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Title: Small airways involvement is associated with bronchial hyperresponsiveness in asthma

Mr. Eef 9260 Telenga e.d.telenga@umcg.nl MD¹, Prof. Dirkje 10828 Postma d.s.postma@umcg.nl MD¹, Dr. Roland 9261 Riemersma ra.riemersma@home.nl MD², Prof. Thys 9262 van der Molen t.van.der.molen@umcg.nl MD², Dr. Maarten 9263 van den Berge m.van.den.berge@umcg.nl MD¹ and Dr. Nick 10827 ten Hacken n.h.t.ten.hacken@umcg.nl MD¹. ¹ Dept. of Pulmonary Diseases, University Medical Center, Groningen, Netherlands and ² Dept. of General Practice, University Medical Center, Groningen, Netherlands .

Body: Background: Bronchial hyperresponsiveness (BHR) is a hallmark of asthma. Although, the role of small airways involvement in asthma has been well established, little is known about the association between BHR and small airways obstruction. We hypothesize that small airways disease contributes to BHR. Methods: A total of 119 patients with a doctor's diagnosis of asthma were included. All subjects underwent spirometry and a BHR testing (PD₂₀ histamine). Small airways involvement was defined as an MEF₅₀ ≤ the lower limit of normal (LLN). We compared the severity of BHR between asthmatics with and without small airways involvement. Results: We found 36 patients with and 83 patients without small airways involvement (MEF₅₀ ≤ LLN and MEF₅₀ > LLN respectively). Patients with small airways involvement showed a more severe BHR than patients without (PD₂₀ histamine 0.2 vs. 1.1 mg). In addition, FEV₁, FEV₁/FVC and reversibility were lower in patients with small airways involvement. Both a lower MEF₅₀ and FEV₁ were independent predictors of more severe BHR in multivariate linear regression models. Conclusion: Small airways involvement is associated with more severe BHR in asthma. Since FEV₁ is used as a read-out in current BHR tests, we hypothesize that further research with small airways measurements during BHR tests will provide more insight into the relation between BHR and small airways involvement.