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**Title:** Airway responsiveness predicts lung function decline differently in subjects with or without asthma: An international study

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**Body:** Increased airway responsiveness is common in non-asthmatics, and its prognostic value may differ for subjects with and without asthma. We investigated whether asthma or asthma-like symptoms modified the association of airway responsiveness with lung function (LF) decline in a 9-y follow-up of the general population. All the subjects (n=4823) who had undergone methacholine challenge test on both ECRHS I and II, and who did not have COPD (FEV1/FVC<LLN in both occasions) were classified at baseline as having: current asthma (n=604: ever asthma or PD20<1mg methacholine, plus current symptoms), asthma-like symptoms without asthma (n=1352), neither of the two (n=2762). Annual change in FEV1 and FVC (% of baseline value) was analysed as a function of annual change in dose-response slope ( $\Delta$ slope=[slope1-slope2]/follow-up). Estimates were adjusted for sex, age, BMI, education, allergen sensitization, slope at baseline; mid-survey FEV1; BMI change, smoking habits and pack-years smoked over follow-up. An increase of airway responsiveness over time was associated with a greater LF decline, and the association was significantly different across groups: 1-SD  $\Delta$ slope was associated with a -0.03

(-0.07; 0.01), -0.12 (-0.17; -0.07) and -0.14 (-0.24; -0.05)  $\Delta$ FEV1 (%/y) ( $p < 0.001$ ); and with a -0.04 (-0.08; -0.01), -0.07 (-0.13; -0.02), -0.12 (-0.21; -0.03)  $\Delta$ FVC (%/y) ( $p = 0.03$ ) in healthy, symptomatic, and asthmatic subjects, respectively. The prognostic value of airway responsiveness may differ for subjects with and without respiratory diseases. Monitoring change of responsiveness over time could predict LF decline even in subjects without asthma.