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Title: Phenotypes of adult-onset asthma by cluster analysis

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**Body:** Rationale: Asthma phenotyping is of increasing importance to identify patients who could benefit from personalised therapeutic strategies. Several studies suggested that adult-onset asthma is a specific phenotype. In order to explore underlying mechanisms of adult-onset asthma, we aimed to identify subphenotypes by using unsupervised clustering, methods Methods: 200 patients with adult-onset (>18yr) asthma (60.5%female; age54(26-75)yr, 45%atopic) were characterized with respect to clinical, functional and inflammatory markers. Initial variable reduction was achieved by elimination of redundant data and factor analysis. K-means non-hierarchical cluster analysis was performed to identify clusters Results: We identified three clusters of adult-onset asthma. Cluster 1 (n=41) consisted of predominantly females, with higher BMI and more often of non-Caucasian descent. They showed higher symptom scores, higher health care utilization and frequent exacerbations. However, they had lower sputum eosinophils and normal exhaled nitric oxide (FeNO) levels. Cluster 2 (n=69) consisted of predominantly females with severe asthma. They showed high symptom scores and frequent exacerbations, with reduced lung function, elevated sputum eosinophils and relatively high FeNO levels. Cluster 3 (n=90) consisted of predominantly males with mild-moderate asthma, normal lung function, minimal symptoms and health care utilization. Conclusions: Non-hierarchical cluster analysis identifies three subphenotypes of adult-onset asthma that can be distinguished by gender, symptom severity, BMI, lung function and airway inflammation. Identifying these subphenotypes can help to investigate the associated pathobiology and provides new directions to

