encompasses lung pathology unequivocally associated with subsequent accelerated lung function decline leading to objectively confirmed incompletely reversible airflow obstruction and other COPD-related manifestations (Table 1).

Characterizing the mechanisms underpinning pathogenesis is a pivotal step toward understanding individuals at risk of COPD and will hopefully lead to novel targets for treatment. However, to validate this hypothesis requires serial sampling in well-powered, long-lasting prospective cohorts.

In this issue of the *Journal*, Çolak and colleagues (pp. 1245–1256) investigate the relationship between early COPD and subsequent development of clinical COPD (8). This well-designed Danish study leveraged the large contemporary Copenhagen General Population Cohort to investigate lung function changes in 20- to 50-year-olds over a 10-year period. The authors identified those with early COPD by applying age and spirometric criteria (FEV_1/FVC ratio less than lower limit of normal), in line with the operational definition proposed by Martinez and colleagues in 2017, to investigate the risk of subsequent clinical disease.

During the study, 5,497 subjects under 50 years old had spirometry performed 10 years apart. At enrollment, the authors found 168 (3%) subjects met their definition of early COPD, whereas 104 (2%) of the cohort went on to develop clinical COPD. At first glance, the number of participants identified with early COPD appears to be much lower than expected given a recent analysis, also from the Copenhagen General population, that found 15% of the general population fulfill the criteria for early COPD (9). However, the reason is that during modeling, the authors took steps to exclude established individuals with clinical COPD and those with an FEV_1/FVC ratio less than 0.70 to ensure that subjects with demonstrable airflow limitation at enrollment were not included in the analysis, thus explaining the apparent low prevalence. Çolak and colleagues then go on to stratify according to tobacco exposure to investigate this effect on COPD development.

In their results, the authors demonstrate that early COPD increases with age and tobacco exposure. Early COPD is present in 4% of smokers with $\geq$10 pack-years, 3% in smokers with $<$10 pack-years, and 2% in never-smokers. The group with early COPD also had lower FEV_1 (2.6 vs. 3.4 L) and was more symptomatic. As the authors correctly identify, there are fewer younger participants found, and they speculate this is because of the time needed for smokers to accumulate tobacco consumption, therefore skewing the distribution toward higher age.

In the early COPD smokers with $>$10 pack-years group, 24% went on to develop clinical COPD compared with 4% in individuals without early COPD. When the effect of tobacco exposure was removed, sensitivity reduced from 24% to 18%. Overall, this highlights the challenges in defining subpopulations at risk of developing COPD. Citing the high 97% specificity they observed, Çolak and colleagues conclude that the operational definition for early COPD may be effective at excluding individuals not likely to develop clinical COPD later in life. Indeed, as the authors acknowledge, less than 4% of individuals without early COPD at baseline developed clinical COPD subsequently. They conclude that among individuals with early COPD, the odds ratios for clinical COPD 10 years later were 7.77 (95% confidence interval, 4.10–14.7) in smokers with $\geq$10 pack years and 8.56 (4.92–14.9) in all smokers. These results were validated independently in the Copenhagen City Heart Study cohort.

Martinez and colleagues' definition proposes FEV_1 decline $>$60 ml/yr is part of the early COPD definition. A further interesting aspect of the study by Çolak and colleagues relates to their evaluation of this. Individuals with versus without early COPD did not differ with regard to FEV_1 decline (23 ml/yr vs. 22 ml/yr). FEV_1 decline $\geq$60 ml/yr was 8% in those with versus 6% in those without early COPD. However, investigating the group that developed clinical COPD at follow up demonstrated a mean FEV_1 decline of 45 ml/yr (31% with FEV_1 decline $\geq$60 ml/yr). It is known that COPD development follows several lung function trajectories: some cases develop because of an accelerated lung function decline, whereas others do not achieve the expected maximally attained lung function in early adulthood (4).

