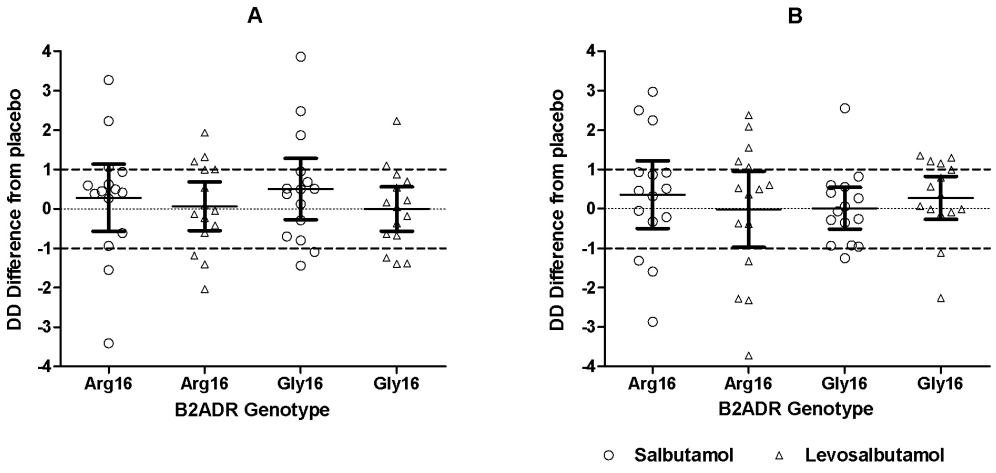

Methacholine challenge doubling dilution (DD) differences from placebo. Scatterplot of individual results with mean (95% CI) doubling dilution differences in methacholine PC20 for salbutamol or levosalbutamol compared to placebo measured at trough 6h after the first (A) and last (B) doses. Interrupted lines represent +/-1 doubling dilution difference from placebo - in order to show individual responses to treatment which were either greater or less than the minimal important difference. All of the 95% CI included zero, confirming that none of the mean responses were statistically significant compared to placebo. B2ADR=beta-2 adrenoceptor gene. Arg16=patients homozygous for Arginine. Gly16=patients homozygous for glycine.

Abstract S7 Figure 1

volunteers (4 mild stable asthmatics and 4 non asthmatic, healthy volunteers) Granulocytes were separated using gradient Ficoll-Paque PLUS 1.084 centrifugation. Superparamagnetic particles coupled to a monoclonal antibody against CD16, a surface marker present in neutrophils, were incubated with the granulocytes (containing eosinophils and neutrophils). CliniMACS system (Miltenyi biotec, Bergisch-Gladbach, Germany; and Becton-Dickinson, Oxford, UK) was used to obtain highly purified (>93% pure) human blood eosinophils or neutrophils (>; 97%). Purified cells were labelled with Tc-99m HMPAO (Ceretec, GE Healthcare) under aseptic cGMP conditions and 75–100 MBq of labelled cells were administered intravenously. Dynamic lung images were acquired for the first 30 minutes. Further static scans of 5 minutes each were acquired at 1; 2 and 4 hours. Results: We were able to obtain highly purified neutrophils (positive selection) or eosinophils (negative selection). Kinetics of eosinophils in lung, liver and spleen differed significantly from kinetics of neutrophils. Initial dynamic lung images revealed a significant difference in the time activity curves for eosinophils and neutrophils. Migration of eosinophils from the lungs followed a monexponential clearance (t1/2) of 4.16 min. While neutrophil had significantly different clearance half-lives of 13.72 min ($p=0.0019$). There were significant differences in eosinophil and neutrophil migration and distribution in the liver and spleen ($p<0.0018$ and $p<0.0325$). There was a trend towards faster neutrophil migration in the asthmatics. This was not statistically significant.

Conclusions For the first time it has been possible to identify distinct patterns of neutrophil and eosinophil migration through lung, liver and spleen in both healthy volunteers and stable asthmatics. This technique provides the opportunity for rapid throughput screening of novel therapeutic agents designed to alter leukocyte migration in disease conditions, or to further phenotype disease such as asthma.

S9 CLUSTER ANALYSIS REVEALS A DISTINCT SMALL AIRWAY-PREDOMINANT PHENOTYPE OF ASTHMA

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Introduction and objectives 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 area), airflow obstruction (FEV_1 [% pred.] and FVC [% pred.]) and ventilation heterogeneity (lung clearance index and S_{acin}). 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, $p<0.01$), 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.

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