Asthma is an inflammatory disease that is treated with inhaled corticosteroids, but some patients manifest persistent symptoms despite this. Small airway dysfunction may account for treatment resistance in asthma. We hypothesised firstly that small airway disease is characterised by multiple and independent domains, and secondly that small airway biomarkers define a distinct phenotype of asthma with altered clinical disease expression.

Methods Ninety-six patients with asthma and eighteen healthy control subjects were recruited. Participants undertook spirometry, body plethysmography, single breath determination of carbon monoxide uptake in the lung, multiple breath inert gas washout and impulse oscillometry. Factor analysis was used to reduce multiple physiological variables to a smaller number of independent components. Hierarchical and k-means cluster analysis was used to classify asthma patients into groups based on physiological biomarkers.

Results Factor analysis showed that the measured physiological biomarkers could be reduced to three independent components, corresponding to abnormal lung mechanics (R5-R20 and reactance), airflow obstruction (FEV1 [% pred.] and FVC [% pred.]) and ventilation heterogeneity (lung clearance index and Scalin). Cluster analysis classified the asthma patients into two groups. Patients in Cluster 1 exhibited multiple physiological abnormalities suggestive of small airway disease, including air trapping, ventilation heterogeneity and abnormal lung mechanics, as well as significant expiratory flow limitation. In contrast, patients in Cluster 2 had largely normal physiology. Patients in Cluster 1 exhibited increased clinical disease expression compared to patients in Cluster 2, with significantly worse median Asthma Control Questionnaire-6 (1.33 vs 1.17, p<0.05), Asthma Quality of Life (5.16 vs 5.97, p=0.0019), visual analogue score (VAS) breathlessness (38.5 vs 19.5, p<0.05) and VAS wheeze (33.0 vs 12.0, p<0.05) scores.

Conclusion Small airway biomarkers define a distinct phenotype of asthma with multiple physiological abnormalities and increased disease expression. Future studies should examine the utility of screening for small airway disease at an early stage as a possible means of stratifying asthma therapy.