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## References

1. Bassetti CLA, Randerath W, Vignatelli L, Ferini-Strambi L, Brill A-K, Bonsignore MR, et al. EAN/ERS/ESO/ESRS statement on the impact of sleep disorders on risk and outcome of stroke. *Eur Respir J* 2020;55:1901104.
2. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *Am J Respir Crit Care Med* 2019;200:493–506.
3. Penzel T. Prospective cohort studies of major disorders can facilitate phenotyping for sleep apnea. *Am J Respir Crit Care Med* [online ahead of print] 2021 Jan 21; DOI: 10.1164/rccm.202012-4414ED.
4. Lees T, Shad-Kaneez F, Simpson AM, Nassif NT, Lin Y, Lal S. Heart rate variability as a biomarker for predicting stroke, post-stroke complications and functionality. *Biomed Insights* 2018;13:1177271918786931.
5. Blanchard M, Gervès-Pinquier C, Feuilloy M, Le Vaillant M, Trzepizur W, Meslier N, et al.; ERMES Study Group. Hypoxic burden and heart-rate variability predict stroke incidence in sleep apnoea. *Eur Respir J* 2021;57:2004022.
6. Blanchard M, Gervès-Pinquier C, Feuilloy M, Le Vaillant M, Trzepizur W, Meslier N, et al.; ERMES Study Group. Association of nocturnal hypoxemia and pulse rate variability with incident atrial fibrillation in patients investigated for OSA. *Ann Am Thorac Soc* [online ahead of print] 2021 Jan 12; DOI: 10.1513/AnnalsATS.202009-1202OC.
7. Schäfer A, Vagedes J. How accurate is pulse rate variability as an estimate of heart rate variability? A review on studies comparing photoplethysmographic technology with an electrocardiogram. *Int J Cardiol* 2013;166:15–29.
8. Liu S, Teng J, Qi X, Wei S, Liu C. Comparison between heart rate variability and pulse rate variability during different sleep stages for sleep apnea patients. *Technol Health Care* 2017;25:435–445.
9. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al.; American Academy of Sleep Medicine; Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. *J Clin Sleep Med* 2012;8:597–619.
10. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–845.
11. Azarbarzin A, Sands SA, Younes M, Taranto-Montemurro L, Sofer T, Vena D, et al. The sleep apnea-specific pulse rate response predicts cardiovascular morbidity and mortality. *Am J Respir Crit Care Med* [online ahead of print] 2021 Jan 6; DOI: 10.1164/rccm.202010-3900OC.
12. Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *Eur Heart J* 2019;40:1149–1157.
13. Raman D, Kaffashi F, Lui L-Y, Sauer WH, Redline S, Stone P, et al. Polysomnographic heart rate variability indices and atrial ectopy associated with incident atrial fibrillation risk in older community-dwelling men. *JACC Clin Electrophysiol* 2017;3:451–460.

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## Asthma with a Smoking History and Pre-Chronic Obstructive Pulmonary Disease

To the Editor:

The Perspective article by Hans and colleagues proposes the term “pre-COPD” to describe current and former smokers with normal spirometry who are at risk of developing chronic obstructive pulmonary disease (COPD) ( $FEV_1/FVC < 0.7$ ) (1). Factors considered helpful in identifying individuals with pre-COPD who are likely to progress to COPD include symptoms, particularly nonobstructive chronic bronchitis, and lung function and imaging biomarker abnormalities (1). Although not discussed in the article, data suggest that asthma in adults with a smoking history and normal spirometry COPD (pre-COPD) is a risk factor for COPD development. Selective studies supporting a role of asthma in smoking-related pre-COPD are briefly outlined below. First, asthma commonly occurs in adult smokers without spirometric COPD because of the high prevalence of cigarette smoking and asthma in many populations worldwide (2). Current smoking in asthma is frequently associated with poor symptom control, corticosteroid insensitivity, and type 2 low airway inflammation (2). The diagnosis of asthma may be uncertain in some symptomatic smokers with normal spirometry because of an overlap in chronic respiratory symptoms among smokers with and without asthma. Second, general population-based surveys and observational cohort studies of current and former smoking volunteers used to investigate smoking-related pre-COPD frequently include individuals with a history of asthma. For example, among symptomatic middle-aged and older current or former smokers with normal spirometry results included in the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) (3) cohort, more than one-quarter reported a history of asthma. Third, chronic bronchitis is a common symptom among cigarette smokers with asthma (2, 4) and may contribute to the development of COPD in this subgroup. Fourth, longitudinal population-based studies have shown accelerated decline in lung function in adult smokers with asthma (2, 4), some of whom develop chronic persistent airflow obstruction. Individuals with specific phenotypes of asthma, such as smokers with late-onset asthma (5) and/or nonatopic asthma, may be at greater risk of developing COPD. Finally, data on computed tomographic imaging in current smokers with asthma, although limited, provide some evidence of radiological abnormalities, including reduced segmental airway lumen area, particularly in those with chronic bronchitis, and occasionally emphysema (6). Collectively, these findings suggest that asthma with a smoking history and pre-COPD should be included as a risk factor for developing COPD. Future research should establish whether the natural history and management of current and/or former smokers with pre-COPD differs in those with or without asthma. ■

