European Respiratory Society
Annual Congress 2012

Abstract Number: 3266

Publication Number: 1833

Abstract Group: 5.2. Monitoring Airway Disease

Keyword 1: Asthma - diagnosis **Keyword 2:** Biomarkers **Keyword 3:** Wheezing

Title: Prediction of new-onset wheeze based on serum inflammation biomarkers – Evaluation using univariate and multivariate techniques

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Body: Asthma is associated with inflammation in the airways and wheeze. The hypothesis is that increased levels of inflammation biomarkers among subjects without respiratory symptoms are a sign of subclinical airways inflammation. Objective: To evaluate if increased levels of inflammation biomarkers in serum predicts later onset of wheeze. Methods: We followed up 2,200 subjects from a general population-based study. At baseline, the subjects were investigated with questionnaires, blood samples, spirometry and FENO. All subjects reporting tobacco smoking, wheeze, asthma, asthma symptoms, or CRP >5 at baseline were excluded. Four years later all subjects got a respiratory questionnaire, which 86.2% completed. The association between baseline levels of a panel of cytokines in serum and incident wheeze was evaluated using non-parametric statistical methods and orthogonal projection to latent structures - discriminant analysis (OPLS-DA). Subjects with FENO levels between the 45th percentile and the 55th percentile served as controls (n=101), and were compared to subjects with new-onset wheeze (n=29). Results: The median levels of TNF, IL-1, IL-2, IL-4 and IL-12 at baseline were significantly higher among those with new-onset wheeze ($p<0.05$). This was supported by OPLS-DA, where TNF, IL-1, IL-4 and IL-12 scored the highest probability. The median levels of IL-5, IL-8, IL-10 and IL-13 at baseline were significantly lower ($p<0.05$). Conclusions: Our results indicate that the levels of serum inflammation biomarkers in respiratorily healthy subjects were associated with an increased risk of developing wheeze.