**Title: Assessing small airway function for early detection of lung function impairment**

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**Abbreviations**

Chronic Obstructive Pulmonary Disease: COPD

Forced expiratory Volume in one second: FEV1

Forced Vital Capacity: FVC

Forced expiratory Volume in one second/Forced Vital Capacity: FEV1/FVC

Forced Expiratory Flow between 25-75: FEF25-75

Post-bronchodilator (Post-BD)

Pre-bronchodilator (Pre-BD)

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**Take Home Message:**

Both impulse oscillometry and spirometry provide comparable information for small to mid-airway function. However, spirometry is more sensitive in detecting bronchodilator reversibility.

Dear Editor,

We thank F. Trinkmann and co-authors for their appreciation of our work and also in raising important questions on the role of small airway function in early detection of lung function impairment associated with asthma and smoking, leading to development of COPD (1), (Trinkman et al 2020). The focus of our study was not simply on small airway function but rather, the onset and trajectories of lung function impairment associated with asthma and smoking. However, we agree that small airway function is an important part of that assessment. The authors raise two important points in this regard. One that (at a microscopic level) significant pathology is present in the small airways before it can be detected by commonly used diagnostic tests and secondly that other tests such as oscillometry, static lung volumes, transfer factor and radiological imaging add to the assessment of small airway function. We agree with both these points. However, we disagree with their assertion that assessment of small airway function using spirometry, and more specifically, FEF25-75 is neither useful nor sensitive (2).

The problem with FEF25-75 is not low sensitivity; indeed it is highly sensitive to changes in small airway function (3). The problem is large variance, both within and between individuals, where longitudinal follow up of those with impaired FEF25-75 does not consistently correlate with persistent airway obstruction. In older age subjects, changes in FEF25-75 parallel those in FEV1 and FVC and as the coefficient of variation is lower in FEV1 and FVC, the FEV1/FVC ratio is often used as a marker of airways obstruction (4). However, whether this was the case for subjects with asthma or smoking exposure during childhood and adolescence is not known. By longitudinally tracking spirometry, we showed that changes in FEF25-75 parallel FEV1 to some extent but not FVC, given the rapid growth in height during this period. Indeed, FEF25-75 was highly sensitive in detecting signals of airflow limitation before any abnormality was observed in FEV1 or FVC in children aged 10 when they were stratified with asthma presence at age 26 (1). Similarly, the first abnormality appearing at age 26 in only smokers was low FEF25-75, at age 26, indicating its usefulness as a marker for early detection of airflow limitation.

Trinkmann et al allude to several other modalities that may inform on small airways dysfunction. Body plethysmography and transfer factor for carbon monoxide do require specific equipment and expertise beyond what is easily available in the outpatient consultation setting. The same is true for imaging techniques such as CT scans and MRI, with CT scan having additional disadvantage of the risk of radiation exposure and does not lend itself to large scale screening to detect early COPD. Fractional exhaled nitric oxide (FeNO) is routinely used in the management of asthma, indicating airway inflammation but it is neither a sensitive, nor specific indicator of small airway dysfunction (5). Longitudinal studies have not confirmed the usefulness of single-breath N2 test in predicting later decline in FEV1 (6). Further, a large cross-sectional study recently also did not find the newer multiple breath washout as a sensitive test for small airway dysfunction (7). These authors concluded that both spirometry and impulse oscillometry were sensitive in defining the presence and severity of small airway dysfunction, are easy to use, and have meaningful association with asthma control and quality of life. We agree that oscillometry is likely to be useful in the management of asthma both in terms of diagnosis, prognosis and control of asthma. We have conducted oscillometry in the Isle of Wight birth cohort at age 26, albeit not at earlier ages. As this data was not longitudinally available in our cohort, we did not include oscillometry data in our published manuscript. We have now analysed airway resistance as R5–R20, as a measure of respiratory resistance of small to mid-sized airways in our four defined groups (controls, only asthma, only smoking, and both asthma and smoking). Both Oscillometry (R5-20) and Spirometry (FEF25-75) show comparable information (Figure 1). However, FEF25-75 was more sensitive for bronchodilator reversibility in asthmatics compared to R5-20 with a greater bronchodilator response and higher post- bronchodilator values in those with “asthma” compared to “both asthma and smoking”. Further, impulse oscillometry still needs to demonstrate its reliability in predicting progressive lung damage overtime, before its use can be recommended in the diagnosis of early COPD.

Finally, we completely agree that further research is needed in assessing the role of small airway dysfunction in asthma and COPD utilizing longitudinal cohorts with a combination of older and novel techniques to identify at risk patients early in the course of disease before permanent damage has occurred. Studies such as ATLANTIS and ALLIANCE that the authors mentioned will add knowledge in this context.(7, 8) However, we would like to emphasize the value of birth cohorts with longitudinal data on spirometry and oscillometry, which provide clinically relevant information that can be replicated and use in clinical practice in identifying those at risk of COPD. We propose a two-stage approach, which might be more practical and clinically applicable. The first stage should be to do spirometry and/ or oscillometry, both easy to use, inexpensive and widely available tests. Patients showing small airway dysfunction on these commonly available tests can then be further assessed using deeper phenotyping including body plethysmography, transfer factor and lung imaging.

**Figure Legends**

Figure describes the pre-bronchodilators (Pre-BD) and post-bronchodilator (Post-BD) mean and standard error for each group defined by the presence of asthma and/or smoking at age 26: “Controls” (no asthma and did not smoke), “Asthma only” (asthma but did not smoke), “Smoking only” (smoked but did not have asthma) and “Both asthma and smoking” (asthma and did smoke).

(A) Spirometry (FEF25-75). The Pre-BD FEF25-75 was significantly higher in “Controls” compared to all other groups (p <0.001) and in “smoking” versus “both asthma and smoking” (p=0.001). Pre-BD asthma was not different to “asthma and smoking”; however, following BD, FEF25-75 improved in asthmatic such that it was significantly higher than “both asthma and smoking” (p=0.005).

(B) Oscillometry (R5-20 Hz): the Pre-BD R5-20 (indicating airway resistance) was significantly lower in “Controls” compared to “asthma” (p=0.0006) and “both asthma and smoking” (p=0.0474); “asthma” was significantly higher than “smoking” (p=0.0198). Others non-significant. Similar pattern was seen for Post-BD.

All comparisons were carried out using one-way ANOVA and t test with Bonferroni correction.

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