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## References

1. Han MK, Agusti A, Celli BR, Criner GJ, Halpin DMG, Roche N, *et al.* From GOLD 0 to Pre-COPD. *Am J Respir Crit Care Med* 2021;203:414–423.
2. Thomson NC. Asthma and smoking-induced airway disease without spirometric COPD. *Eur Respir J* 2017;49:1602061.
3. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, *et al.*; SPIROMICS Research Group. Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med* 2016;374:1811–1821.
4. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194–1200.
5. Hancox RJ, Gray AR, Poulton R, Sears MR. The effect of cigarette smoking on lung function in young adults with asthma. *Am J Respir Crit Care Med* 2016;194:276–284.
6. Thomson NC, Chaudhuri R, Spears M, Messow C-M, MacNee W, Connell M, *et al.* Poor symptom control is associated with reduced CT scan segmental airway lumen area in smokers with asthma. *Chest* 2015;147:735–744.

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## Exposing Pre-Chronic Obstructive Pulmonary Disease: When Physiology Matters!

To the Editor:

We read with great interest a recent Pulmonary Perspective on the early manifestations (i.e., before the development of airflow obstruction on spirometry) of chronic obstructive pulmonary disease (COPD) (1). The authors outline some convincing pieces of evidence indicating that the identification of smokers at higher risk of developing COPD (called “pre-COPD”) is not only feasible but also of substantial societal and economical relevance. It called our attention, however, that their keen interest in structural abnormalities signaling toward pre-COPD was not paralleled by a similar enthusiasm concerning more detailed physiological measurements. Although the authors do list “low lung diffusing capacity for carbon monoxide ( $DL_{CO}$ ),” “hyperinflation,” “small airways obstruction,” and “accelerated forced expiratory volume in one second ( $FEV_1$ ) decline” as functional markers of pre-COPD in their Figure 2 (1), only the latter topic is adequately supported by

published evidence. For instance, a single study is cited to endorse some potential value of an isolated low  $DL_{CO}$  to point out pre-COPD; regrettably, however, no mechanistic insights are provided to justify why  $DL_{CO}$  might decrease before the  $FEV_1/FVC$  ratio crosses the 0.7 threshold.

In this context, our research group has investigated in detail the physiological characteristics of subjects in the transition from “pre-” to “established” COPD (2–4). The following two features consistently stood out in smokers with largely preserved  $FEV_1$  who were dyspneic on exertion: a reduced  $DL_{CO}$  and excessive ventilation at low exercise intensities. What does a low  $DL_{CO}$  tell us about the nature of pre-COPD?  $DL_{CO}$  (or, more properly, the transfer factor) is influenced not only by the surface area for gas exchange but also by ventilation distribution and ventilation/perfusion (mis)matching. Apart from any incipient emphysema (sometimes below the limits of resolution of conventional computed tomography [CT]) (5), impaired perfusion due to microvascular dysfunction in emphysema-free areas may decrease  $DL_{CO}$  (6). The tenuous small pulmonary vessels might also be compressed by patchy areas of localized gas trapping due to small airway dysfunction. A low  $DL_{CO}$  might also be a consequence of a reduced accessible  $V_A$  due to early ventilation distribution inhomogeneities; of note, we did find a reduced  $V_A/TLC$  (by body plethysmography) ratio in these subjects. Regardless of the contributing mechanisms, a low  $DL_{CO}$  signals high ventilation/perfusion. Indeed, we found that increased “wasted” ventilation underpins the excessive ventilation observed in subjects with low  $DL_{CO}$  (2–4). Breathlessness is the sensory translation of an increased neural drive to breathe secondary to such high ventilatory demands. Closing the loop, the report of activity-related dyspnea may precede the diagnosis of COPD in smokers (1).

How do small airway dysfunction and gas trapping fit into this scenario? Dynamic hyperinflation develops at a faster rate 1) the slower the expiratory flows through the smaller airways and 2) the higher the volume at which they close on tidal breathing. These assertions explain why dyspneic smokers may show low midexpiratory flows and increased residual volume (RV) and/or RV/TLC ratio, respectively (2). When these abnormalities conflate with high ventilatory demands (predicted by a low  $DL_{CO}$ ), critically high operating lung volumes are reached earlier during exercise. To avoid the uncomfortable respiratory sensations associated with activity, smokers with pre-COPD adopt a sedentary lifestyle that fuels the downward spiral of deconditioning and worsening breathlessness.

In summary, integrative respiratory pathophysiology has much to contribute to the understanding of “incipient” pre-COPD. Using a Bayesian approach that considers symptoms and abnormal CT features, the pulmonologist should look for early marks of disrupted physiology despite preserved  $FEV_1/FVC$  (decreased  $DL_{CO}$ , decreased midexpiratory flows, and increased RV and/or RV/TLC ratio) to identify smokers who are in the process of eventually developing airflow obstruction consistent with COPD. We echo the authors of this Pulmonary Perspective that such a proactive approach may enable early therapeutic interventions with the potential to modify the course of the disease (1). ■

**Author disclosures** are available with the text of this letter at [www.atsjournals.org](http://www.atsjournals.org).

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