Limitations of the study must focus on the use of prebronchodilator spirometry, which does not allow the authors to exclude the

Originally Published in Press as DOI: 10.1164/rccm.202011-4176ED on December 3, 2020

Table 1. The Operational Criteria for Early Chronic Obstructive Pulmonary Disease

Required	One or More of the Following
<50 yr of age ⩾10 pack-years smoking history	FEV_1/FVC less than the lower limit of normal Compatible CT abnormalities (visual emphysema, air trapping, or bronchial thickening graded mild or worse) Evidence of accelerated FEV_1 decline (⩾60 ml/yr)

Definition of abbreviaton: CT = computed tomography.
Reproduced from Reference 5.

possibility that some of the signal reported is contributed to by reversible airflow limitation, indicating asthma. This was unavoidable in this particular study given the cohort investigates the Copenhagen general population but adds further weight to the need for a dedicated prospective study, which assesses both pre- and postbronchodilator spirometry. Furthermore, despite the large and robust nature of the data set, only 168 subjects with early COPD were identified. A lack of available computed tomography data meant that it was not possible to know if subjects with visual emphysema, air trapping, and/or bronchial thickening were included. Work presented by Ritchie and colleagues from a novel cohort of young smokers highlights that whereas 11 (10.7%) individuals had an FEV_1/FVC ratio below the lower limit of normal, 43 (42.1%) demonstrated computed tomography abnormalities, suggesting the possibility of underrepresentation in this Copenhagen cohort (5, 10).

Overall, the authors should be commended for their methodological approach to address a clinically important question. Their hypothesis that early COPD and tobacco consumption risks a diagnosis of clinical COPD 10 years later is not accepted wholly by the findings in this intriguing study. That less than 24% of individuals defined with early COPD at baseline developed clinical COPD at final examination 10 years later demonstrates the difficulty in defining early COPD. There is a need for dedicated cohorts designed to prospectively study lung function change with multiple measurements and comprehensive sampling to characterize the mechanisms underpinning the development of COPD. Çolak and colleagues' study may herald the beginning of a new era in which we evolve to understand the formative events that lead to clinical COPD later in life. Ultimately, the hope is that this increased understanding will have huge implications for the development of new efficacious treatments. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Andrew I. Ritchie, M.D.
National Heart and Lung Institute
Imperial College
London, United Kingdom

Fernando J. Martinez, M.D., MS.*
Department of Medicine
Weill Cornell Medicine
New York, New York

*F.J.M. is the Deputy Editor of the *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

References

1. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.
2. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Am J Respir Crit Care Med* 2017;195:557–582.
3. Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. Combined impact of smoking and early-life exposures on adult lung function trajectories. *Am J Respir Crit Care Med* 2017;196:1021–1030.
4. Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, *et al*. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med* 2015;373:111–122.
5. Martinez FJ, Han MK, Allinson JP, Barr RG, Boucher RC, Calverley PMA, *et al*. At the root: defining and halting progression of early chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2018;197:1540–1551.
6. Jones RC, Price D, Ryan D, Sims EJ, von Ziegenweidt J, Mascarenhas L, *et al*.; Respiratory Effectiveness Group. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. *Lancet Respir Med* 2014;2:267–276.
7. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. *Lancet* 2015;385:1778–1788.
8. Çolak Y, Afzal S, Nordestgaard BG, Lange P, Vestbo J. Importance of early COPD in young adults for development of clinical COPD: findings from the Copenhagen general population study. *Am J Respir Crit Care Med* 2021;203:1245–1256.
9. Çolak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Prevalence, characteristics, and prognosis of early chronic obstructive pulmonary disease: the Copenhagen general population study. *Am J Respir Crit Care Med* 2020;201:671–680.
10. Ritchie AI, Donaldson GC, El-Emir E, Calverley PM, Vestbo J, Wedzicha JA. The British Lung Foundation early COPD consortium - recruitment and results from an initial pilot [abstract]. *Am J Respir Crit Care Med* 2019;199:A3280.