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**Title:** Gender differences in bronchial responsiveness: A population-based cohort

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**Body:** Background Incidence of adult asthma, particularly non-allergic asthma, is higher in women but underlying mechanisms remain unclear. Cross-sectional studies have shown that bronchial hyper-responsiveness (BHR) is more frequent in women but gender differences in the onset and prognosis of BHR have been little studied. Methods Gender differences in BHR were studied in men and women without asthma or asthma-like symptoms participating in the European Community Respiratory Health Survey (baseline 1991-93; n=7521, age 20-44 years). BHR was defined as  $\geq 20\%$  decrease in FEV<sub>1</sub> for a methacholine dose  $\leq 1$  mg. Results At baseline, BHR was more frequent in women (12.6%) than in men (6.0%) (adjusted odds-ratio (OR); 2.33 95%CI 1.82-2.98). In subjects without BHR at baseline, BHR at follow-up (1998-2002) was observed in 8.2% (119/1449) women and 4.1% (76/1834) men (adjusted OR 2.74; 95%CI 1.92-3.91). Gender difference in BHR onset was significant in never-smokers, smokers and non-atopic subjects but was not observed in atopic subjects. In subjects with BHR at baseline, no gender difference in BHR persistence and prognosis of BHR as regards asthma was observed: in 172 women and 105 men with BHR at baseline, respectively 54.6% vs. 48.6% still had BHR at follow-up (p=0.33); 20.4% vs. 23.8% had developed asthma-like symptoms (p=0.50), and 12.8% vs. 15.2% had asthma-like symptoms and BHR (p=0.56). BHR was a significant predictor for asthma development in both sexes. Conclusions This study suggests that female sex is a risk factor for the development of BHR during adult life. Further research on the influence of sex-specific factors on BHR is needed to understand the mechanisms underlying the development of asthma in men and women.