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**Title:** Additive role of exhaled NO and blood eosinophil count to predict wheezing in a random population sample

Andrei 316 Malinowski Andrei.Malinowski@medsci.uu.se MD <sup>1</sup>, Joao 1350 Fonseca fonseca.ja@gmail.com MD <sup>2</sup>, Tiago 1351 Jacinto tajacinto@gmail.com <sup>2</sup>, Kjell 1352 Alving Kjell.Alving@kbh.uu.se <sup>3</sup> and Christer 1353 Janson Christer.Janson@medsci.uu.se MD <sup>4</sup>. <sup>1</sup> Dept. of Medical Sciences: Clinical Physiology, Uppsala University, Uppsala, Sweden, 751 85 ; <sup>2</sup> Dept. of Health Information and Decision Sciences, University of Porto, Portugal, 4200-319 ; <sup>3</sup> Dept. of Women's and Children's Health, Uppsala University, Uppsala, Sweden, 75185 and <sup>4</sup> Dept. of Medical Sciences: Respiratory Medicine and Allergology, Uppsala University, Uppsala, Sweden, 75185 .

**Body:** The fraction of nitric oxide in exhaled air (FeNO) and blood eosinophil count (B-Eos), markers of local and systemic eosinophil activation, respectively, are increased in asthma. Little is known about the relation to reported wheezing in a random population sample or the additive value of these two methods. FeNO (NIOX Mino) and B-Eos were measured in 12,408 subjects aged 6-79 years from the National Health and Nutrition Examination Survey 2007-08 and 2009-10. Current wheezing, hay fever and smoking habits were questionnaire-assessed. Subjects with wheezing had higher FeNO and B-Eos than subjects without wheezing ( $p < 0.001$ ). Slightly increased FeNO (25-50 ppb) and high FeNO (>50 ppb) related to a higher wheezing prevalence than normal FeNO (14% and 25% vs 12% for normal FeNO,  $p = 0.001$ ). Slightly increased B-Eos (300-500 Eos/mm<sup>3</sup>) and high B-Eos (>500 Eos/mm<sup>3</sup>) related to a higher wheezing prevalence than normal B-Eos (17% and 22% vs 11% for normal B-Eos,  $p < 0.001$ ). The risk of wheezing increased with increased B-Eos for subjects with high FeNO and, similarly, with increased FeNO for subjects with high B-Eos (Table).

Risk of wheezing (odds ratios) with increased FeNO and B-Eos.

	Normal B-Eos	Intermediate B-Eos	High B-Eos
Normal FeNO	1	1.41	1.51
Intermediate FeNO	1.29	1.81	2.68
High FeNO	1.81	3.51	5.56

Adjusted for gender, age, BMI, smoking and hay fever.

In conclusion, the prevalence of wheezing increased in this random population sample with increased FeNO

and blood eosinophil count and the predictive values of these biomarkers for wheezing is additive. The clinical importance of these findings in asthma with regard to phenotyping and individualized treatment has to be determined.