European Respiratory Society
Annual Congress 2012

Abstract Number: 1042

Publication Number: P553

Abstract Group: 1.12. Clinical Problems - COPD

Keyword 1: Breath test **Keyword 2:** COPD - diagnosis **Keyword 3:** Biomarkers

Title: COPD subphenotypes in a population-based survey by factor and cluster analysis

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Body: Background Classification of COPD is currently based on symptoms, airways obstruction and exacerbations. However, this may not fully reflect the phenotypic heterogeneity of COPD in the (ex-) smoking community. We hypothesized that factor analysis followed by cluster analysis of functional, clinical, radiological and exhaled breath metabolomic features identifies subphenotypes of COPD in a community-based population of heavy (ex-) smokers. Methods Adults (50-75 yrs) with ≥15 packyears derived from a random population-based survey underwent pulmonary function testing, chest CT scanning, questionnaires and exhaled breath molecular profiling using an electronic nose. Factor analysis followed by K-means cluster analysis was performed on subjects fulfilling the GOLD criteria for COPD with post-BD $FEV_1/FVC<0.70$. Results 157 of 300 subjects fulfilled the criteria for COPD. Factor analysis revealed 12 factors representing different domains of COPD including lung function, radiologic features, exhaled breath metabolomics, symptoms and quality of life. Four clusters were identified: cluster 1 (n=35; 22%): mild airways obstruction and no emphysema; cluster 2 (n=48; 31%): severe airways obstruction with emphysema and low diffusion capacity, chronic bronchitis, low quality of life and a distinct breath profile; cluster 3 (n=60; 38%): mild COPD with a close to normal lung function, but with radiologic signs of emphysema and a distinct breath profile; cluster 4 (n=14; 9%): highly symptomatic males with dyspnea and low quality of life with moderately impaired lung function. Conclusions This unbiased taxonomy for COPD confirms and extends clusters found in previous studies and allows better phenotyping of COPD.