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**Invited EDITORIAL**

**Title: Respiratory symptoms and small airway dysfunction in current and former smokers without spirometric COPD**

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## Main text

Chronic respiratory symptoms are commonly reported by current and former cigarette smokers who lack spirometric evidence of COPD. These individuals are more likely to experience wheezing, breathlessness, limitation in exercise, chronic bronchitis, worse quality of life, exacerbations and more co-morbidities than healthy never-smokers (1-4) (Figure). The natural history, pathophysiology and management of smokers without evidence of COPD is poorly understood (3, 4). Smoking-induced airway diseases include chronic bronchitis, emphysema, and small airway disease, occurring either alone or in combination. These diseases also occur in smokers with asthma (3). Previous studies of inflammation, physiology and computed tomography (CT) imaging provides indirect evidence that small airway disease (<2 mm in diameter) contributes to respiratory symptoms in smokers with normal spirometry. Cigarette smoking induces respiratory bronchiolitis of small airways before the development of emphysema (5, 6). The function of peripheral airways is abnormal in some smokers without COPD assessed by physiological techniques, such as multiple breath nitrogen washout (MBNW) (7) and impulse oscillometry (IOS) (8, 9). Analysis of expiratory and inspiratory computed tomography (CT) images detects increased nonemphysematous air trapping, a surrogate for functional small airways disease, in ever-smokers with normal spirometry (10-12). However, little is known about whether small airway dysfunction assessed by physiological tests, such as MBNW or IOS are worse in symptomatic smokers without COPD compared to asymptomatic smokers. In this issue of *Respirology*, Jetmalani *et al* (13) report the results of a prospective, observational study designed to determine the prevalence of respiratory symptoms (chronic bronchitis, dyspnoea, wheeze) and small airway dysfunction and their interrelationship in

eighty young to middle-aged current and former smokers without spirometric COPD. Small airway dysfunction was assessed by measuring ventilation heterogeneity in diffusion-dependent ( $S_{acin}$ ) and convection-dependent ( $S_{cond}$ ) airways by MBNW and by measuring respiratory resistance at 5 (R5) and 20 (R20) Hz and reactance at 5 (X5) Hz by IOS.

An important finding of the study was that abnormalities in either MBNW (predominantly  $S_{acin}$ ) or IOS (predominantly R5) were found in three quarters of current and former smokers without spirometric COPD. Half the subjects had an abnormal MDNW or IOS measurement, and in one quarter there was an overlap in abnormal IOS and MBNW variables. The results of the study and those from previous studies using physiological tests (7-9) and CT imaging biomarkers (10-12) demonstrate that small airway dysfunction is commonly found in this group of current and former smokers. Interestingly, smokers without spirometric COPD following smoking cessation show sustained improvements of conductive airway dysfunction ( $S_{cond}$ ), but not in acinar airway function ( $S_{acin}$ ) suggesting that some abnormalities of small airway disease are reversible, possibly due to reduced inflammation or hypersecretion (14).

Of interest, Jetmalani *et al* (13) found that 68% of the young to middle-aged smokers without COPD reported at least one respiratory symptom (chronic bronchitis 39%, dyspnoea at rest or on exertion 38%, and episodic wheeze 49%). The prevalence rate of respiratory related impairment is slightly higher than that reported in the SPIROMICS (50%)(1) and COPDGene (54%) (2) cohorts of older smokers with normal spirometry. Jetmalani *et al* (13) found that symptoms of chronic bronchitis related to peripheral conductive airway function ( $S_{cond}$ ), while

wheeze was related to measures of large airway function (R5 and spirometry). Nevertheless, the difference in abnormalities between symptomatic and asymptomatic subjects was relatively small. Previous studies in older smokers with normal spirometry have reported that CT air trapping is associated with worse clinical outcomes (12) and lung function decline (10), whereas CT airway wall thickness is associated with symptoms of chronic bronchitis (1).

Although important, the study by Jetmalani *et al* (13) has some limitations. The symptoms questionnaire did not provide information on exacerbations or quality of life of the participants to determine if these clinical outcomes related to physiological tests of small airway dysfunction. Information on a history of current asthma or previous asthma is lacking despite half of the young and middle-aged smokers reporting episodic wheeze. Smokers with asthma without spirometric COPD experience clinical features that overlap with symptomatic current and former smokers with normal spirometry (3), including small airway dysfunction (15). It is not stated whether the participants received treatment with inhaled bronchodilators or inhaled corticosteroids, which might have influenced measures of small airway function. As the authors acknowledge, it would have been informative if CT imaging had been included for comparison with MBNW and IOS measures.

What are the implications of the study by Jetmalani *et al* (13) for future research in smokers without spirometric COPD? The findings when taken together with previous research show that a considerable proportion of smokers and former smokers have abnormal small airway function and that certain measures of small airway dysfunction correlate with specific respiratory

symptoms. Nevertheless, the role of small airway dysfunction in causing respiratory symptoms and impairment is not established. The investigation of research questions arising from these findings will require large long-term studies. For example, do physiological and imaging biomarkers of small airway disease in smokers without COPD have variable relationships with different respiratory symptom? Do factors, such as heterogeneity in phenotypes of smoking-induced airway diseases, age or intensity of smoking history influence relationships between symptoms and small airway dysfunction? Do physiological tests, such as IOS and MBNW identify smokers with normal spirometry who are at risk of developing COPD and do these measures relate to imaging-based biomarkers? Importantly, is the assessment of small airway function in symptomatic smokers useful in predicting benefits from different treatments?

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## Figure legend

**Figure 1: Clinical outcomes and mechanisms of airway disease in current and former smokers without spirometric evidence of COPD ( $FEV_1/FVC$  ratio  $>0.7$ )**

\*: It is not known whether current and former smokers with smoking-induced airway disease without spirometric evidence of COPD or a history of asthma demonstrate corticosteroid insensitivity or have pathological features of 'asthma-associated' airway remodelling